CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 090548

Name: Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base)

Sponsor: Apotex Corp.

Approval Date: May 29, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090548

Apotex Corp.
U.S. Agent for: Apotex Inc.
Attention: Kiran Krishnan
Director, North American Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 1, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base).

Reference is also made to the tentative approval letter issued by this office on April 24, 2012, and amendments dated April 25, and May 9, 2012.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lipitor Tablets, 10 mg (base), 20 mg (base), 40 mg (base) and 80 mg (base) of Pfizer Inc. (Pfizer). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Pfizer's Lipitor Tablets, is subject to periods of patent protection. The following patents with their expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,686,104 (the '104 patent)	May 11, 2015
5,969,156 (the '156 patent)	January 8, 2017
6,126,971 (the '971 patent)	July 19, 2013

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg

(base), and 80 mg (base), under this ANDA. You notified the agency that Apotex Corp. (Apotex) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of any of these patents was brought against Apotex within the statutory 45-day period.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

05/29/2012

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090548

Apotex Corp.
U.S. Agent for: Apotex Inc.
Attention: Kiran Krishnan
Director, North American Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 1, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base).

Reference is made to your amendments dated August 6, and December 24, 2008; February 11, May 20, and June 23, 2009; February 22, February 26, March 1, and November 9, 2010; February 22, March 17, May 18, July 12, July 14, August 10, August 18, August 29, September 19, September 28, October 20, November 8, November 16, November 17, November 21, and November 22, 2011; and March 21, 2012.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Pfizer Inc.'s Lipitor Tablets, is subject to periods of patent protection. The following patents and their expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

U.S. Patent Number	Expiration Date
5,686,104 (the '104 patent)	May 11, 2015
5,969,156 (the '156 patent)	January 8, 2017
6,126,971 (the '971 patent)	July 19, 2013

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), under this ANDA. You have notified the agency that Apotex Inc. (Apotex) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of these patents was brought against Apotex.

However, we are unable at this time to grant final approval to your ANDA because your application is blocked by another applicant's 180 day exclusivity. Prior to the submission of your ANDA, another applicant submitted a substantially complete ANDA providing for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), and containing paragraph IV certifications to the '104, '156 and '971 patents. Your ANDA will be eligible for final approval on the date that is 180 days after the 1) date the agency receives notice, with respect to the other ANDA, of the commercial marketing or 2) court decision dates identified in section 505(j)(5)(B)(iv) of the Act.[1] In addition, your ANDA will be eligible for final approval if, prior to those dates, the other applicant's exclusivity ceases to be a barrier to subsequent ANDA approval for any reason.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" upon receipt of this tentative approval letter. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the

[1] Because the other ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Robert Gaines, Project Manager, at (240) 276-8495.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

04/24/2012

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

LABELING

630 mm
5 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm
22 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 32 mm | 400 mm

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Atorvastatin Calcium Tablets safely and effectively. See full prescribing information for Atorvastatin Calcium Tablets.

Atorvastatin Calcium Tablets for oral administration

Initial U.S. Approval: 1996

----------RECENT MAJOR CHANGES----------

Drug Interactions (7) (02/2012)

----------INDICATIONS AND USAGE----------

Atorvastatin calcium tablets are an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use

Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------

Dose range: 10 to 80 mg once daily (2.1).

Recommended start dose: 10 or 20 mg once daily (2.1).

Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).

Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

10, 20, 40, and 80 mg tablets (3).

----------CONTRAINDICATIONS----------

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).

Women who are pregnant or may become pregnant (4.3).

Nursing mothers (4.4).

Hypersensitivity to any component of this medication (4.2).

----------WARNINGS AND PRECAUTIONS----------

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine, and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. In cases of myopathy or rhabdomyolysis, therapy should be temporarily withheld or discontinued (5.1,5.5).

Atorvastatin Calcium Tablets

296637

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzymes tests before initiating therapy and as clinically indicated thereafter (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the atorvastatin calcium 80 mg group vs. placebo (5.5).

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS contact Apotex Corp. at 1-800-667-4708 or FDA at 1-800-FDA-1088 or, *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir), fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥1 g/ day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin (7).
- Digoxin: Patients should be monitored appropriately (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with atorvastatin (7.7).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [03/2012]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:
  - there is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines*). After initiation and/ or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Dosage should be individualized according to the recommended goal of therapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors and fibric acid derivatives should generally be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1)*, *Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1)*, *Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients with HIV taking nelfinavir, therapy with atorvastatin should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed [see *Warnings and Precautions, Skeletal Muscle (5.1)*, *Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, oval, biconvex, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir), fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.11)*].

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/ or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/ or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin [see *Contraindications (4.1)*].

5.3 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0 to 24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0 to 24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin calcium 80 mg vs. placebo was administered to 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium 80 mg group compared to placebo (55, 2.2% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label: Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*]
Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin calcium placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium vs. 7311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin calcium (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patents treated with any dose of atorvastatin calcium and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.9	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction ≥ 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include:

Body as a whole: malaise, pyrexia, fatigue, abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system:* musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system:* transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system:* nightmare; *Respiratory system:* epistaxis; *Skin and appendages:* urticaria; *Special senses:* vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin calcium 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin calcium 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)
In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin calcium 10 mg daily (n=5006) or atorvastatin calcium 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)
In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin calcium 80 mg/ day (n=4439) or simvastatin 20 to 40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL involving 4731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin calcium 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4 to 10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin calcium vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin calcium vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin calcium 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin calcium 80 mg group (5.0%) than in the placebo group (4.0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of atorvastatin calcium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin calcium therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10 to 17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided; in patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg and should be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefru

630 mm
90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm
400 mm | 22 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 32 mm

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets are stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium tablets and if you have symptoms of liver problems while you take atorvastatin calcium tablets. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
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- nausea and vomiting.
- passing brown or dark-colored urine.
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In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, tendon problems, memory loss and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

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Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

Manufactured By: Apotex Inc. Toronto, ON Canada, M9L 1T9

Manufactured For: Apotex Corp. Weston, Florida 33326

Revised: March 2012
Rev. 3

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Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin calcium should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Atorvastatin calcium is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

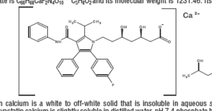
10 OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

11 DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

The drug substance used in atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis[(3*R*,5*R*)-7-[2-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate] propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{82}CaF_2N_4O_{12}$ • $C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:



Atorvastatin calcium is a white to off-white solid that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL production and the number of LDL particles. Atorvastatin calcium reduces LDL-C in humans in patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with various other metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be excreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *In Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-C lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5)*, *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[A]	Change in C_{max}[A]
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[‡]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
[#]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
[#,‡]Saquinavir 400 mg BID/ ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[#]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[#]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[#]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[#]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[#]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[A]	Change in C_{max}[A]
[#]Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[#]Rifampin 600 mg QD, 7 days (coadministered) [†]	40 mg SD	↑ 30%	↑ 2.7 fold
[#]Rifampin 600 mg QD, 5 days (doses separated) [†]	40 mg SD	↓ 80%	↓ 40%
[#]Gemfibrozil 600mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
[#]Fenofibrate 160mg QD, 7 days	40mg SD	↑ 3%	↑ 2%

[A] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

[#] See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or C_{max} (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL to 1.2 liters per day).

** Single sample taken 8 to 16 h post dose.

[†] Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

[‡] The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C_{max}
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	[#]Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg - ethinyl estradiol 35µg	↑ 28% ↑ 19%	↑ 23% ↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

[#] See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represented approximately 16 times the human AUC (0 to 24) value at approximately 11 times the maximum human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 10, 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0 to 24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats administered at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (18 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin was found to adversely affect male reproductive parameters, of reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

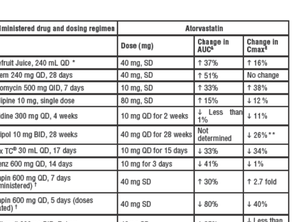
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), microalbuminuria or proteinuria (24.2%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin calcium on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium group)] with a relative risk reduction of 36% [based on incidences of 1.9% for atorvastatin calcium vs. 3.0% for placebo), p=0.0005] (see Figure 1). The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin Calcium 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT LLA)



Atorvastatin calcium also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), aged 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin calcium 10 mg daily (1428) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA1c 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

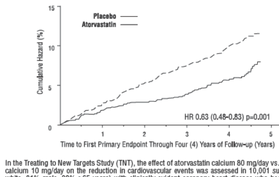
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin calcium significantly reduced the risk of stroke by 48% (21 events in the atorvastatin calcium group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin calcium group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) is CARDS



In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium 80 mg/day vs. atorvastatin calcium 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <100 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium.

Treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p<0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 3: Effect of Atorvastatin Calcium 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

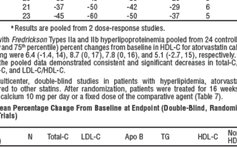


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR* (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	288	(5.8)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PTA/ angioplasty	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure†	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint‡	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

LABELING REVIEWS

****LABELING APPROVAL SUMMARY#4****
(Supercedes LBL AP SUM #3 dated 11/18/11)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90548 Date of Submission: March 21, 2012, November 16, 2011, and May 20, 2009

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

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BASIS OF APPROVAL:

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Electronic Submission

Container Labels: (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
80 mg= bottles of 30s, 90s, 500s, and 2500s):

Final print labels acceptable in 11/16/11 e-submission.

Carton 100 Tablets (10 x 10): All strengths

Final print labels acceptable in 11/16/11 e-submission.

Blister (Blister card of 10s):
Final print labels acceptable in 5/20/09 e-submission.

Blister Insert: All strengths.
Final print labels acceptable in 3/21/2012 e-submission

Professional Package Insert Labeling:
Final printed labeling acceptable in 3/21/2012 e-submission.

Patient Information Sheet:
Final printed labeling acceptable 3/21/2012 e-submission. Apotex submitted a print pad for the patient information.

SPL

DLDE acceptable as of 3/21/2012 e-submission

Revisions needed post- approval: Yes. I will notify the firm of the comments below.

CONTAINER and CARTON LABELS:

- Revise the "Each tablet contains…" statement to read "*Each film-coated tablet contains…"
- Add an asterisk after the strength (e.g. 80 mg*) and before "*Each film-coated tablet contains…"

INSERT:

- **HOW SUPPLIED**- Add "Atorvastatin Calcium Tablets are supplied as white, (b) (4), film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin." as the first sentence.

The above post-approval comments will be communicated to the firm to Kiran Krishnan at (954) 384-3986 once the review has been signed off.

BASIS OF APPROVAL

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 020702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 020702/S-060 approved 2/28/2012

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

As of November 17, 2011:

Apotex revised their side panel, container labels to state "atorvastatin calcium propylene gycol solvate equivalent to atorvastatin X mg" per chemistry recommendations on 8/18/2011.

Apotex reverted back to the original container labels, stating "atorvastatin calcium equivalent to atorvastatin X mg" per chemistry recommendation on 11/16/2011.

The DESCRIPTION section remains the same: "The drug substance used in atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate... Atorvastatin calcium is a white to off-white solid.."

As of August 30, 2011,

Chemistry has NOT decided if the propylene glycol solvate meets the DS definition in USP. There is an

internal discussion within Chemistry. However, as of right now, the labeling and labels are acceptable because the DS is correctly stated as “atorvastatin calcium propylene glycol solvate”. If Chemistry decided that the propylene glycol solvate form DOES NOT meet the definition in USP, then Apotex MUST revise their labels.

Email received on 3/4/09

As you might have known "atorvastatin" is (b) (4)
Thus, one can say "atorvastatin calcium equivalent to 10 mg atorvastatin" or (b) (4) of atorvastatin calcium equivalent to (b) (4)" and technically both are correct.
Thus, from technical perspective, the Apotex labeling is accurate.
However, it is your call if you want the Apotex to change the words similar to RLD.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Wednesday, March 04, 2009 8:56 AM
To: Vaithiyalingam, Sivakumar
Cc: Grace, John F
Subject: Atorvastatin 90-548 (Apotex's atorvastatin)

Siva,

I have a problem with the label of 90-548. Please take a look at the attached pdf file. Apotex's label states:

* Each tablet contains (b) (4) of atorvastatin calcium equivalent to (b) (4).

Lipitor's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

TEVA's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Is Apotex's label accurate? Could Apotex state this because their drug substance is atorvastatin calcium in the form of propylene glycol solvate instead of atorvastatin calcium in the hydrate form. I'm concerned because the label should be consistent between the generic and brand.

Thanks
Ann

Email received on 3/3/09:

Ann,

The RLD is a hydrate whereas the ANDA is a solvate with propylene glycol. Under our current guidance, these drug substances are considered equivalent.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Tuesday, March 03, 2009 1:56 PM
To: Vaithiyalingam, Sivakumar
Cc: Vu, Thuyanh (Ann)
Subject: 90-548 (Apotex's atorvastatin calcium)

The DS in Apotex's atorvastatin is different than the RLD's Lipitor and is this equivalent/acceptable? Thanks Ann

This is Apotex's atorvastatin:

The drug substance used in Atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{68}CaF_2N_4O_{10} * C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:

Lipitor's insert:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, ð-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:

FOR THE RECORD: Please note that the previous review cycles were completed by Thuyanh Vu, labeling reviewer. Portions of this review were taken from the review submitted on 11/18/2111 in DARRTS.

1. MODEL LABELING: This review was based on the labeling of the RLD, Lipitor® Tablets (NDA 020702/S-060), approved February 28, 2012.

   In the amendment submitted 3/22/2012, the firm submitted the revised insert labeling and patient information leaflet to match the labeling for the RLD approved February 28, 2012. The SPL labeling has also been updated.

   Supplement 056, approved 6/17/09 provided for the PLR labeling format.

   Please see the email string with the chemist above. I asked the firm to revise the label to state ""Each tablet contains atorvastatin calcium equivalent to YY mg atovastatin" to be consistent with the RLD and other generic manufacturers even though Apotex is technically/chemically correct.

   8/18/2011 AF: Apotex changed the labels. See Chemist Notes above for further information about the solvate form.

   In this amendment, the carton and container labels have been revised to specifically indicate Atorvastatin Calcium Propylene Glycol Solvate as the drug substance. The statement on the

container and carton labels has been revised from:

Each tablet contains atorvastatin calcium equivalent to X mg atorvastatin.
to:

Each tablet contains atorvastatin calcium propylene glycol solvate equivalent to X mg of atorvastatin.
(where X mg is either 10 mg, 20 mg, 40 mg or 80 mg)

11/16/2011 AF: See Chemist Notes above from further info.

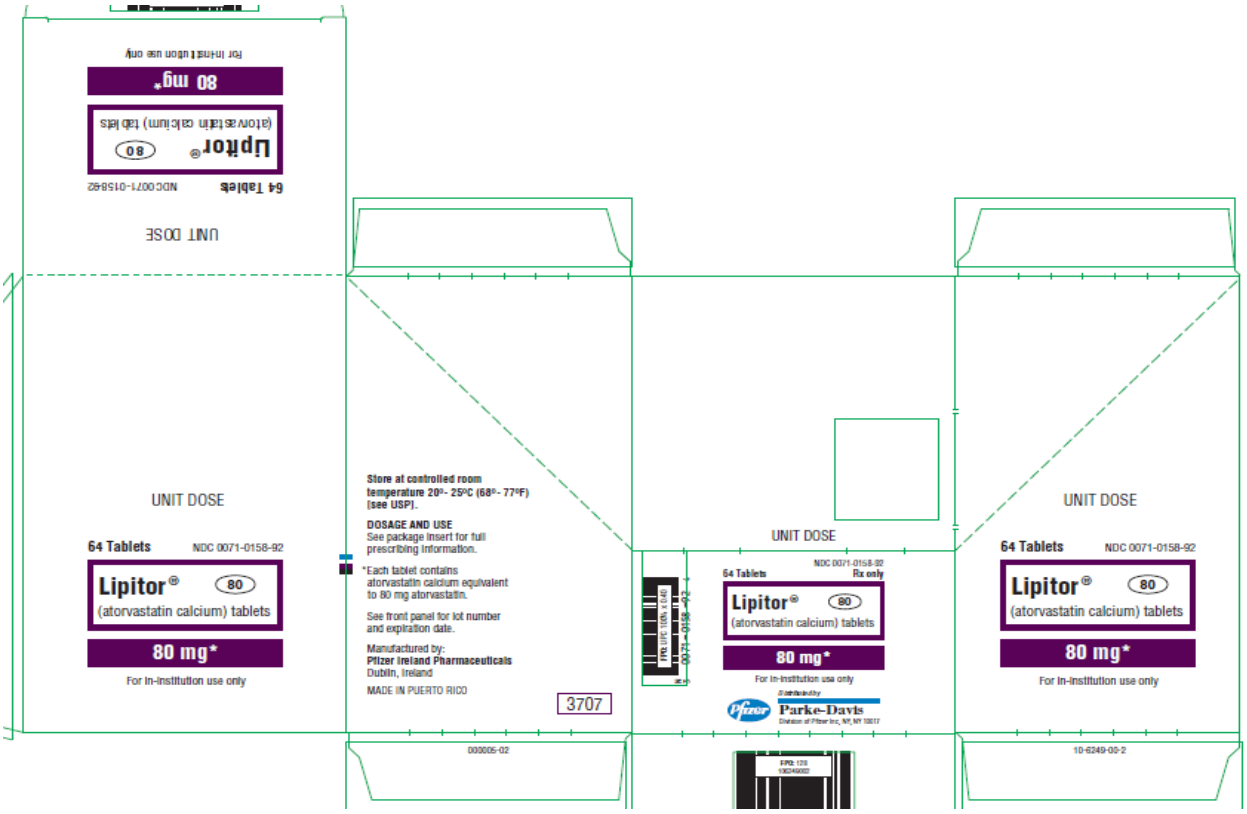
Apotex changed their container labels back to:

"Each tablet contains atorvastatin calcium equivalent to X mg of atorvastatin" per advice from Chemistry. The insert remains the same.

Container



CARTON



Blister labels



2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL: 020702

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	PIII	Same As
5273995	Dec 28, 2010 PED Jun 28, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As
5686104	Nov 11, 2014 PED May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 PED Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 PED July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011* PED	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As, certified in 3/19/09 labeling amendment

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None
I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

Exclusivity Data from OB (checked 4/11/2012)
There is no unexpired exclusivity for this product

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:calcium acetate, croscramellose sodium, sodium carbonate (b) (4), microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide,

hypromellose, hydroxypropyl cellulose [(b) (4)], polyethylene glycol [(b) (4)], titanium dioxide,

[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.1-original submission]

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T 9 Canada

5. CONTAINER/CLOSURE

- HDPE bottles containing 30 or 90 tablets closed with [(b) (4)] screw caps with a [(b) (4)] desiccant. When originally packed, the bottles are also sealed with a [(b) (4)].
- HDPE bottles containing 500 tablets or greater closed with [(b) (4)] screw caps with a [(b) (4)] desiccant. When originally packed, the bottles are also sealed with a [(b) (4)].
- Blister packs comprised of plain [(b) (4)] and a [(b) (4)]. Packed in cartons containing 10 strips of 10 tablets (100 tablets total).

6. FINISHED DOSAGE FORM

RLD:

10 mg: coded "PD 155" on one side and "10" on the other

20 mg: coded "PD 156" on one side and "20" on the other

40 mg: coded "PD 157" on one side and "40" on the other

80 mg: coded "PD 158" on one side and "80" on the other

ANDA:

10 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "A10" on the other side.

20 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "ATV20" on the other side.

40 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "ATV40" on the other side.

80 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "ATV80" on the other side.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: DS is compendial ONLY
RLD: store at CRT 20-25°C (68-77°F) [see USP].
ANDA label: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [See USP Controlled Room Temperature]

8. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight container (see USP).

The carton states: “This unit-dose package is not child-resistant”

9. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the propolyne glycol solvate form rather than the trihydrate

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

RLD: 10 mg, 20 mg = bottles of 90s, 5000s and blisters of 100 (10 x 10) unit dose blisters
40 mg: bottles of 90s, 500s, 2500s and blisters of 100 (10 x 10) unit dose blisters
80 mg: bottles of 90s, 500s, 2500s and blisters of 64 (8 x 8) unit dose blisters

ANDA: 10 mg, 20 mg = bottles of 30s, 90s, 1000s, 5000s and blisters of 100 (20 mg= violet color, 10 mg= green color)
40 mg= bottles of 30s, 90s, 500s, 1000s, 4000s and blisters of 100 (container color= yellow)
80 mg= bottles of 30s, 90s, , 500s, 2500 and blisters of 100 (container color= red)

Date of Review: April 16, 2012

Date of Submission: March 22, 2012, November 16, 2011, and May 20, 2009

Primary Reviewer: Betty Turner

Team Leader: James, Barlow

630 mm
5 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm | 90 mm
22 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 42 mm | 32 mm | 400 mm

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Atorvastatin Calcium Tablets safely and effectively. See full prescribing information for Atorvastatin Calcium Tablets.

Atorvastatin Calcium Tablets for oral administration

Initial U.S. Approval: 1996

----------RECENT MAJOR CHANGES----------

Drug Interactions (7) (02/2012)

----------INDICATIONS AND USAGE----------

Atorvastatin calcium tablets are an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use

Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

10, 20, 40, and 80 mg tablets (3).

----------CONTRAINDICATIONS----------

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who are pregnant or may become pregnant (4.3).
Nursing mothers (4.4).
Hypersensitivity to any component of this medication (4.2).

----------WARNINGS AND PRECAUTIONS----------

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine, and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. In cases of myopathy or rhabdomyolysis, therapy should be temporarily withheld or discontinued (5.1,5.5).

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Atorvastatin Calcium Tablets

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Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzymes tests before initiating therapy and as clinically indicated thereafter (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the atorvastatin calcium 80 mg group vs. placebo (5.5).

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS contact Apotex Corp. at 1-800-667-4708 or FDA at 1-800-FDA-1088 or, *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥1 g/ day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin (7).
- Digoxin: Patients should be monitored appropriately (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with atorvastatin (7.7).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [03/2012]

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:
  - there is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (*Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*). After initiation and/ or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Dosage should be individualized according to the recommended goal of therapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors and fibric acid derivatives should generally be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1)*, *Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1)*, *Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients with HIV taking nelfinavir, therapy with atorvastatin should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed [see *Warnings and Precautions, Skeletal Muscle (5.1)*, *Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, oval, biconvex, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir), fosamprenavir, fosamprenavir plus ritonavir	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.11)*].

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal (ULN) occurring in 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/ or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/ or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin [see *Contraindications (4.1)*].

5.3 Endocrine Function

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0 to 24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0 to 24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin calcium 80 mg vs. placebo was administered to 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium 80 mg group compared to placebo (55, 2.2% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label: Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*]
Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin calcium placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium vs. 7311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin calcium (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patents treated with any dose of atorvastatin calcium and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.9	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction ≥ 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include:

Body as a whole: malaise, pyrexia, fatigue, abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system:* musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system:* transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system:* nightmare; *Respiratory system:* epistaxis; *Skin and appendages:* urticaria; *Special senses:* vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin calcium 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin calcium 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)
In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin calcium 10 mg daily (n=5006) or atorvastatin calcium 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)
In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin calcium 80 mg/ day (n=4439) or simvastatin 20 to 40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL involving 4731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin calcium 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4 to 10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin calcium vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin calcium vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin calcium 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin calcium 80 mg group (5.0%) than in the placebo group (4.0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of atorvastatin calcium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin calcium therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10 to 17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided; in patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg and should be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

**7.3 Cy

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What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets are stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium tablets and if you have symptoms of liver problems while you take atorvastatin calcium tablets. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
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- nausea and vomiting.
- passing brown or dark-colored urine.
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In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, tendon problems, memory loss and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

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How do I store Atorvastatin Calcium Tablets

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Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

Manufactured By: Apotex Inc. Toronto, ON Canada, M9L 1T9

Manufactured For: Apotex Corp. Weston, Florida 33326

Revised: March 2012
Rev. 3

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Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin calcium should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Atorvastatin calcium is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

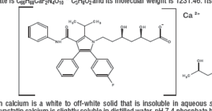
10 OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

11 DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

The drug substance used in atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis[(3*R*,5*R*)-7-[2-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate] propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{82}CaF_2N_4O_{12}$ • $C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:



Atorvastatin calcium is a white to off-white solid that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL production and the number of LDL particles. Atorvastatin calcium reduces LDL-C in humans in patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with various other metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be excreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *In Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-C lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5)*, *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[A]	Change in C_{max}[A]
[C]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[C]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
[C]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
[C]Saquinavir 400 mg BID/ ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[C]Darithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[C]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[C]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[C]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[C]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[A]	Change in C_{max}[A]
[C]Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[C]Rifampin 600 mg QD, 7 days (coadministered) [I]	40 mg SD	↑ 30%	↑ 2.7 fold
[C]Rifampin 600 mg QD, 5 days (doses separated) [I]	40 mg SD	↓ 80%	↓ 40%
[C]Gemfibrozil 600 mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
[C]Fenofibrate 160mg QD, 7 days	40mg SD	↑ 3%	↑ 2%

[A] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

[C] See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or C_{max} (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL to 1.2 liters per day).

** Single sample taken 8 to 16 h post dose.

[I] Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C_{max}
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	[C]Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg - ethinyl estradiol 35µg	↑ 28% ↑ 19%	↑ 23% ↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

[C] See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represented approximately 16 times the human AUC (0 to 24) value at approximately 11 times the maximum human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 10, 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0 to 24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (18 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin was found to have no adverse effects on female reproducers, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

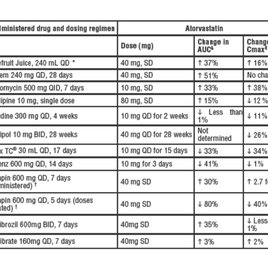
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), cigarette smoking (33.2%), diabetes (24.2%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with atorvastatin calcium 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin calcium on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium group)] with a relative risk reduction of 36% [based on incidences of 1.9% for atorvastatin calcium vs. 3.0% for placebo], p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin Calcium 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT LLA)



Atorvastatin calcium also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), aged 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin calcium 10 mg daily (1428) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA1c 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

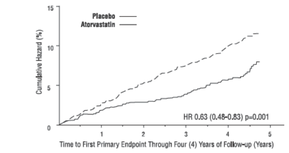
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin calcium significantly reduced the risk of stroke by 48% (21 events in the atorvastatin calcium group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin calcium group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium 80 mg/day vs. atorvastatin calcium 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <100 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium.

Treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p<0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 3: Effect of Atorvastatin Calcium 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

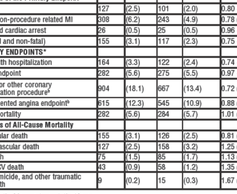


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR* (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PTA/ angioplasty	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure#	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint#	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.

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Atorvastatin Calcium Tablet
10 mg MFD. FOR APOTEX CORP. WESTON, FL 33326
(01)0(03)60505257805
(L) GE4444 EXP. 10 2009

2 MM KEY LINE
PRINTABLE AREA

62.3MM 4.5MM 62.3MM 4.5MM 62.3MM

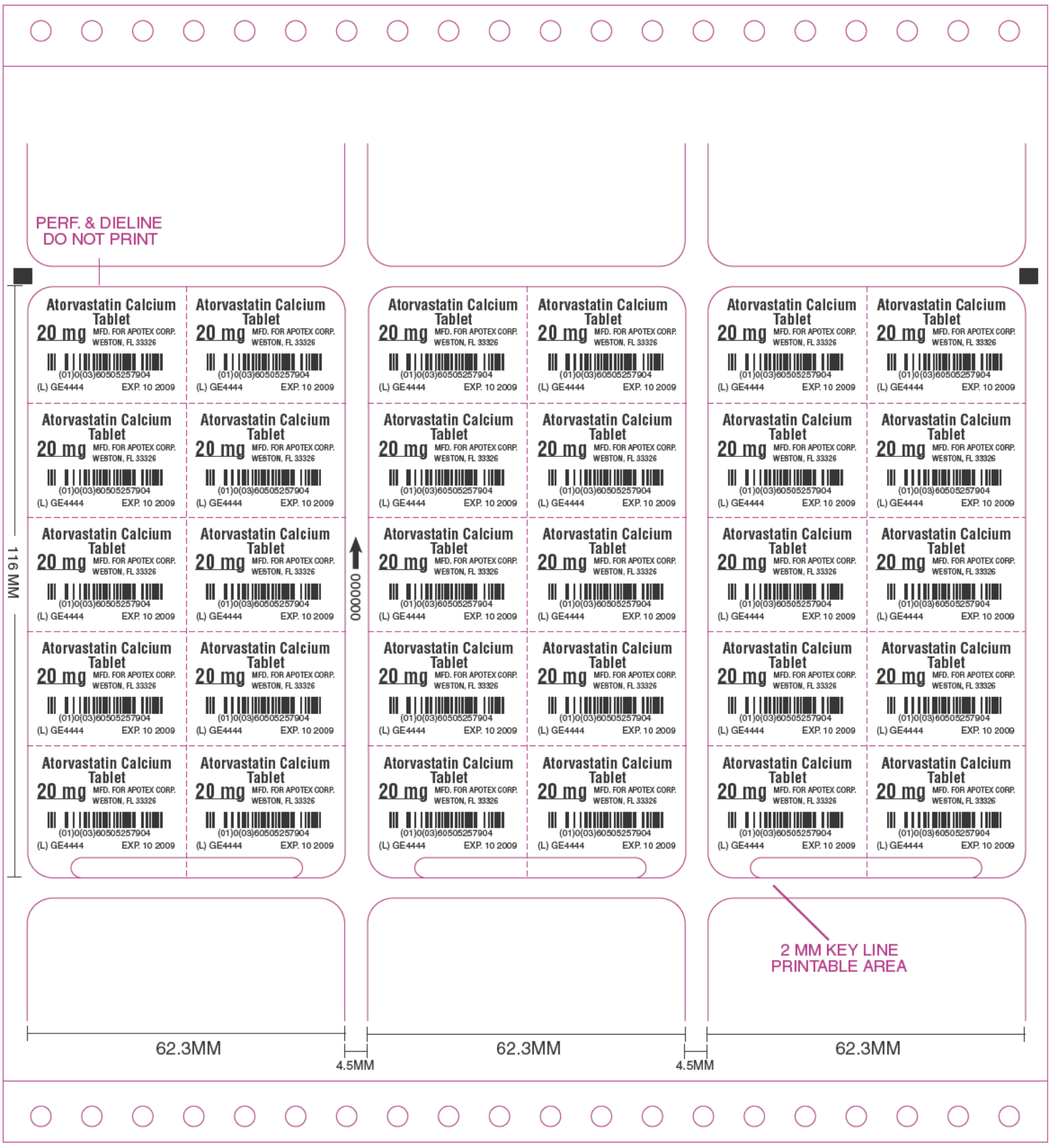
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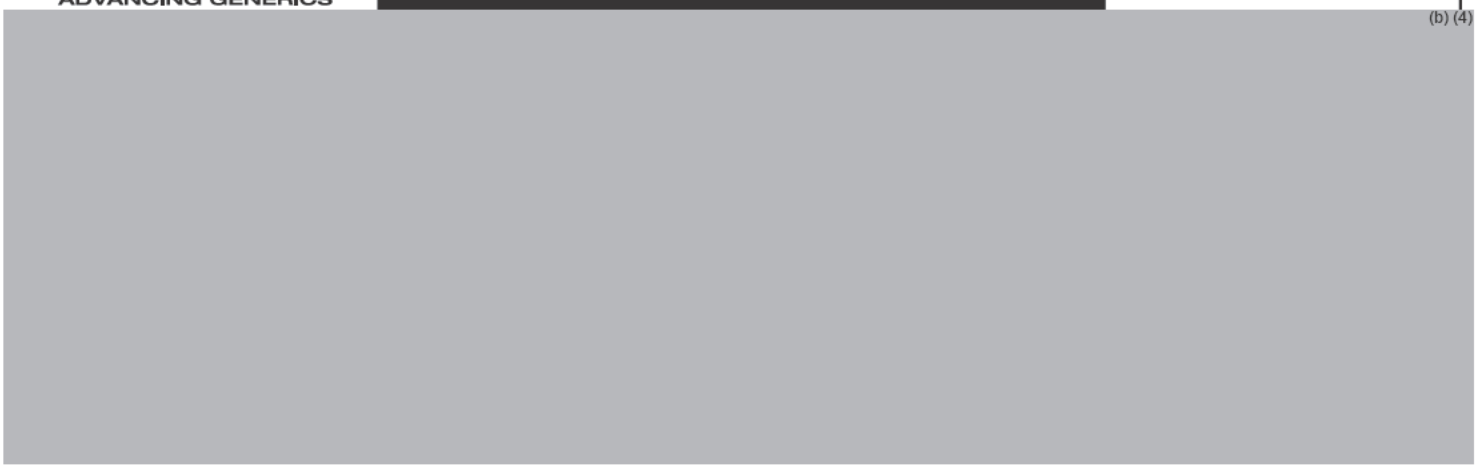


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Atorvastatin Calcium Tablet
MFD. FOR APOTEX CORP.
WESTON, FL 33326
40 mg
(01)0(03)60505258000
(L) GE4444 EXP. 10 2009

2 MM KEY LINE
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Atorvastatin Calcium Tablets safely and effectively. See full prescribing information for Atorvastatin Calcium Tablets.

Atorvastatin Calcium Tablets for oral administration

Initial U.S. Approval: 1996

----------RECENT MAJOR CHANGES----------

Drug Interactions (7) (02/2012)

----------INDICATIONS AND USAGE----------

Atorvastatin calcium tablets are an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with

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primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

10, 20, 40, and 80 mg tablets (3).

----------CONTRAINDICATIONS----------

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who are pregnant or may become pregnant (4.3).

2

Nursing mothers (4.4).
Hypersensitivity to any component of this medication (4.2).

----------WARNINGS AND PRECAUTIONS----------

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine, and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. In cases of myopathy or rhabdomyolysis, therapy should be temporarily withheld or discontinued (5.1,8.5).

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzymes tests before initiating therapy and as clinically indicated thereafter (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the atorvastatin calcium 80 mg group vs. placebo (5.5).

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

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To report SUSPECTED ADVERSE REACTIONS contact Apotex Corp. at 1-800-667-4708 or FDA at 1-800-FDA-1088 or, *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

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- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin (7).
- Digoxin: Patients should be monitored appropriately (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with atorvastatin (7.7).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [03/2012]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

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1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

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1 2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels *(Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:
  - there is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patient

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1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*). After initiation and/or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this

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patient population). Doses should be individualized according to the recommended goal of therapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see *Warnings and Precautions*, *Skeletal Muscle (5.1)*, *Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary [see *Warnings and Precautions*, *Skeletal Muscle (5.1)*, *Clinical Pharmacology*, *Pharmacokinetics (12.3)*].

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2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients with HIV taking nelfinavir, therapy with atorvastatin should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, oval, biconvex, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

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Women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

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5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent

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administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

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Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary (12.3)

18 Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-

administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.11)*].

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5 2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

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It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin [see *Contraindications (4.1)*].

5.3 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

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5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0 to 24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0 to 24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

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5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin calcium 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:
Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*]
Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

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6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin calcium placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium vs. 7311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

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Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin calcium (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patents treated with any dose of atorvastatin calcium and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6

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Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction ≥ 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include:
Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin calcium 10 mg daily (n=5,168) or placebo (n=5,137), the safety 25

and tolerability profile of the group treated with atorvastatin calcium was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin calcium 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)
In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin calcium 10 mg daily (n=5006) or atorvastatin calcium 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%). 26

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)
In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin calcium 80 mg/day (n=4439) or simvastatin 20 to 40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL involving 4731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin calcium 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4 to 10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic 27

stroke was similar between groups (17 atorvastatin calcium vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin calcium vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin calcium 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin calcium 80 mg group (5.0%) than in the placebo group (4.0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of atorvastatin calcium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin calcium therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson 28

syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10 to 17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*]. 29

7.1 Strong Inhibitors of CYP 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitiors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg and should be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1) and Dosage and Administration (2.6)*]. 30

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin alone [see *Clinical Pharmacology (12.3)*]. The co-administration of atorvastatin with cyclosporine should be avoided.[see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Gemfibrozil: Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of atorvastatin with gemfibrozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 Other Fibrates: Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, atorvastatin 31

should be administered with caution when used concomitantly with other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin: The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin; a reduction in atorvastatin dosage should be considered in this setting [see *Warnings and Precautions (5.1)*].

7.7 Rifampin or other Inducers of Cytochrome P450 3A4: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin: When multiple doses of atorvastatin and digoxin were co-administered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.9 Oral Contraceptives: Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. 32

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7.10 Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

7.11 Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Atorvastatin calcium is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate

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expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2) [see *Contraindications, Pregnancy (4.3)*].

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant

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while taking atorvastatin calcium, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin treatment should be advised not to nurse their infants [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin calcium had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.**

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In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10 to 17 years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age) (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin calcium should be prescribed with caution in the elderly.

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8.6 Hepatic Impairment

Atorvastatin calcium is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

10 OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

11 DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

The drug substance used in atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin

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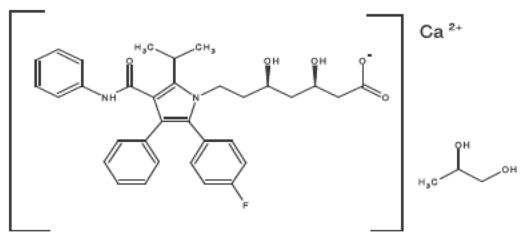
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calcium propylene glycol solvate is $C_{66}H_{68}CaF_2N_4O_{10} * C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:



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Atorvastatin calcium is a white to off-white solid that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human

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atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL production and the number of LDL particles. Atorvastatin calcium reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate

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density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12 2 Pharmacodynamics

Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is

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approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin,

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a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

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Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5)*, *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4.1)*].

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TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[#]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
[#]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
[#], [‡]Saquinavir 400 mg BID/ ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[#]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold

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Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
[#]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[#]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[#]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[#]Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
[#]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
[#]Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change

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Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[#]Rifampin 600 mg QD, 7 days (coadministered) [†]	40 mg SD	↑ 30%	↑ 2.7 fold

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Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
[#]Rifampin 600 mg QD, 5 days (doses separated) [†]	40 mg SD	↓ 80%	↓ 40%
[#]Gemfibrozil 600mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
[#]Fenofibrate 160mg QD, 7 days	40mg SD	↑ 3%	↑ 2%

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

[#] See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or C_{max} (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL to 1.2 liters per day).

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** Single sample taken 8 to 16 h post dose.

† Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in Cmax
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	‡ Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %

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40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg - ethinyl estradiol 35µg	↑ 28% ↑ 19%	↑ 23% ↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in

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another, there was a fibrosarcoma. This dose represents a plasma AUC (0 to 24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0 to 24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

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14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients; <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin calcium 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

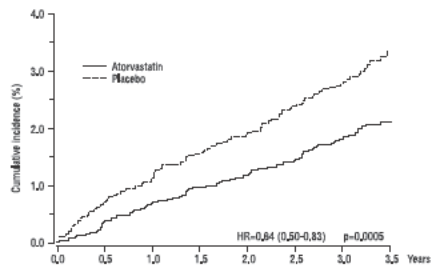
The effect of 10 mg/day of atorvastatin calcium on lipid levels was similar to that seen in previous clinical trials.

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Atorvastatin calcium significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin calcium vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

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Figure 1: Effect of Atorvastatin Calcium 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



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Atorvastatin calcium also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin calcium 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA1c 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

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The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin calcium significantly reduced the risk of stroke by 48% (21 events in the atorvastatin calcium group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin calcium group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

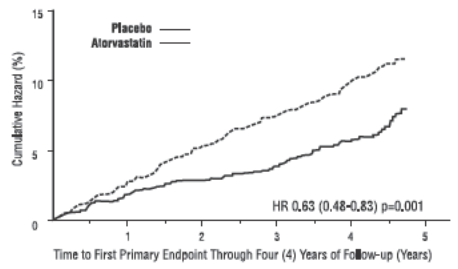
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Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



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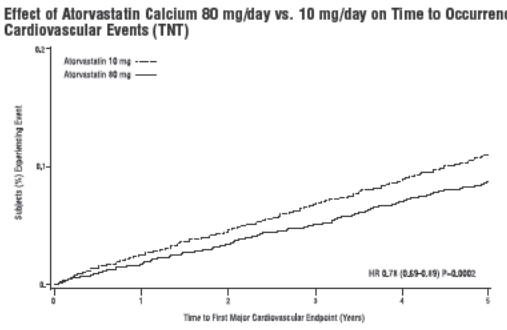
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In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium 80 mg/day vs. atorvastatin calcium 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium.

Treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

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Figure 3: Effect of Atorvastatin Calcium 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)



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TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)

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SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)

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Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

[a] Atorvastatin 80 mg: atorvastatin 10 mg
[b] Component of other secondary endpoints
* Secondary endpoints not included in primary endpoint

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

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Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin calcium 80 mg group than in the atorvastatin calcium 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin calcium 80 mg group than in the atorvastatin calcium 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium 80 mg/day was compared to treatment with simvastatin 20 to 40 mg/day in 8,888 subjects up to 80 years of age with a history of

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CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin calcium and 105, 179, 142, 47, and 132 mg/dL during treatment with 20 to 40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin calcium 80 mg/day group vs. 463 (10.4%) in the simvastatin 20 to 40 mg/day group, HR 0.89, 95% CI (0.78, 1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin calcium 80 mg/day group vs. 374 (8.4%) in the simvastatin 20 to 40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin calcium 80 mg group and the simvastatin 20 to 40 mg group.

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14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin calcium is effective in a wide variety of patient populations with hyperlipidemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, atorvastatin calcium given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 6.)

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TABLE 6. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin calcium 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and

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5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, atorvastatin calcium was compared to other statins. After randomization, patients were treated for 16 weeks with either atorvastatin calcium 10 mg per day or a fixed dose of the comparative agent (Table 7).

TABLE 7. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28

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95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

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[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$
[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$
[c] Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 7 is not known. Table 7 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

The response to atorvastatin calcium in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the atorvastatin calcium -treated patients, median (min, max) baseline TG level was 565 (267 to 1502).

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TABLE 8. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

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14.4 Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below (Table 9).

TABLE 9. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)

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IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10 to 17 years of age (mean age 14.1 years) with heterozygous familial

72 hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to

(b) (4)

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atorvastatin calcium (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5 to 385.0 mg/dL) in the atorvastatin calcium group compared to 230.0 mg/dL (range: 160.0 to 324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 10).

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TABLE 10. Lipid-altering Effects of Atorvastatin Calcium in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin Calcium Tablets	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0 to 242.0 mg/dL) in the atorvastatin calcium group compared to 228.5 mg/dL (range: 152.0 to 385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

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15 REFERENCES

[1]National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, *Pediatrics*. 89(3):495-501. 1992.

16 HOW SUPPLIED/STORAGE AND HANDLING

10 mg tablets: Atorvastatin calcium tablets, 10 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "A10" on the other side.

Bottles of 30 (NDC 60505-2578-3)

Bottles of 90 (NDC 60505-2578-9)

Bottles of 1000 (NDC 60505-2578-8)

Bottles of 5000 (NDC 60505-2578-7)

Blister of 100 (NDC 60505-2578-0)

20 mg tablets: Atorvastatin calcium tablets, 20 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV20" on the other side.

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Bottles of 30 (NDC 60505-2579-3)

Bottles of 90 (NDC 60505-2579-9)

Bottles of 1000 (NDC 60505-2579-8)

Bottles of 5000 (NDC 60505-2579-7)

Blister of 100 (NDC 60505-2579-0)

40 mg tablets: Atorvastatin calcium tablets, 40 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV40" on the other side.

Bottles of 30 (NDC 60505-2580-3)

Bottles of 90 (NDC 60505-2580-9)

Bottles of 500 (NDC 60505-2580-5)

Bottles of 1000 (NDC 60505-2580-8)

Bottles of 4000 (NDC 60505-2580-7)

76 Blister of 100 (NDC 60505-2580-0)

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80 mg tablets: Atorvastatin calcium tablets, 80 mg, are available for oral administration as white, oval, biconvex film-coated tablets, engraved "APO" on one side, "ATV80" on the other side.

Bottles of 30 (NDC 60505-2671-3)

Bottles of 90 (NDC 60505-2671-9)

Bottles of 500 (NDC 60505-2671-5)

Bottles of 2500 (NDC 60505-2671-7)

Blister of 100 (NDC 60505-2672-0)

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Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in a tight container [see USP].

17 PATIENT COUNSELING INFORMATION

Patients taking atorvastatin calcium tablets should be advised that cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program as appropriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin *[see Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking atorvastatin calcium tablets.

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17.1 Muscle Pain

All patients starting therapy with atorvastatin calcium tablets should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver enzyme tests be performed before the initiation of atorvastatin calcium tablets and if signs or symptoms of liver injury occur. All patients treated with atorvastatin calcium tablets should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using atorvastatin calcium tablets. Discuss future pregnancy plans with your patients, and discuss when to stop atorvastatin calcium tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking atorvastatin

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calcium tablets and call their healthcare professional.

17.4 Breastfeeding

Women who are breastfeeding should be advised to not use atorvastatin calcium tablets. Patients who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

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Manufactured For:
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PATIENT INFORMATION

Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment. If you have any questions about atorvastatin calcium tablets, ask your doctor or pharmacist.

What are Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets is a prescription medicine that lowers cholesterol in your blood. It lowers the "bad" cholesterol (LDL-C, "bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. Atorvastatin calcium tablets are for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin calcium tablets can lower the risk for heart attack, or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

Atorvastatin calcium tablets start to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower "bad" cholesterol if you have heart disease, stroke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take atorvastatin calcium tablets if you:

- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.
- have liver problems.
- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium tablets may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast feeding. Atorvastatin calcium tablets can pass into your breast milk and may harm your baby.

Before You Start Atorvastatin Calcium Tablets

Tell your doctor if you:

- have muscle aches or weakness after taking more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems
- your immune system
- cholesterol
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

How Should I Take Atorvastatin Calcium Tablets?

- Take atorvastatin calcium tablets exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium tablets without talking to your doctor. Your doctor may do blood tests to check your treatment with atorvastatin calcium tablets. Your dose of atorvastatin calcium tablets may be changed based on these blood test results.
- Take atorvastatin calcium tablets each day at any time of day, at about the same time each day. Atorvastatin calcium tablets can be taken with or without food.
- Your doctor should start you on a low-fat diet before giving you atorvastatin calcium tablets. Stay on this diet while taking atorvastatin calcium tablets.
- If you miss a dose of atorvastatin calcium tablets, take it as soon as you remember. Do not take atorvastatin calcium tablets if it has been more than 12 hours since you missed your last dose. Wait and take your next dose at your regular time. Do not take 2 doses of atorvastatin calcium tablets at the same time.
- If you take too much atorvastatin calcium tablets or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects. Do not start taking any medicine during treatment with atorvastatin calcium tablets without first talking to your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people taking atorvastatin calcium tablets. Your doctor may check you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets are stopped. Call your doctor right away if you have any of these serious side effects including:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney failure. You have a higher chance for muscle problems if you are taking atorvastatin calcium tablets with certain other medicines.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium tablets. Call your doctor right away if you have symptoms of liver problems. These symptoms may include:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain with fever or feel tired
- eyes get yellow.
- allergic reactions. In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, gas, indigestion, heartburn, muscle and joint pain, upset stomach, muscle cramps, and abnormal results in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: memory loss and confusion. Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of atorvastatin calcium tablets. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

- Store atorvastatin calcium tablets at room temperature, 68 to 77°F (20 to 25°C).
- Throw away any medicine that is out of date or that you no longer need.

- you also have a fever or feel more tired than usual.
- swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- your skin and whites of your eyes turn yellow.
- stomach pain.

Keep atorvastatin calcium tablets and all medicines out of the reach of children. Be sure that no one else takes your medicine. Do not give your medicine to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

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Manufactured For:
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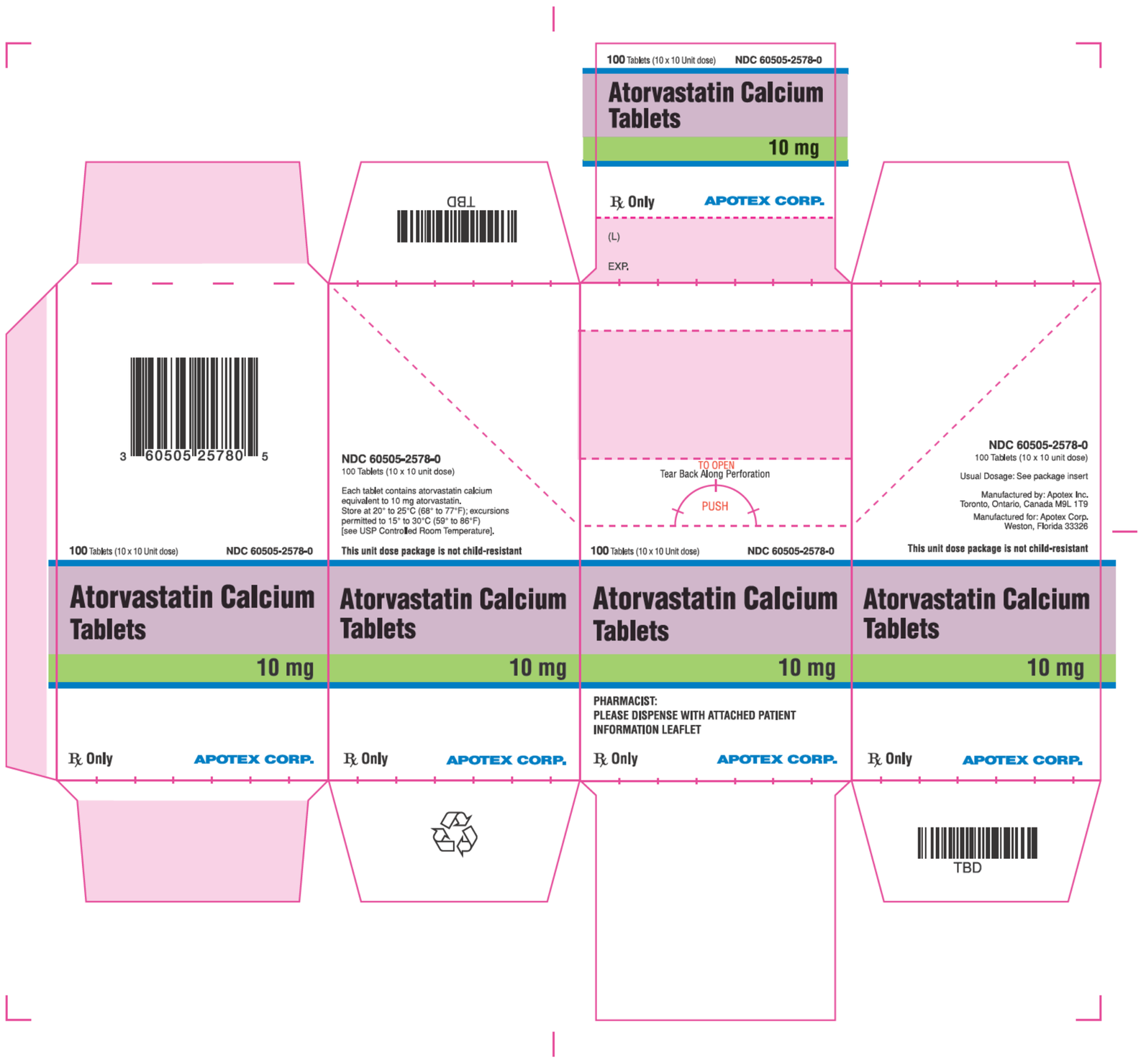
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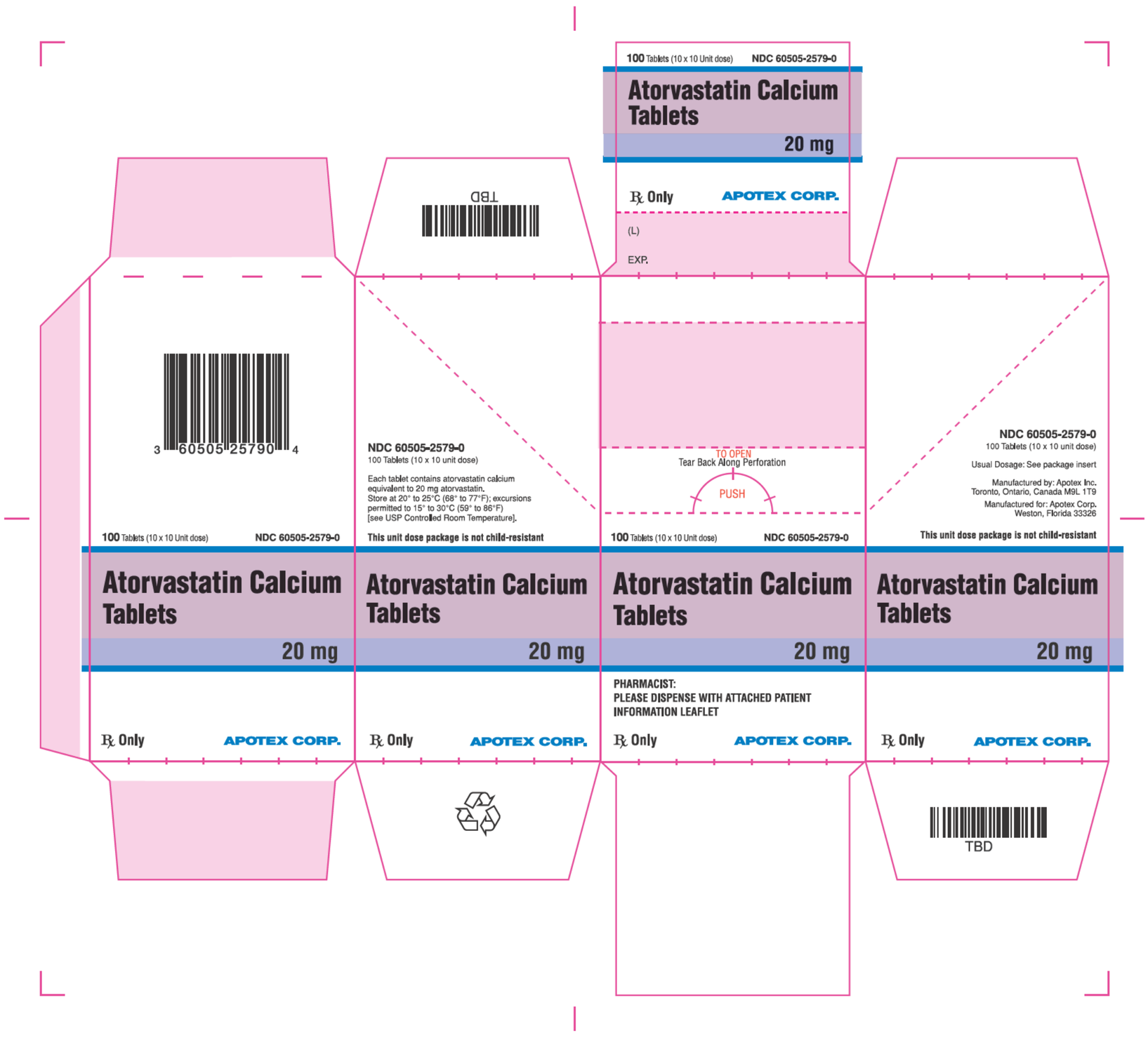
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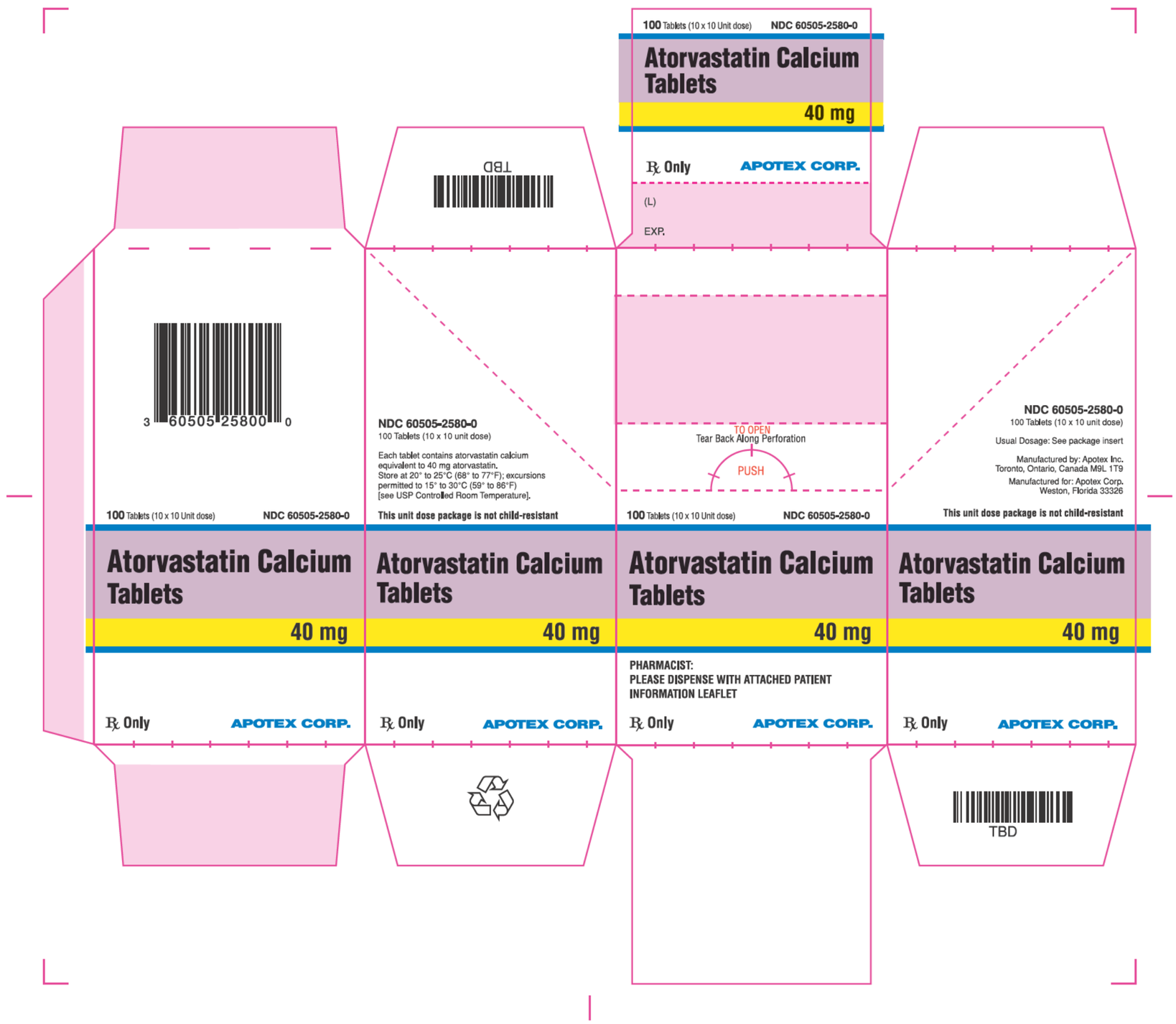


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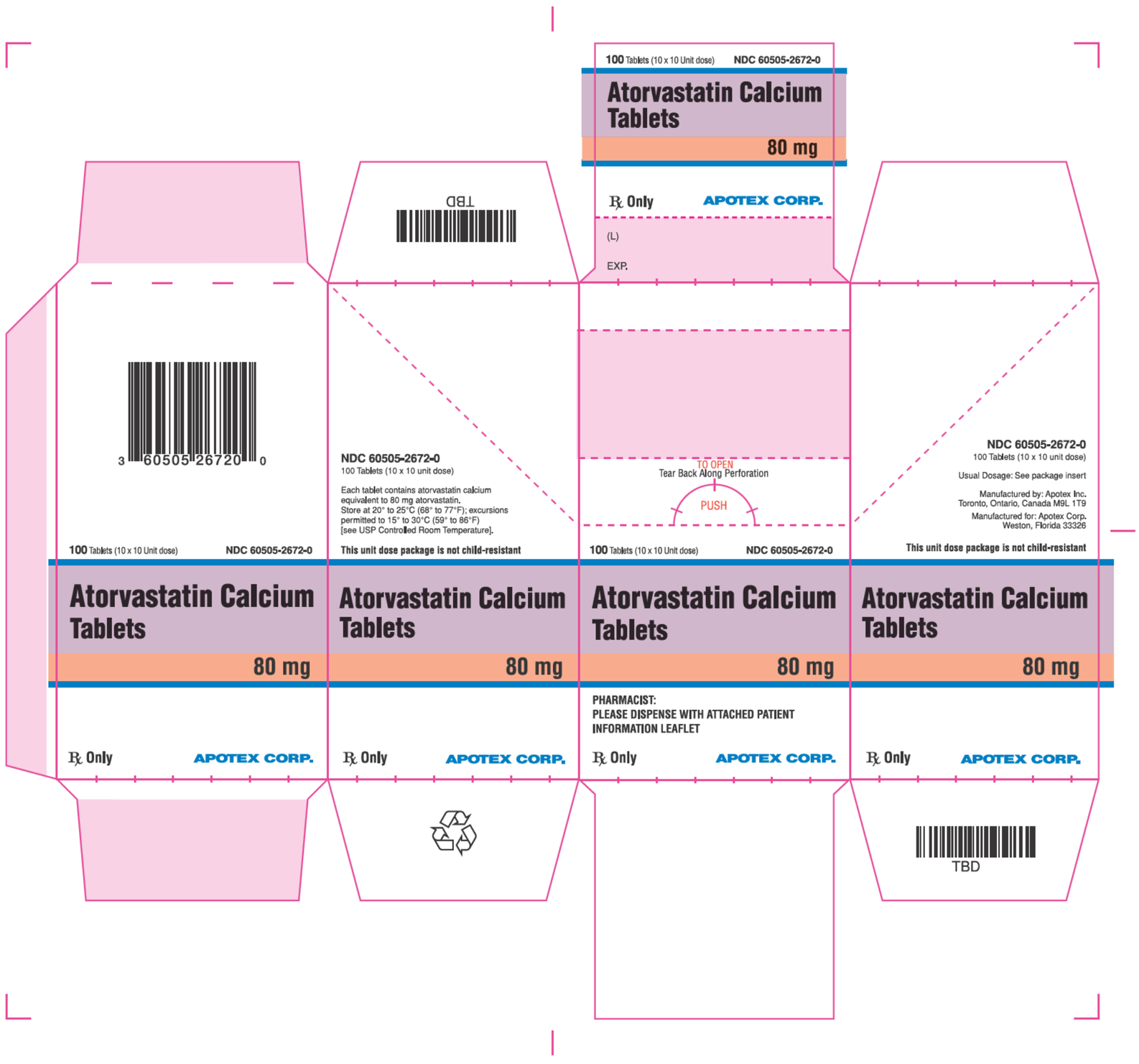


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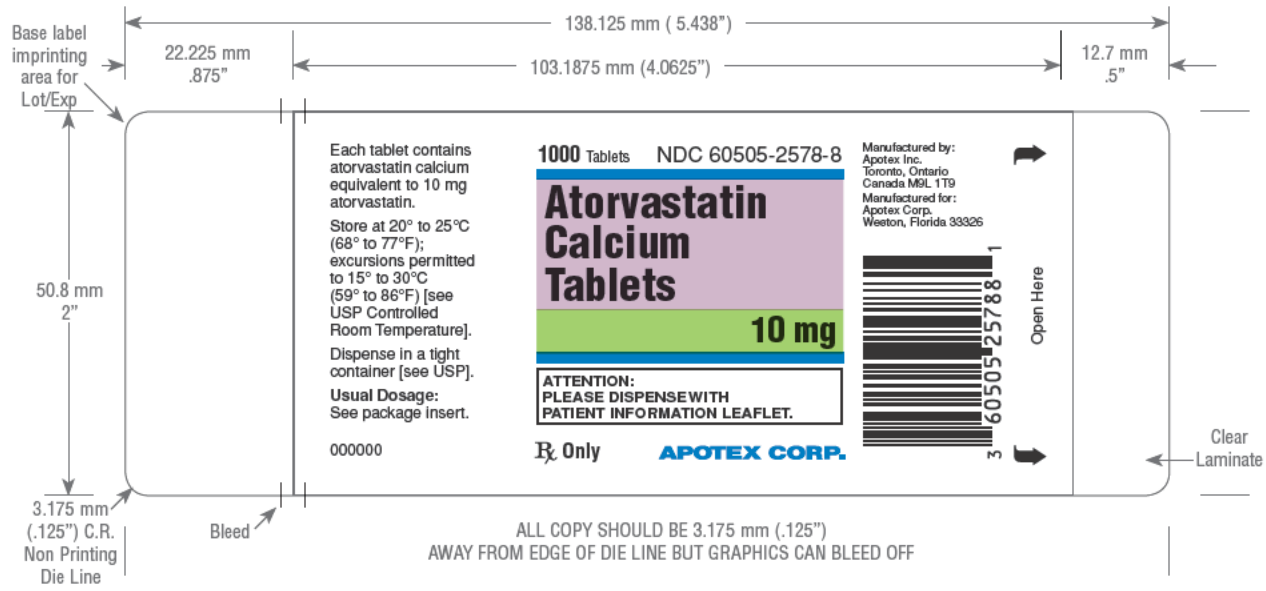
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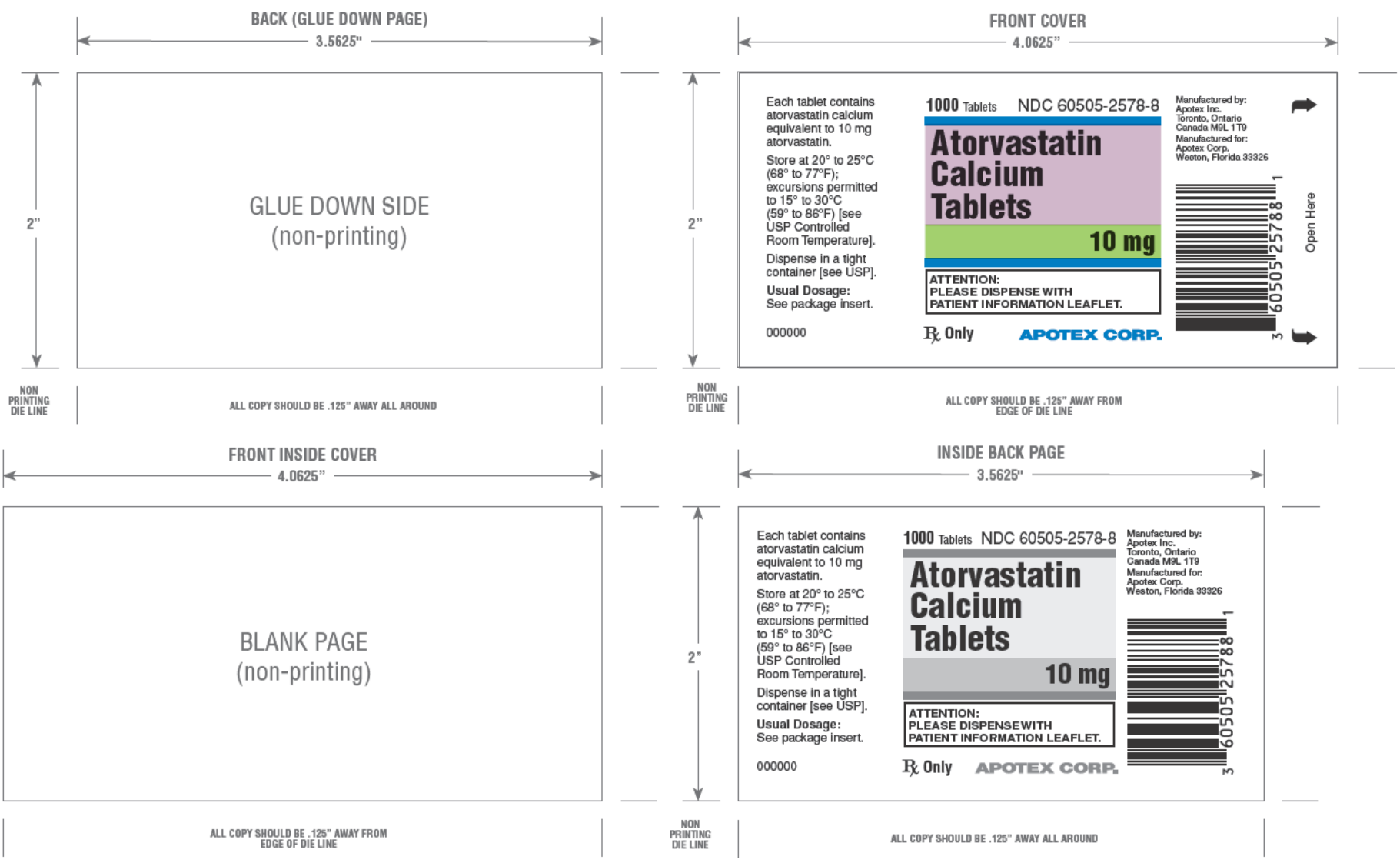
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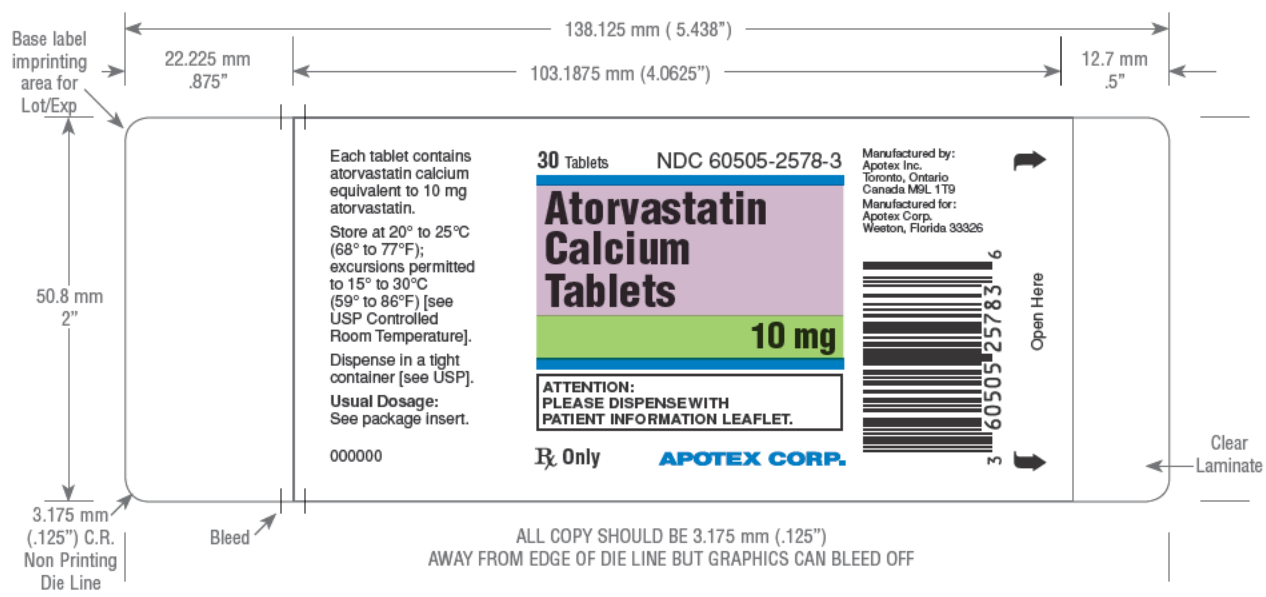
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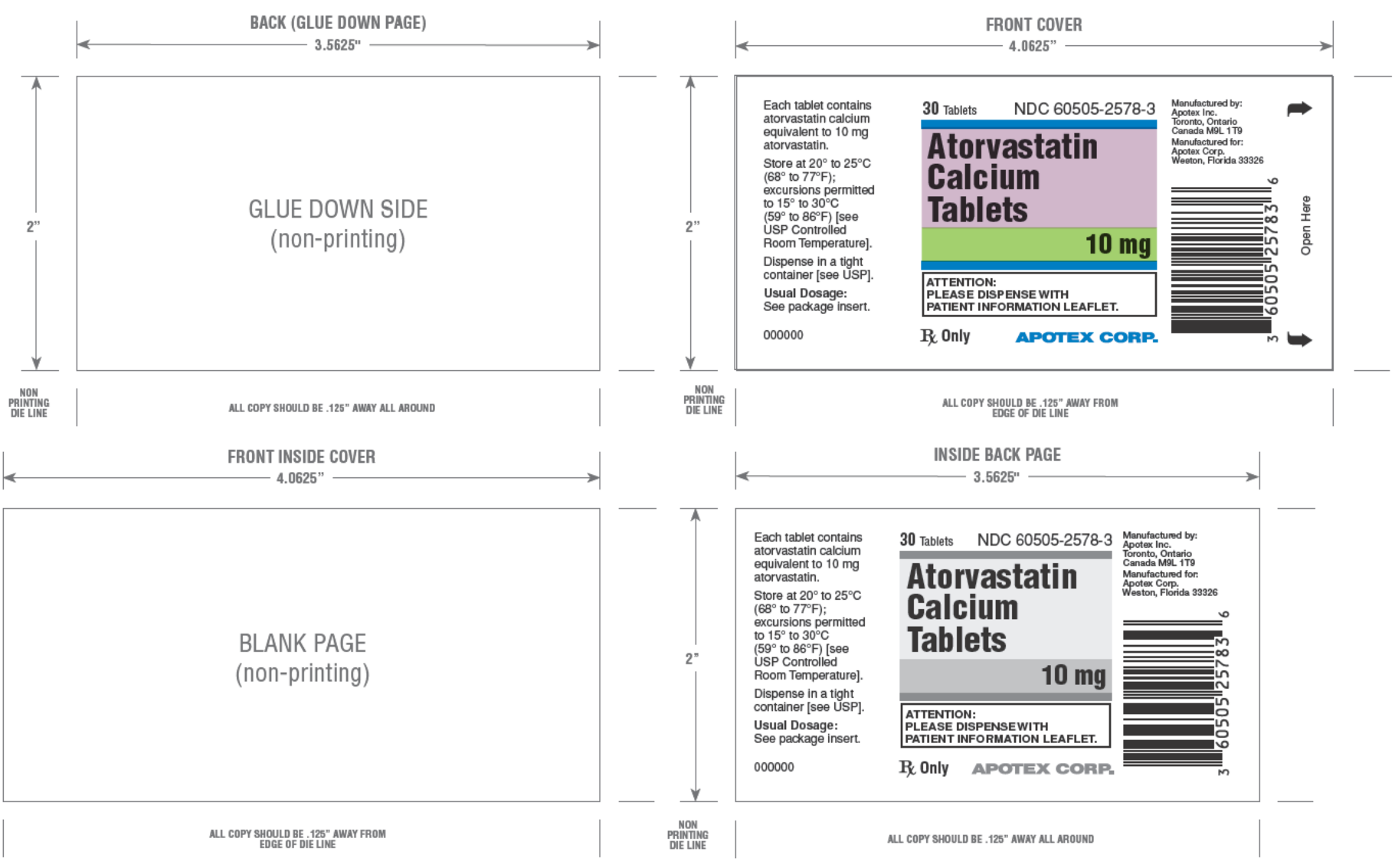
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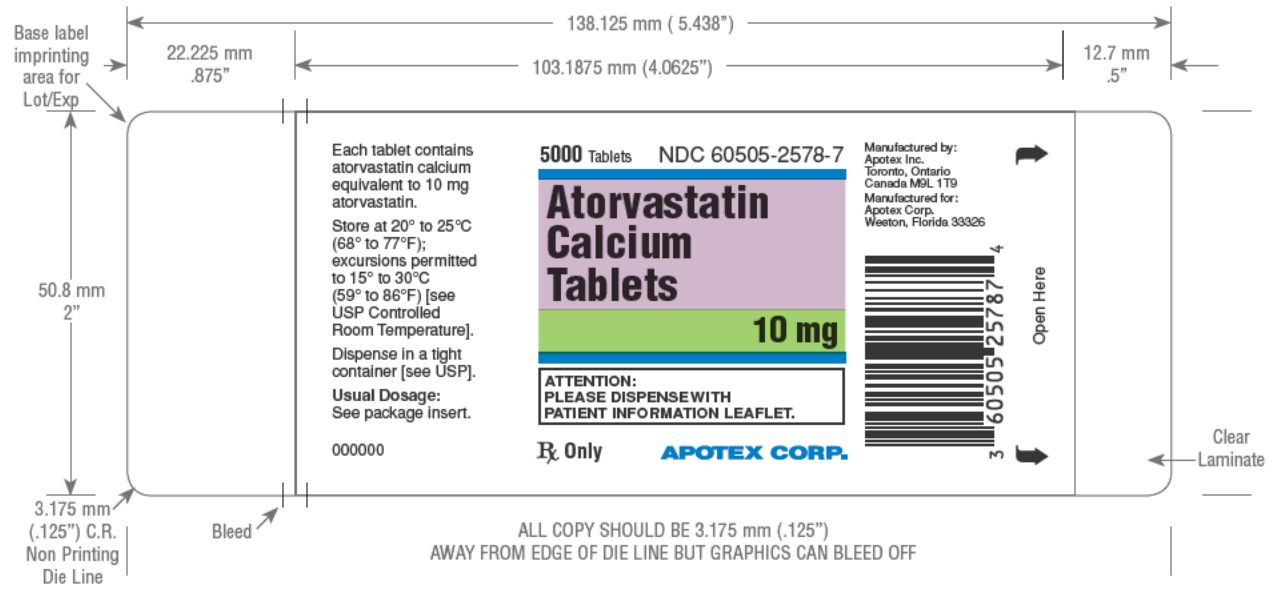
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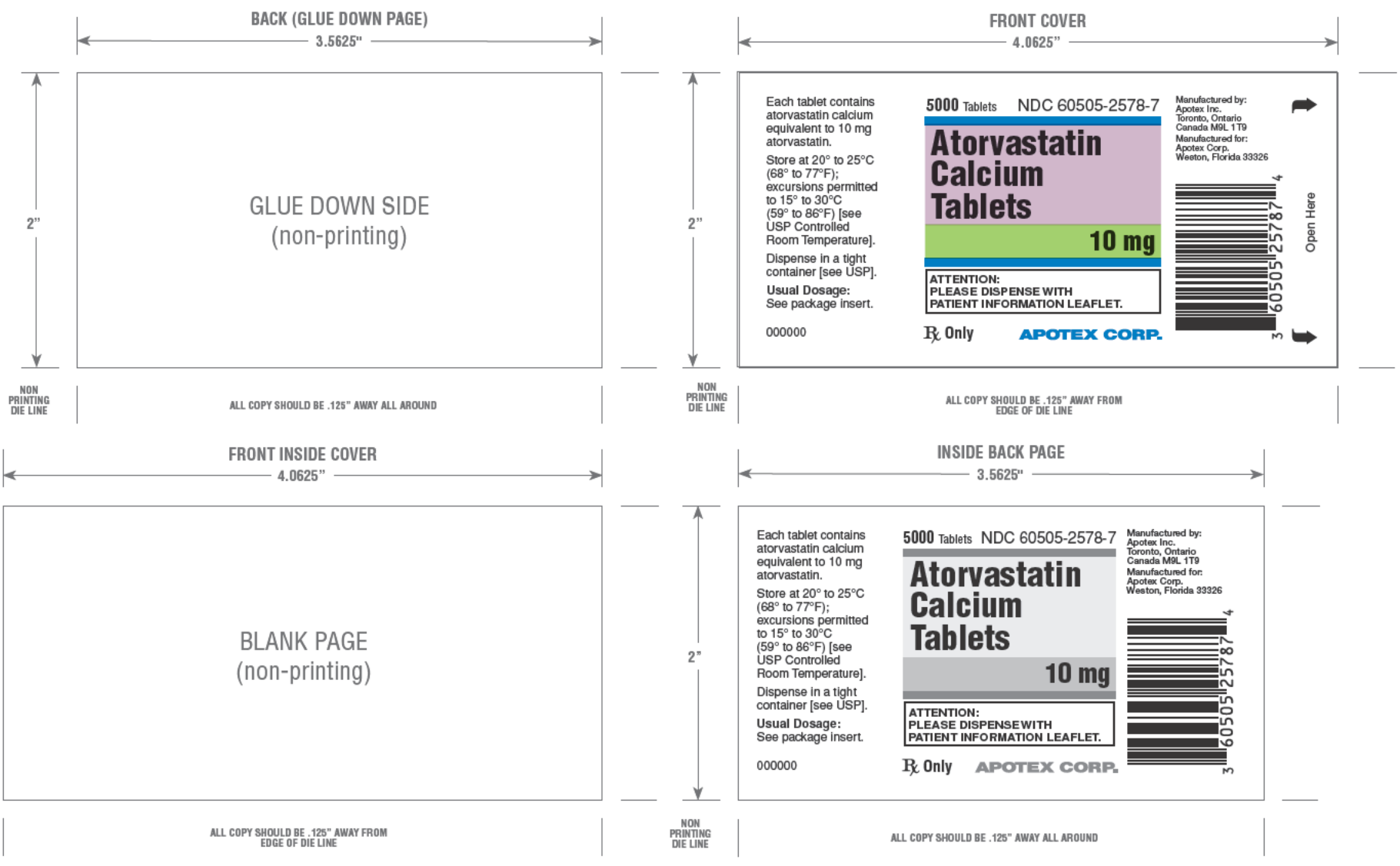
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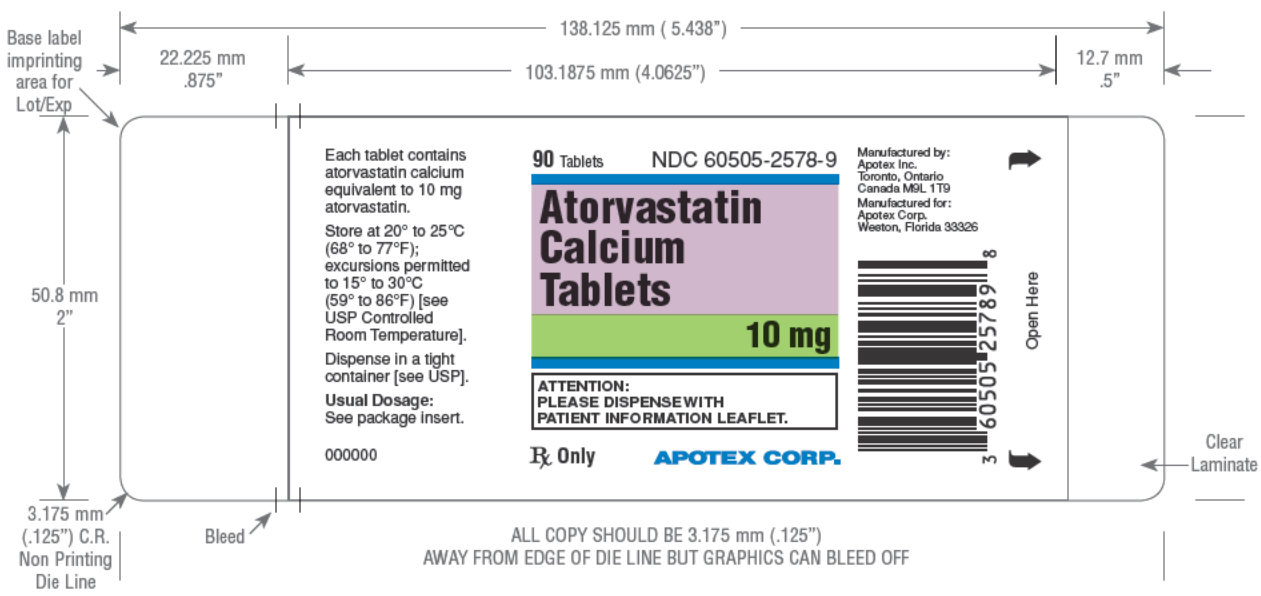
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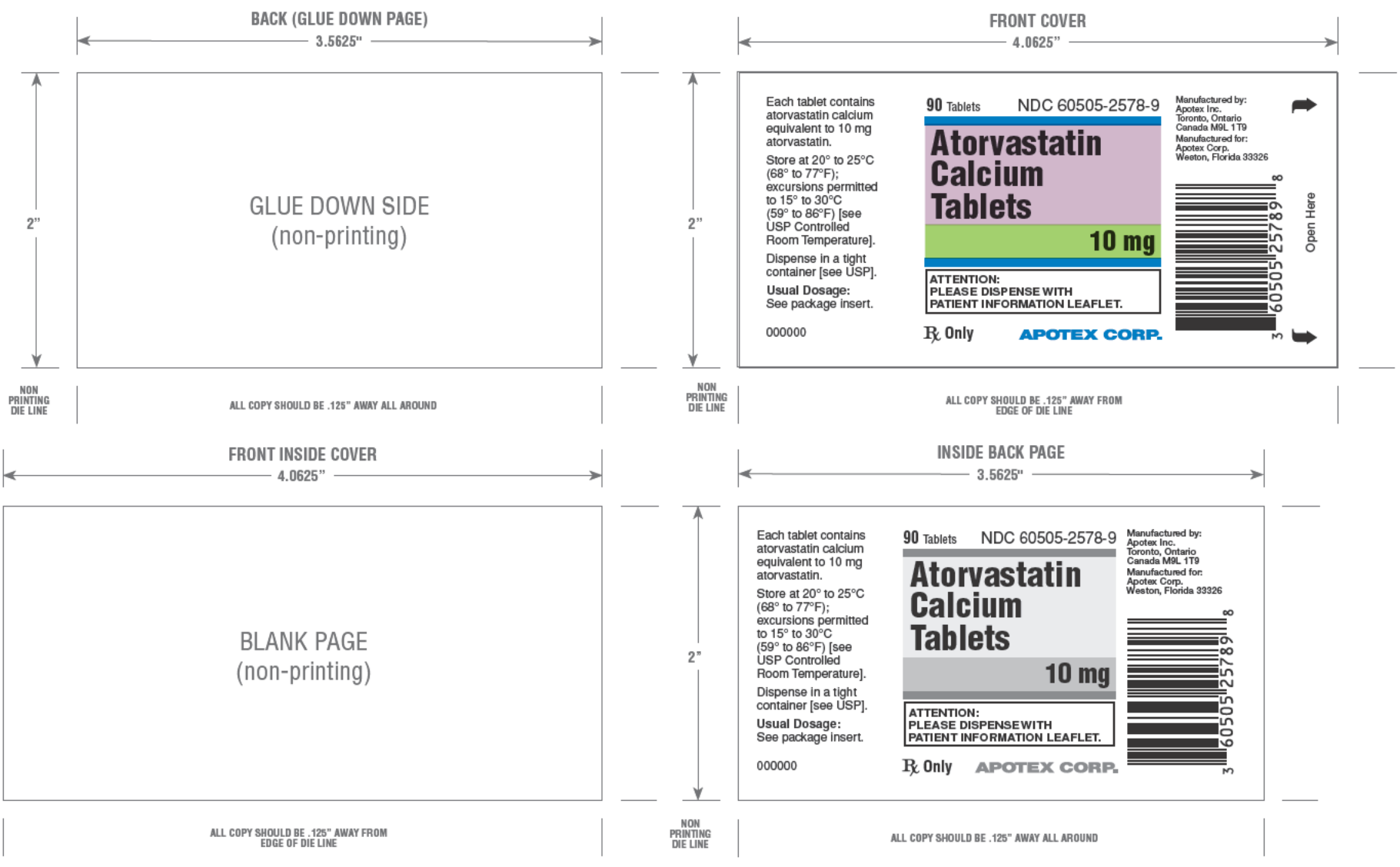
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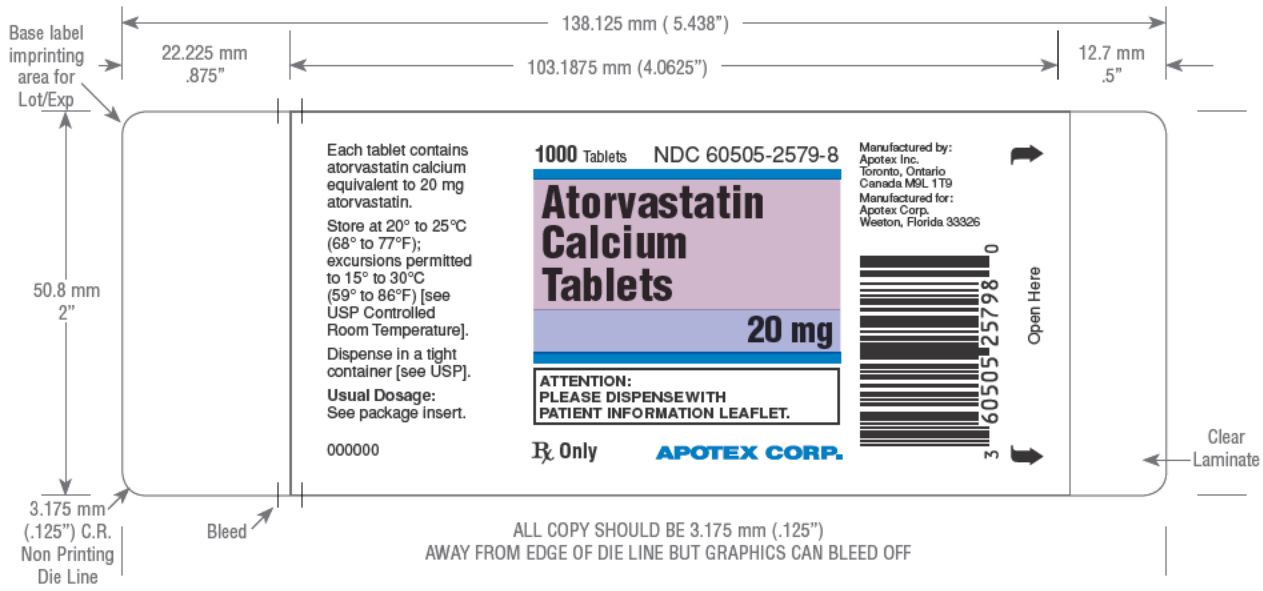


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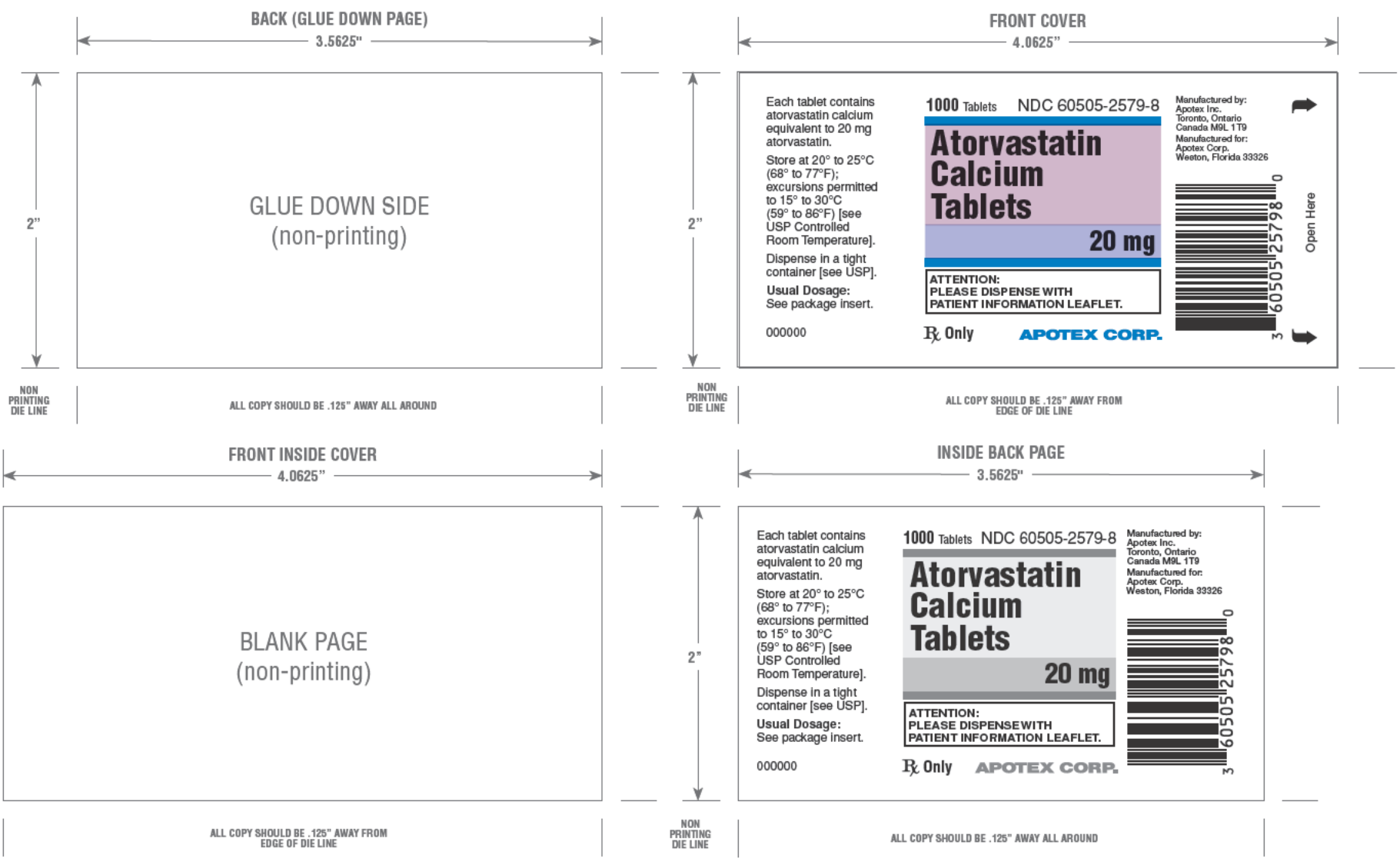
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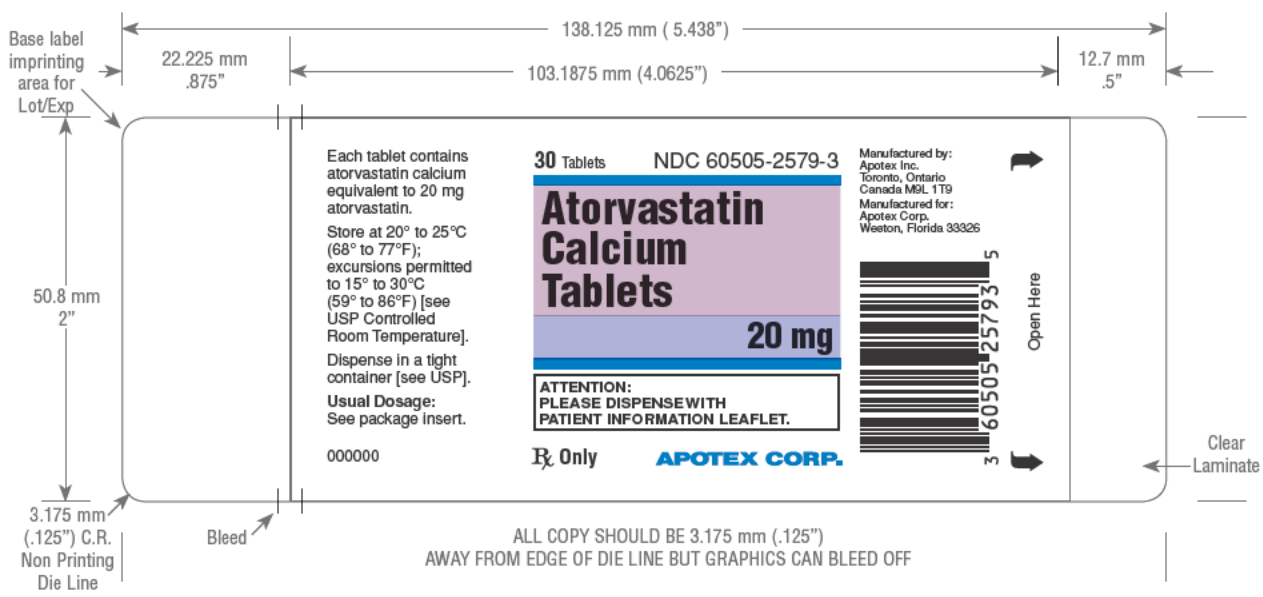
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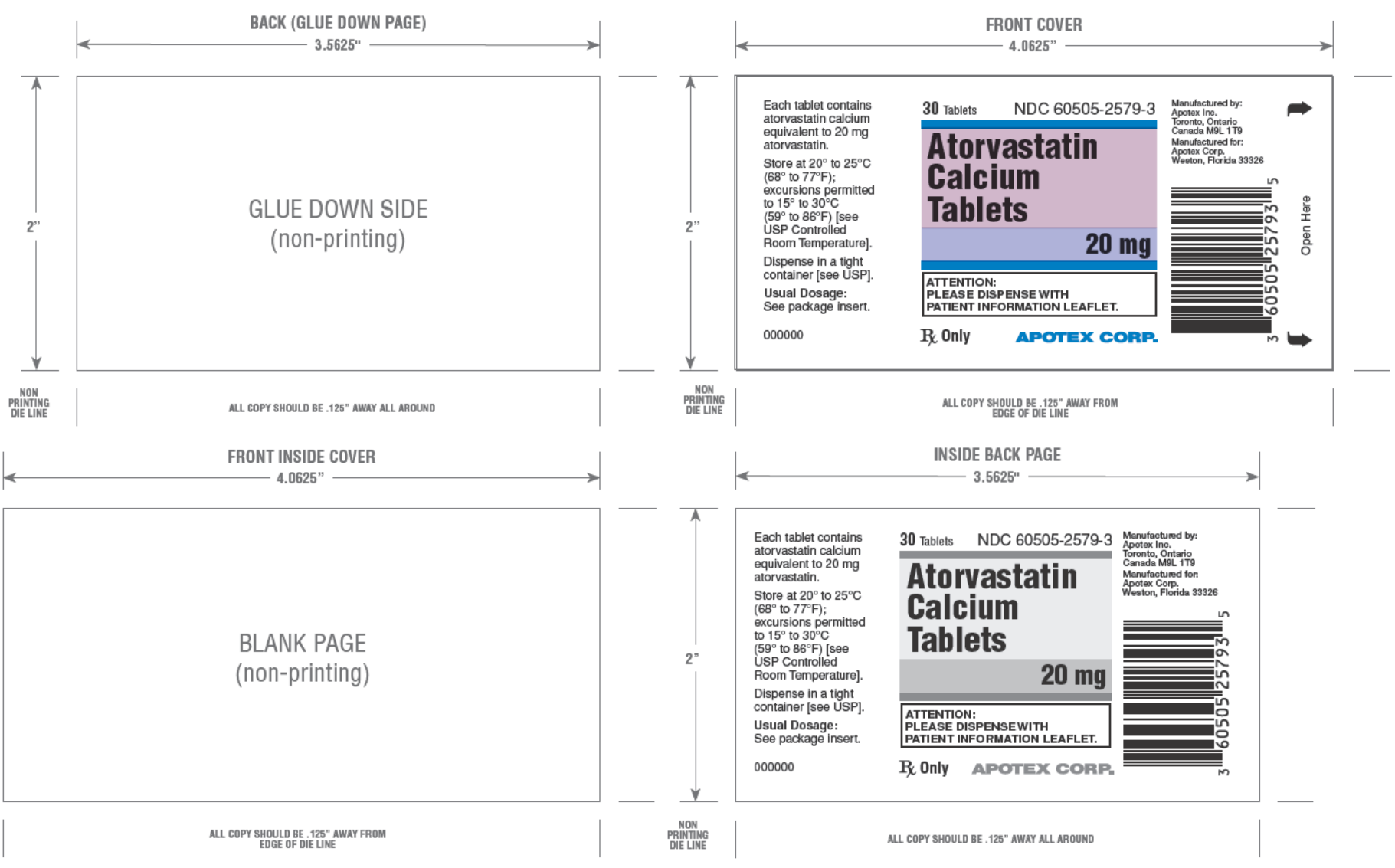
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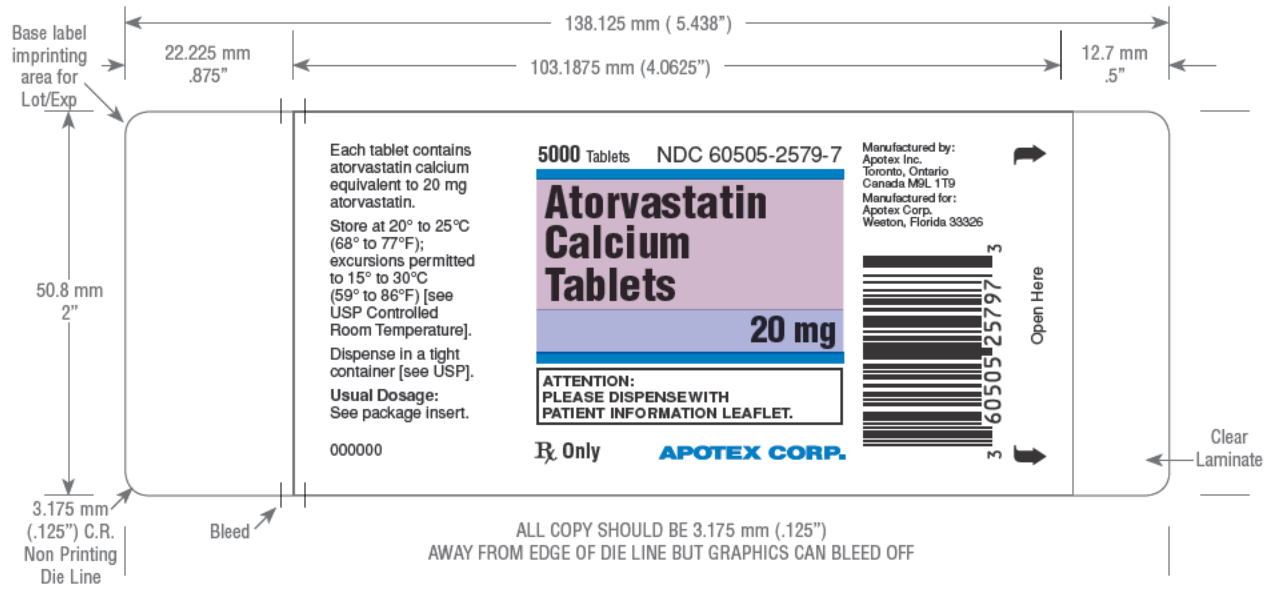
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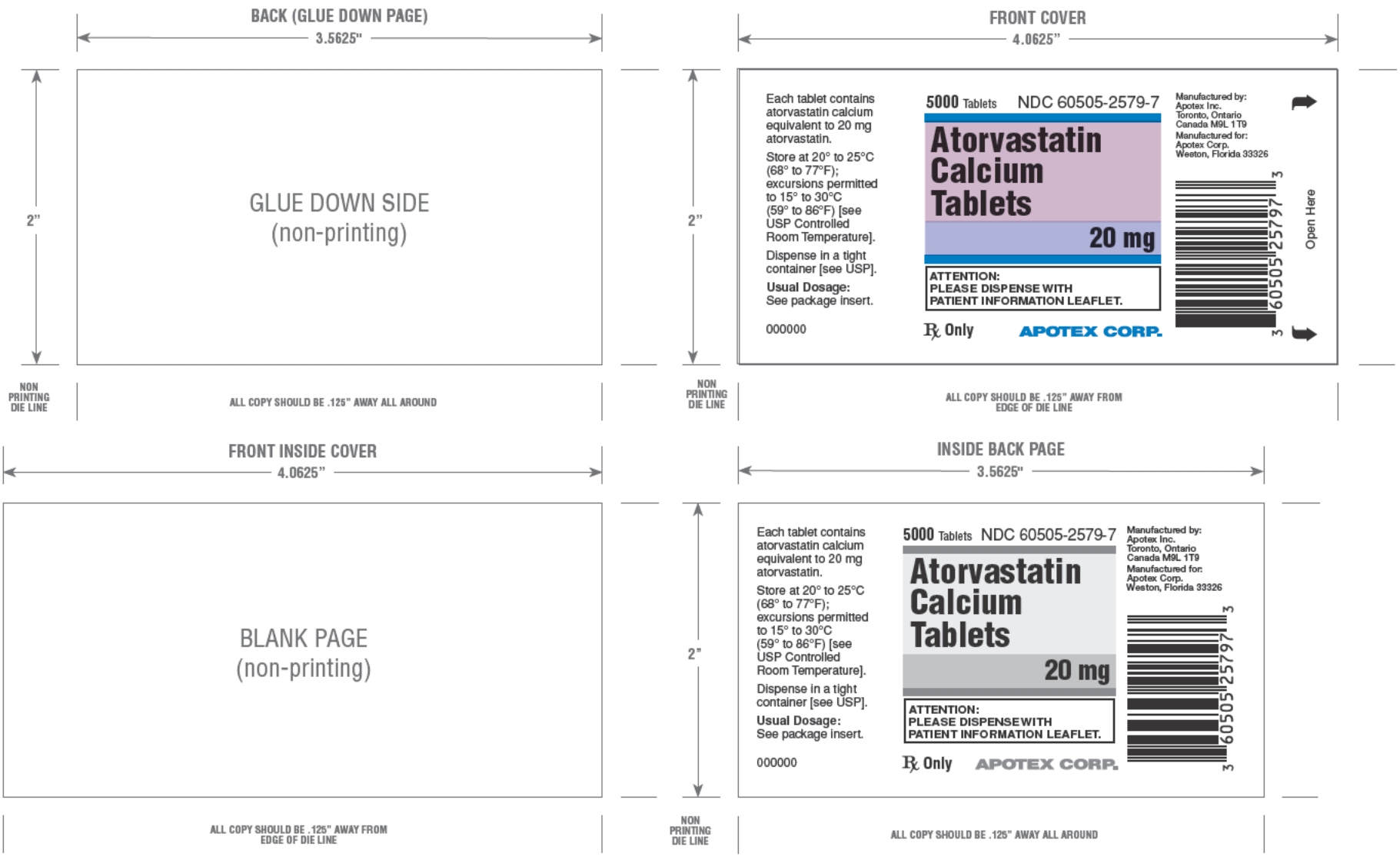
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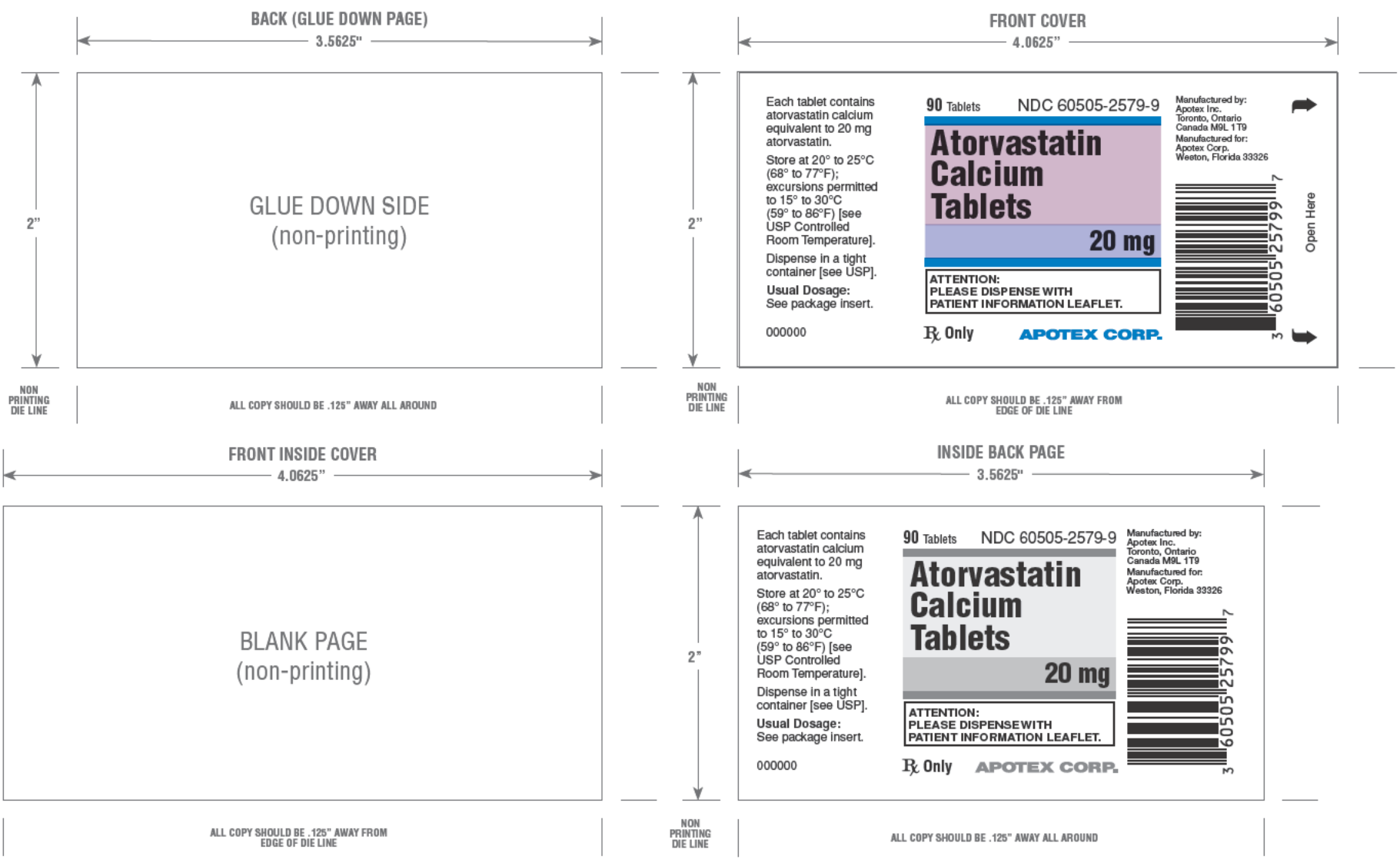
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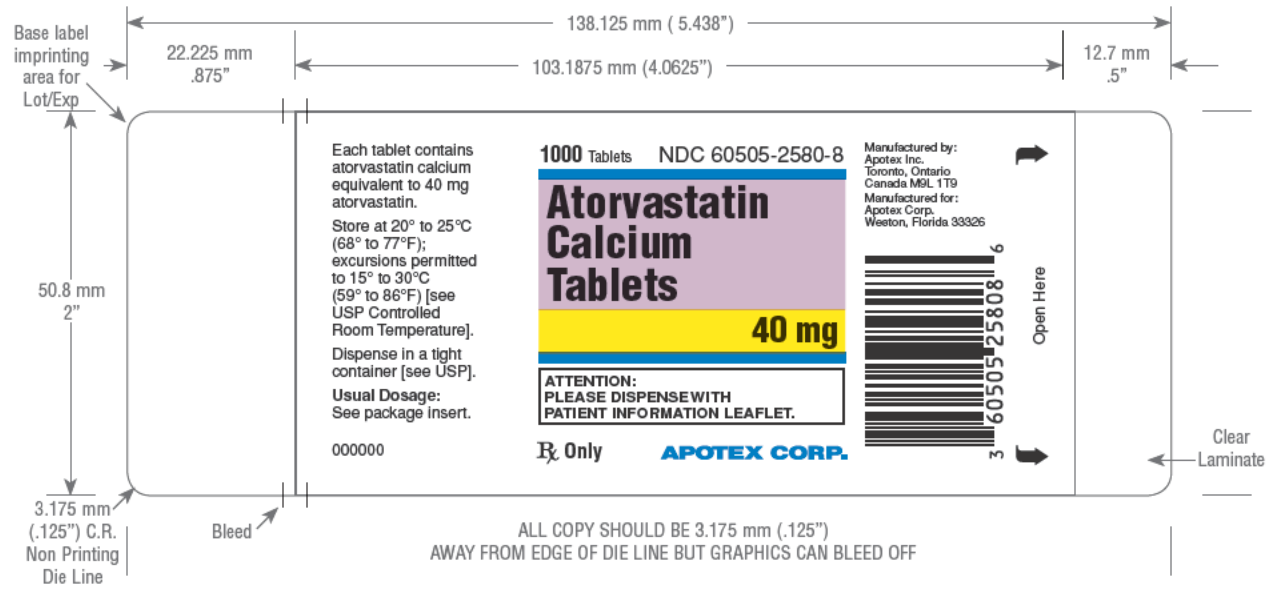
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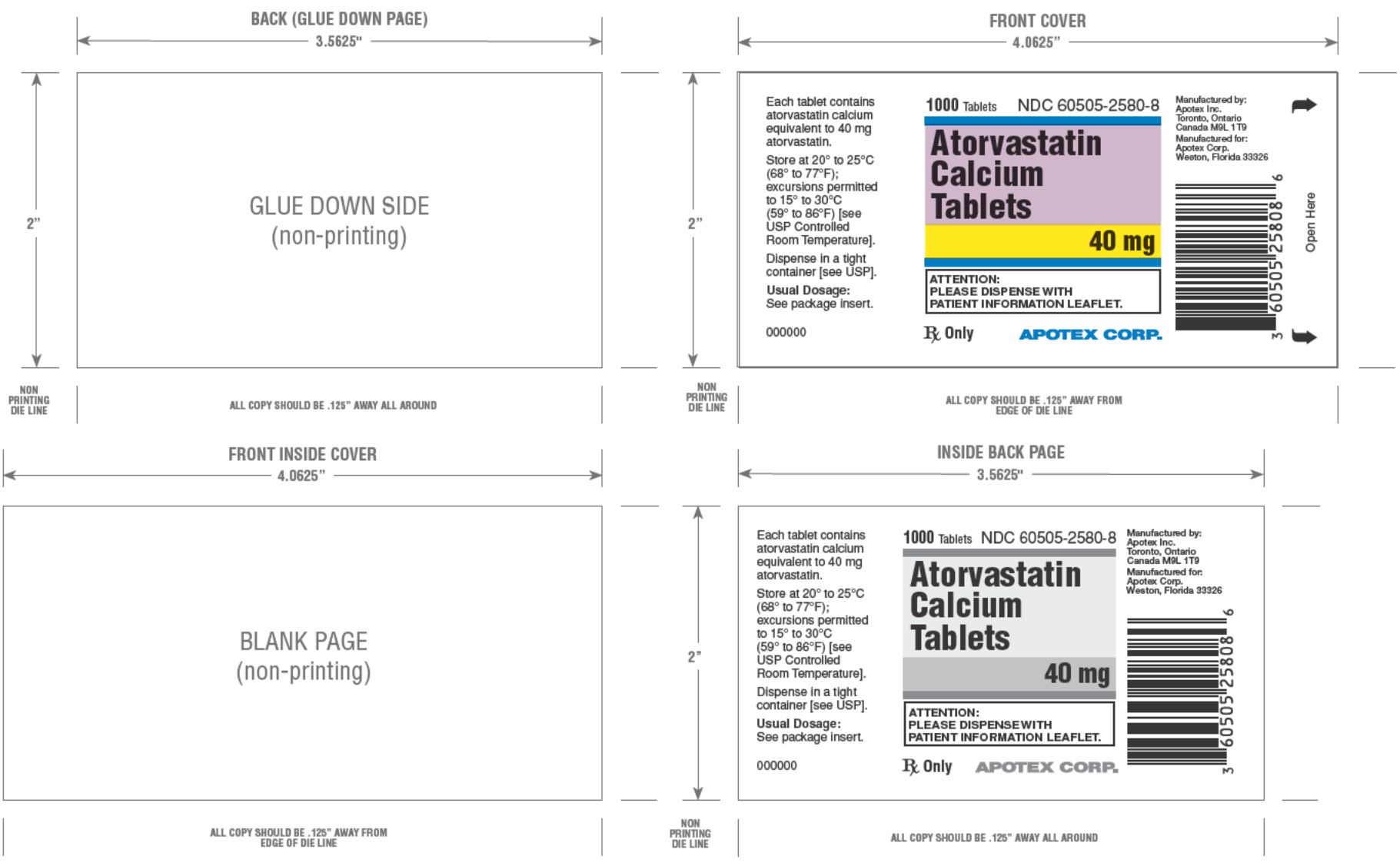
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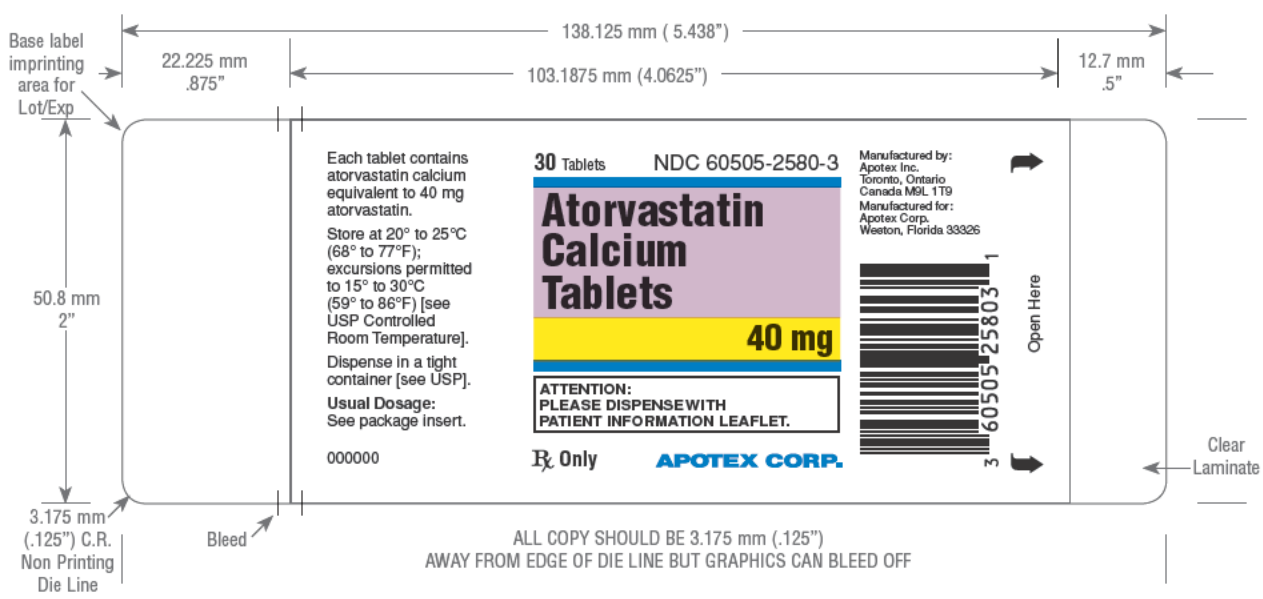
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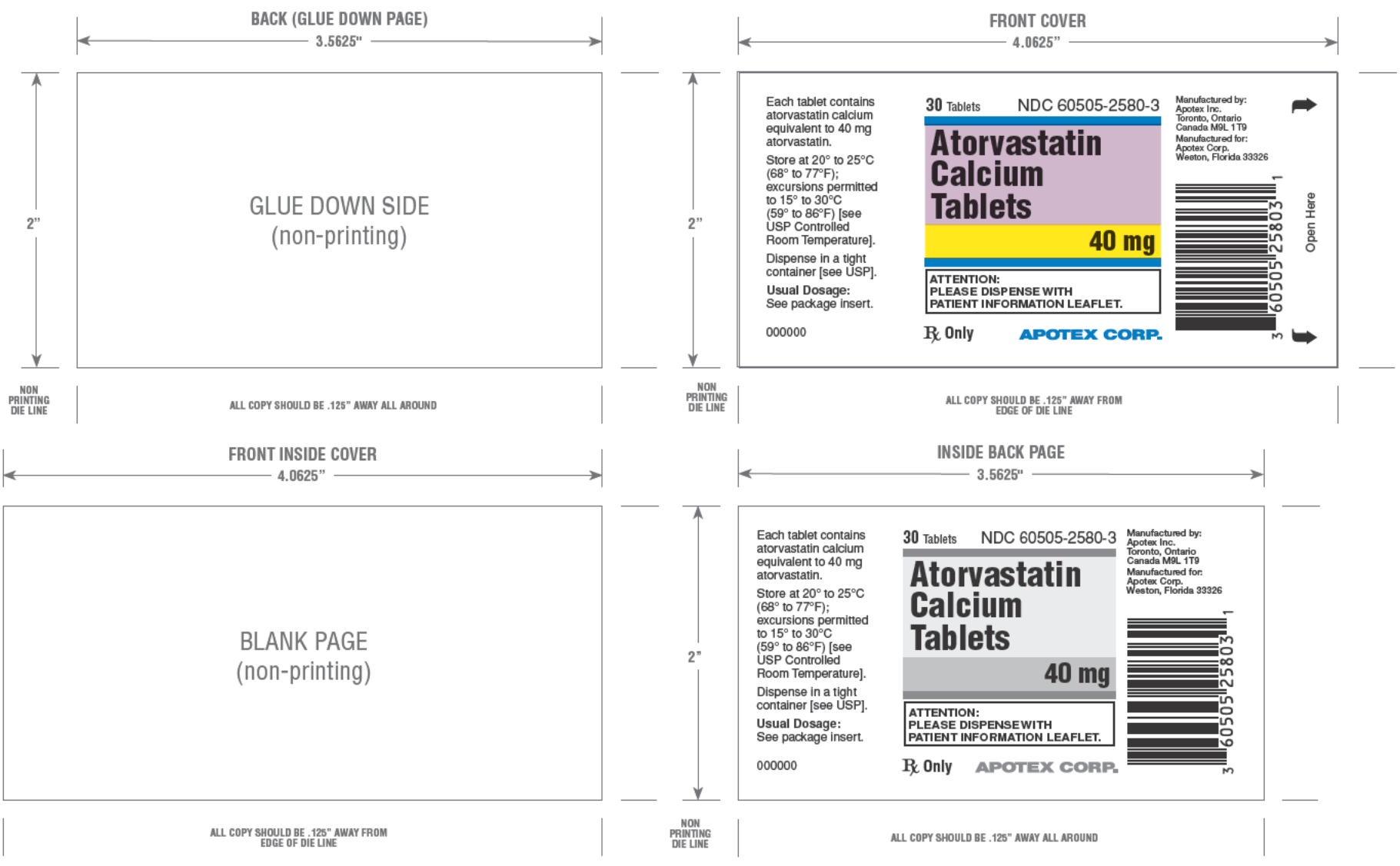
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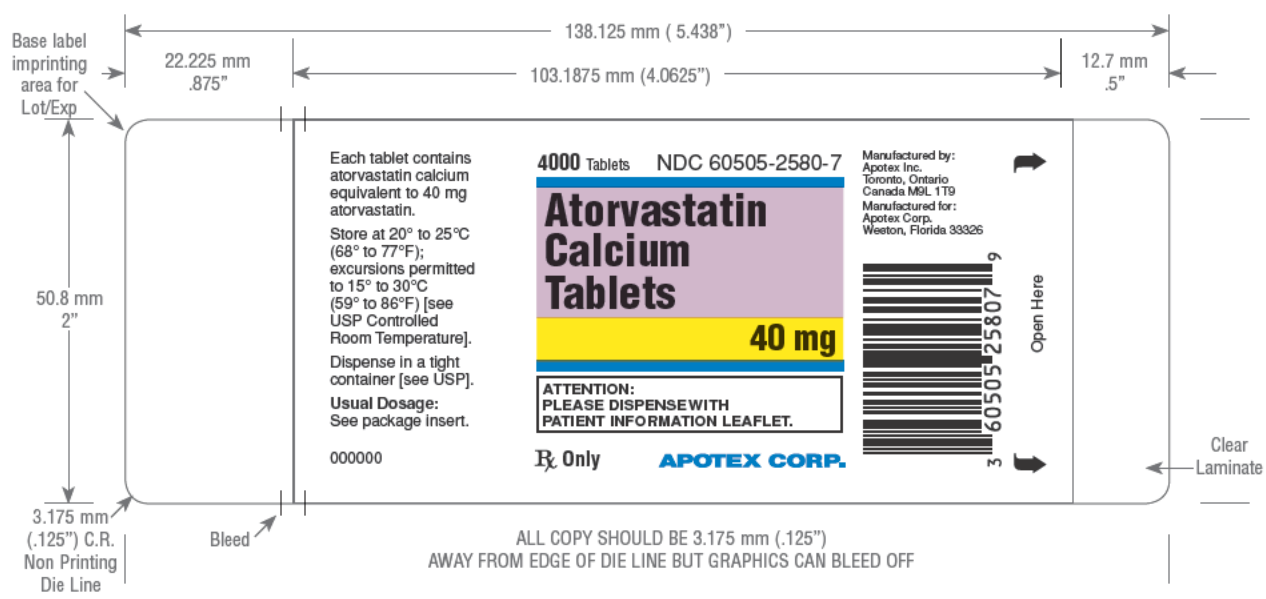
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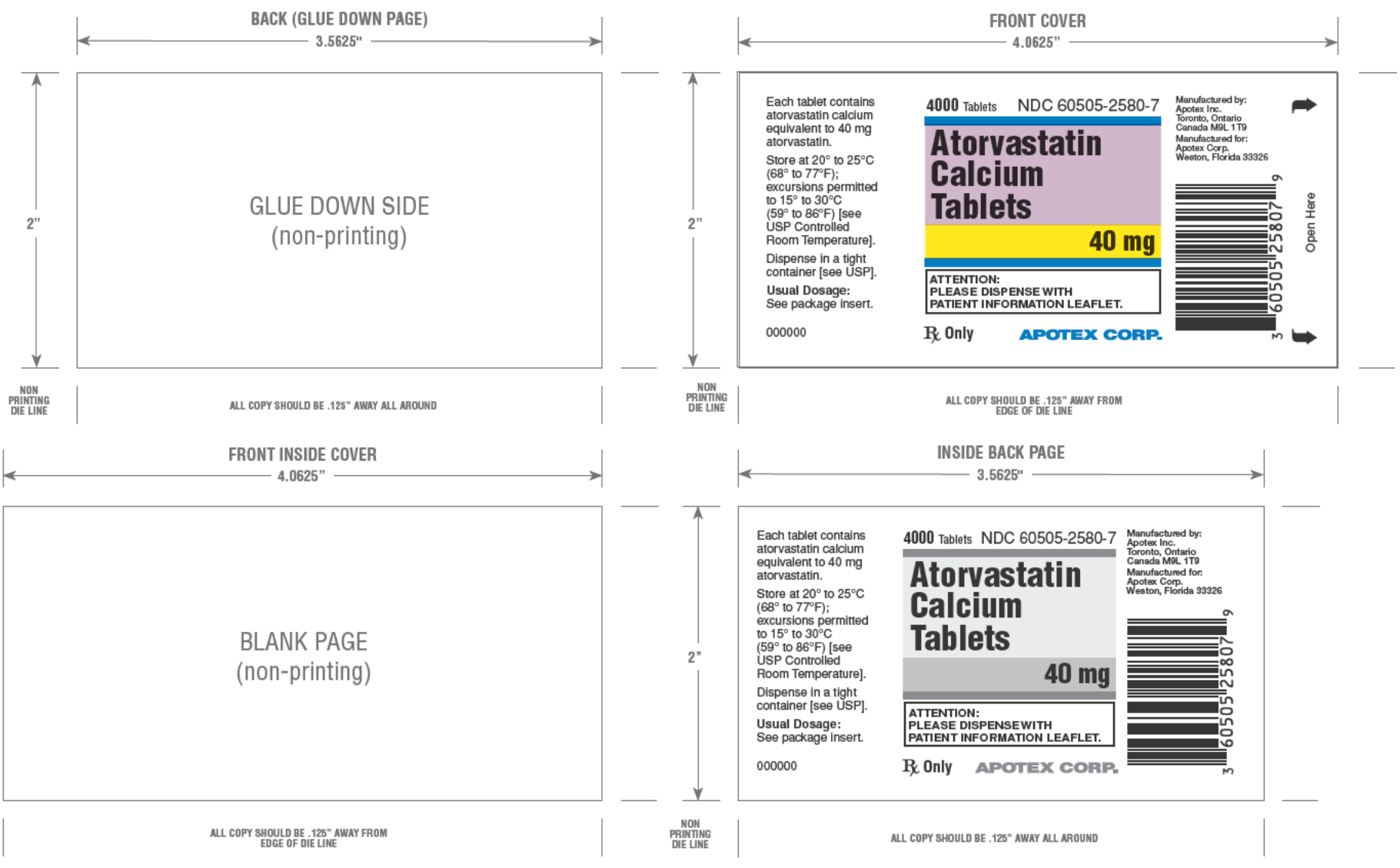
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COMPOSITE



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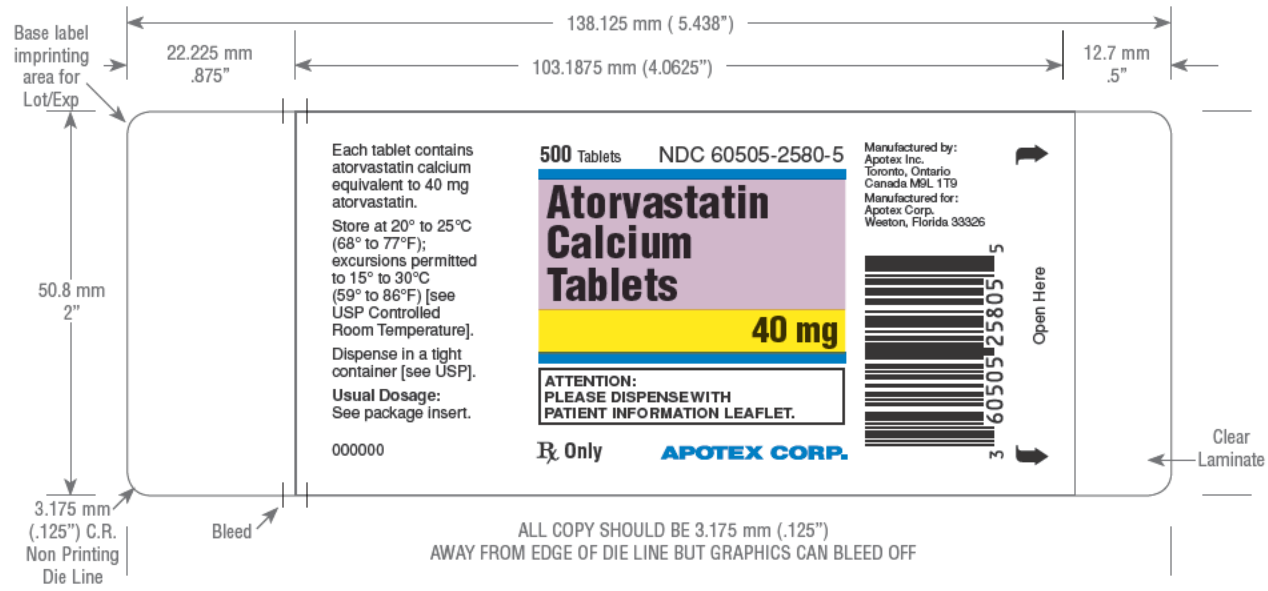
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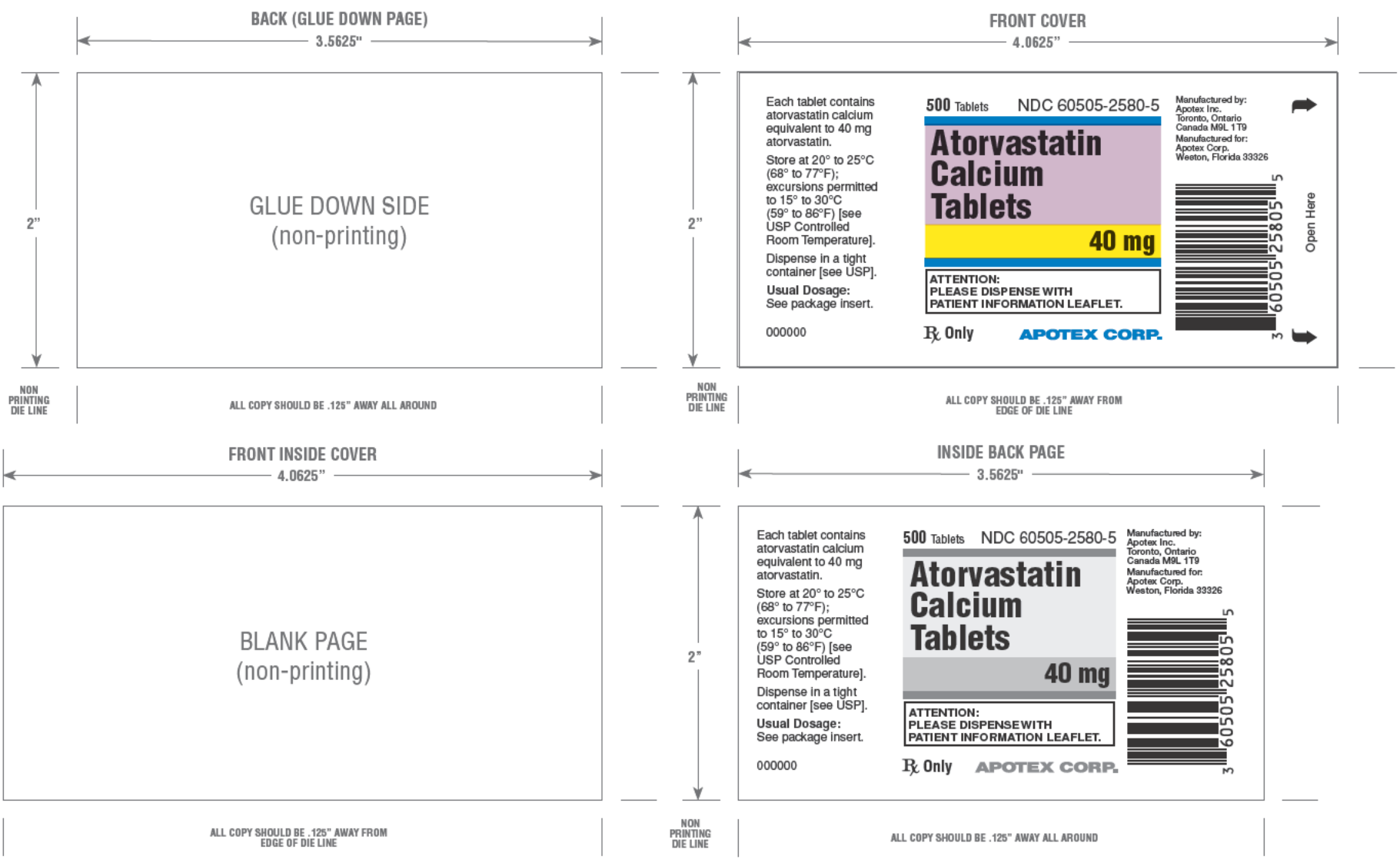
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COMPOSITE



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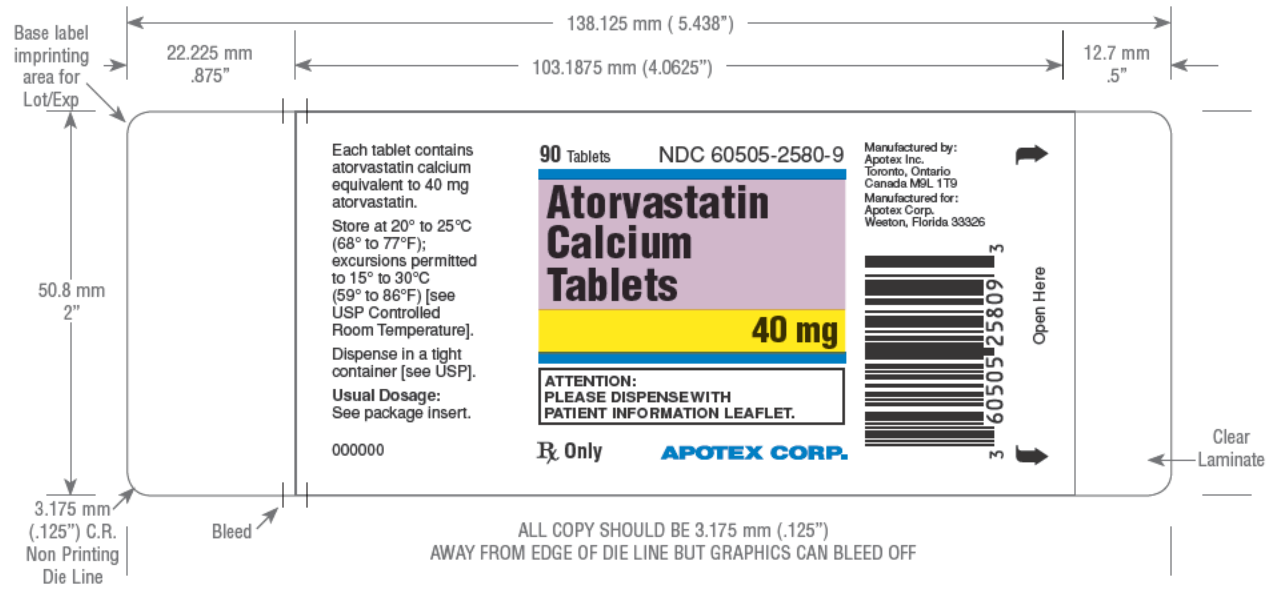


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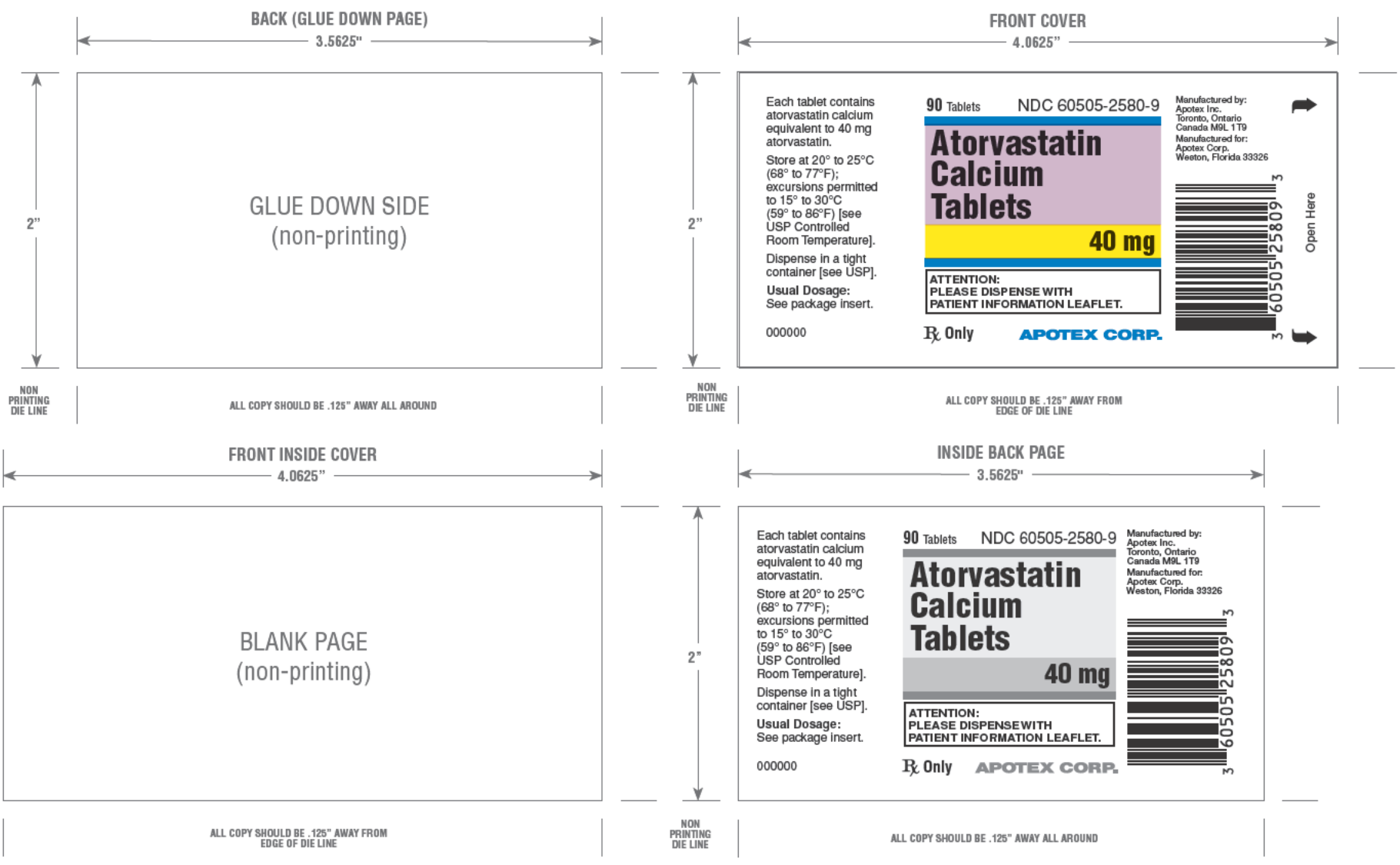
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COMPOSITE



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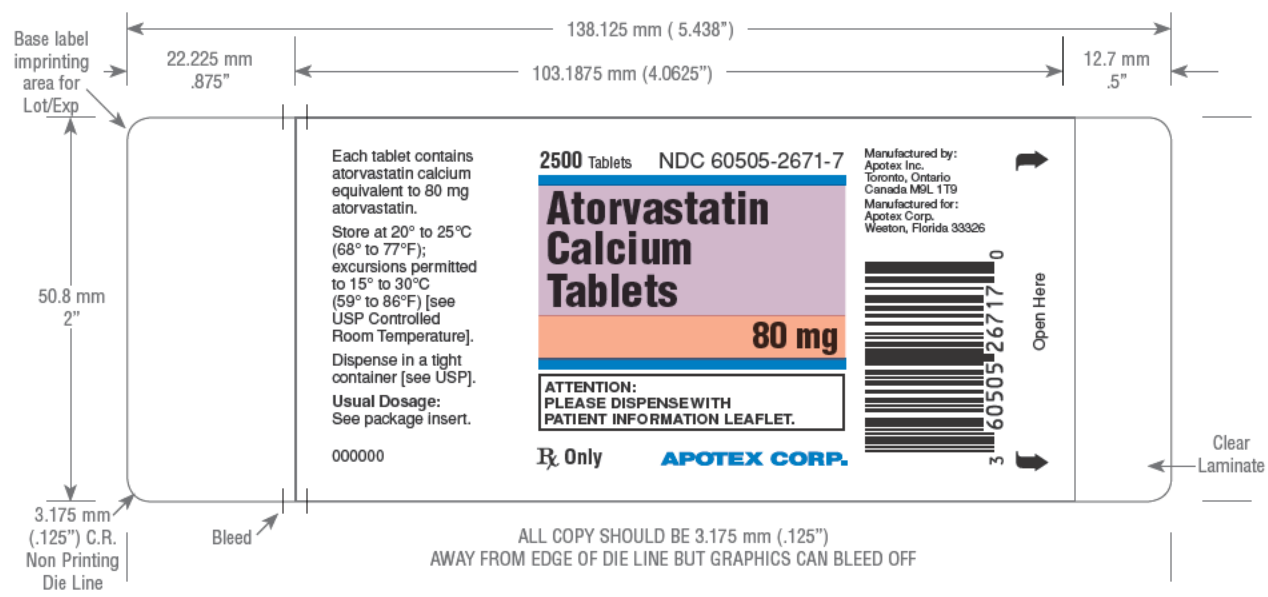


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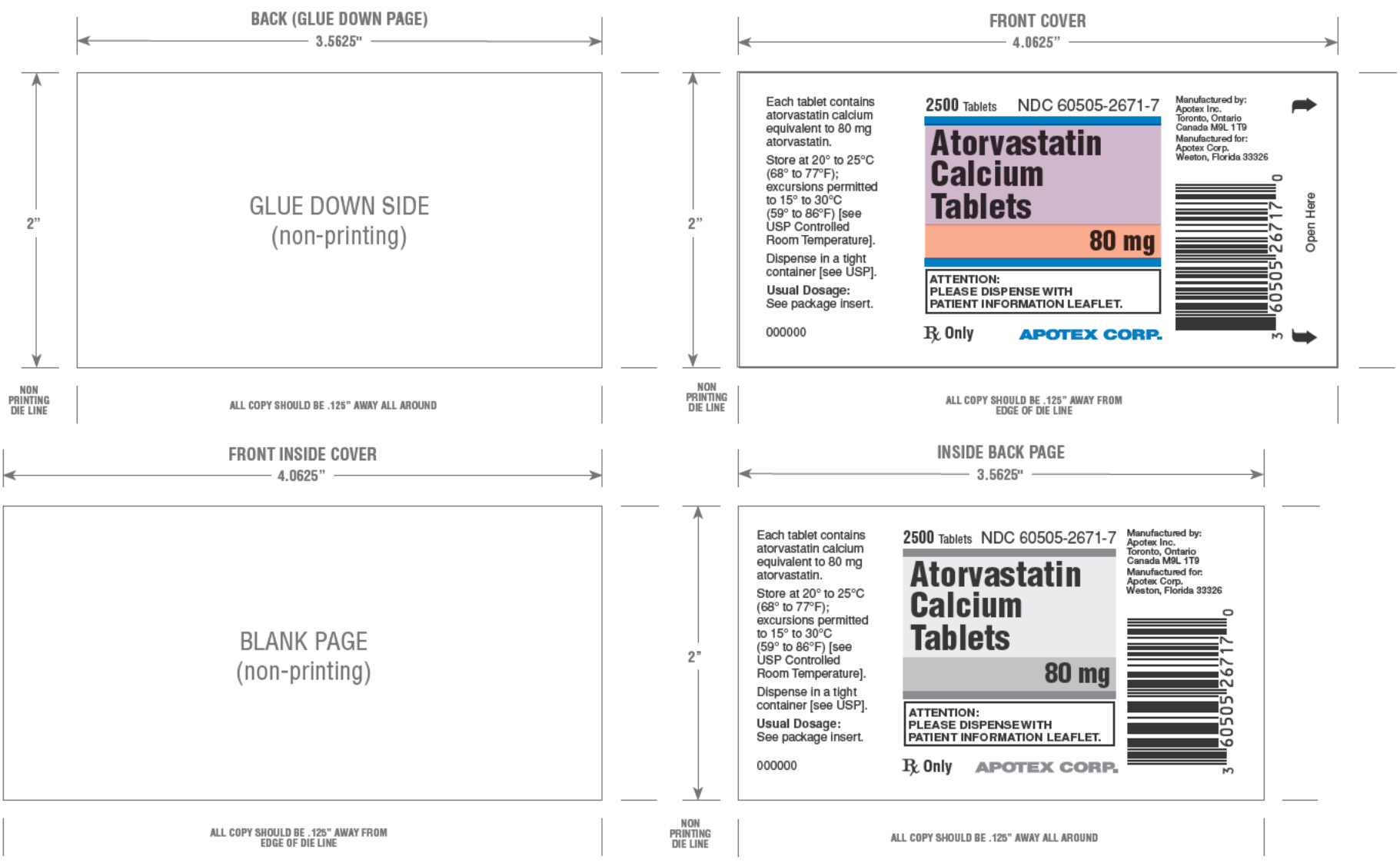
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COMPOSITE



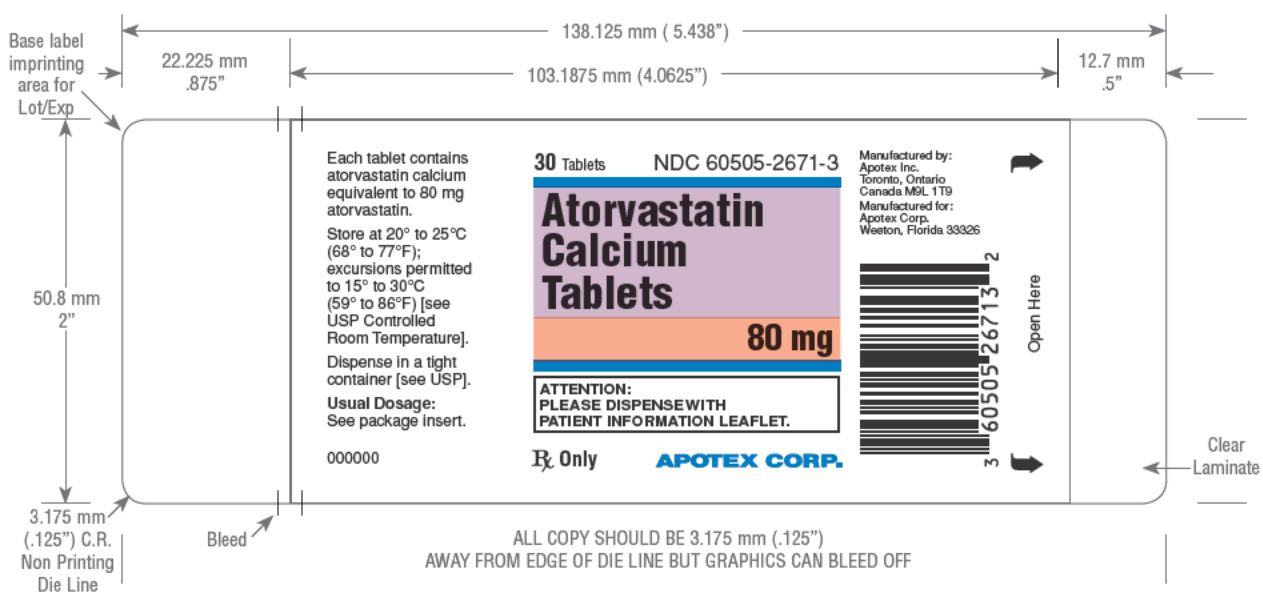
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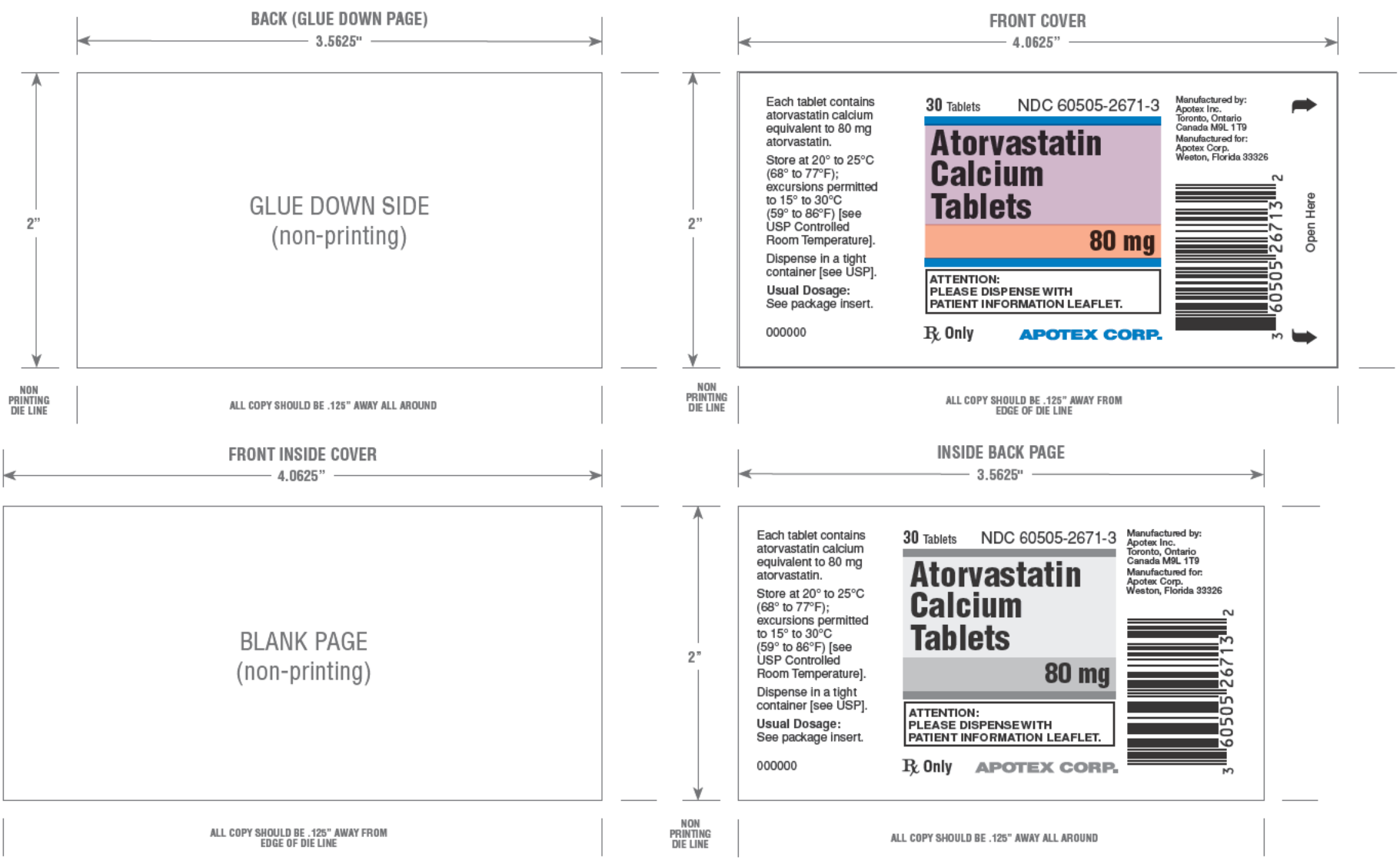
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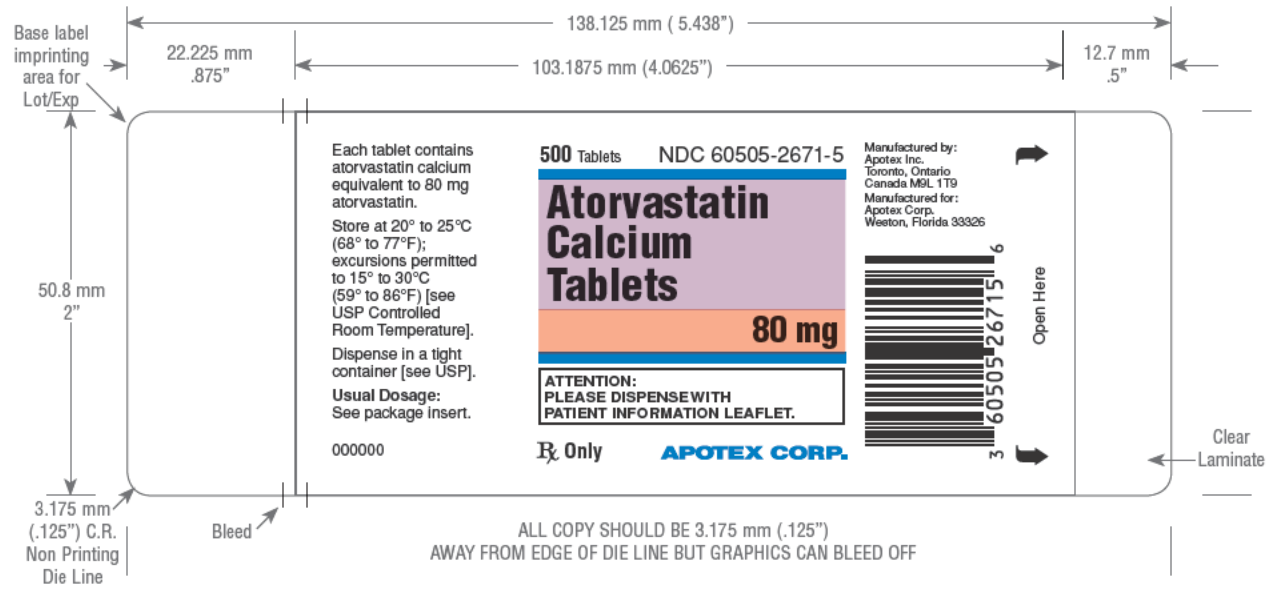
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ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

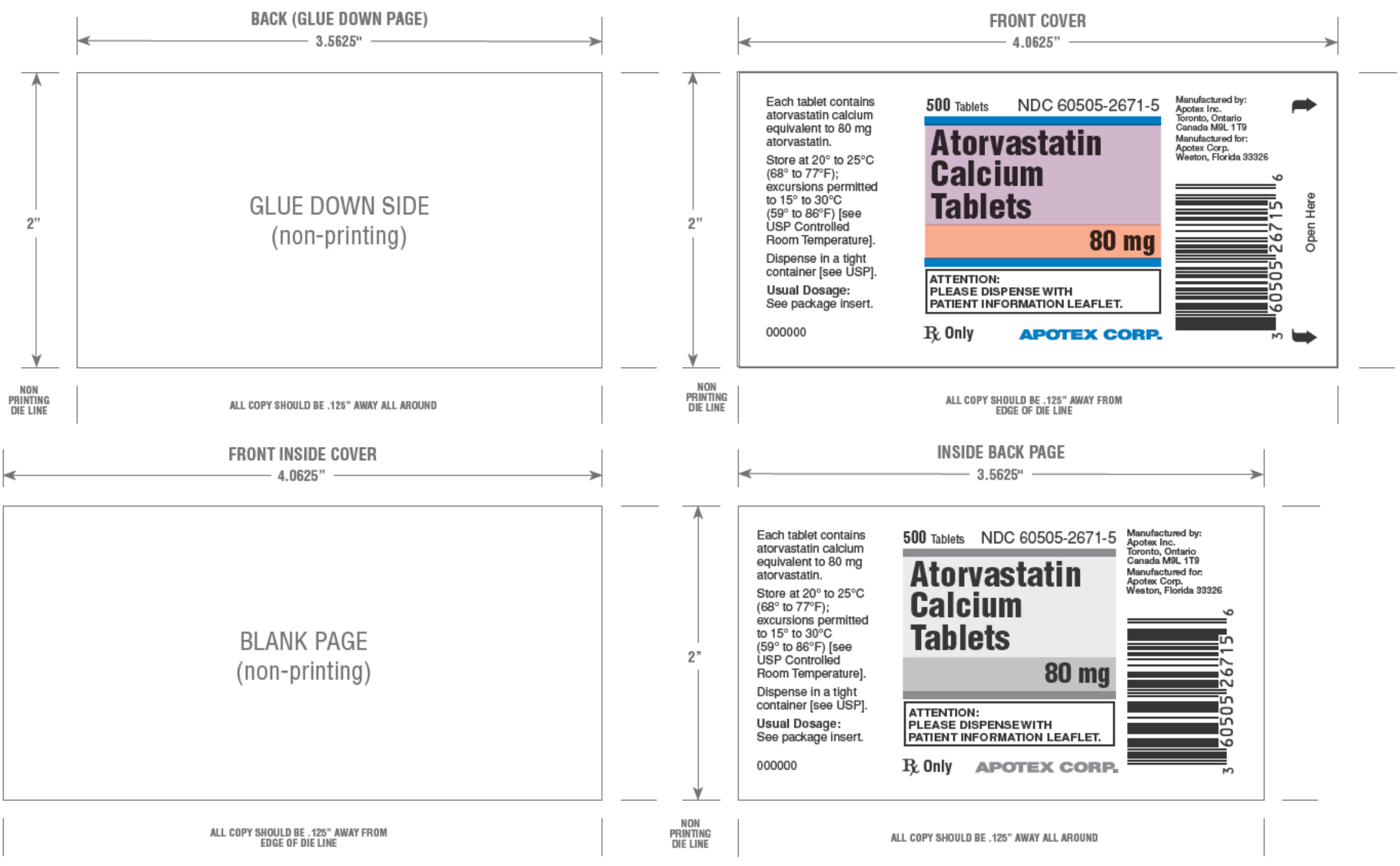
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COMPOSITE



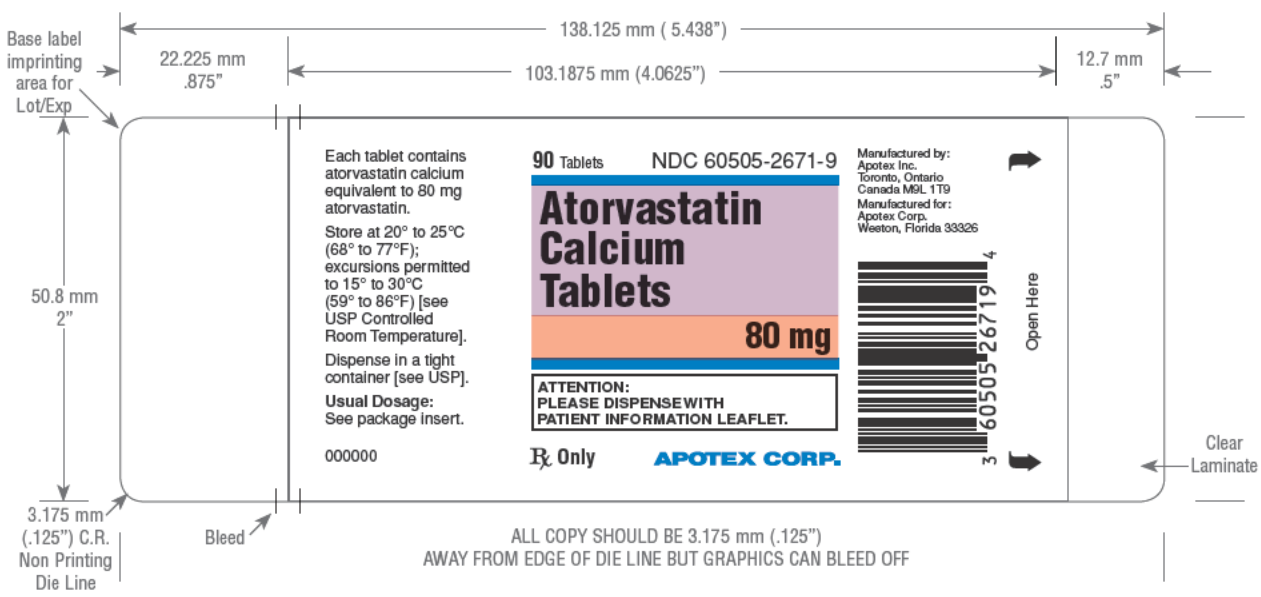
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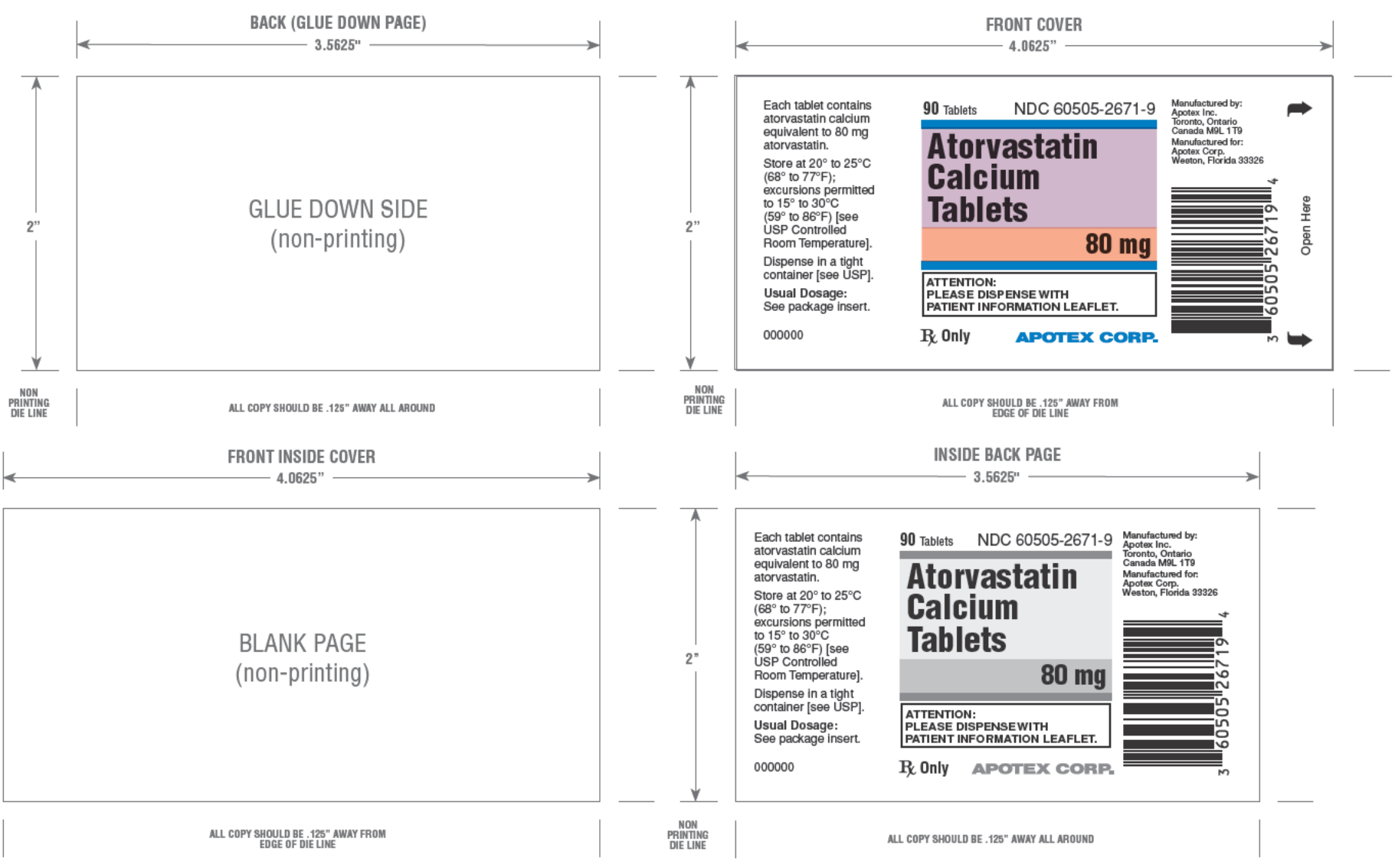
Reference ID: 3118468

(b) (4)

COMPOSITE



COVER



Reference ID: 3118468

APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

(D) (4)

FRONT PPI PAD

STD PPI PAD
04/25/09

66 mm
2.598"

NON-PRINTING DIELINE

142 mm
5.5905"

145 mm
5.7085"

287 mm
11.299"

FRONT PANEL #1

PATIENT INFORMATION

Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about atorvastatin calcium tablets, ask your doctor or pharmacist.

What are Atorvastatin Calcium tablets?

Atorvastatin calcium tablets is a prescription medicine that lowers cholesterol in your blood. It lowers the "bad" cholesterol (LDL-C) and triglycerides in your blood. It can raise your "good" cholesterol (HDL-C) as well. Atorvastatin calcium tablets are for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin calcium tablets can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

Atorvastatin calcium tablets start to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take atorvastatin calcium tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium tablets may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast feeding. Atorvastatin calcium tablets can pass into your breast milk and may harm your baby.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.
- have liver problems.



Atorvastatin calcium tablets have not been studied in children under 10 years of age.

Before You Start Atorvastatin Calcium Tablets

Tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with atorvastatin calcium tablets. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take Atorvastatin Calcium Tablets?

- Take atorvastatin calcium tablets exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium tablets. Your dose of atorvastatin calcium tablets may be changed based on these blood test results.
- Take atorvastatin calcium tablets each day at any time of day at about the same time each day. Atorvastatin calcium tablets can be taken with or without food.

Don't break atorvastatin calcium tablets before taking.

- Your doctor should start you on a low-fat diet before giving you atorvastatin calcium tablets. Stay on this low-fat diet when you take atorvastatin calcium tablets.
- If you miss a dose of atorvastatin calcium tablets, take it as soon as you remember. Do not take atorvastatin calcium tablets if it

INSIDE PPI PAD

FOLD 1

INSIDE PANEL #1

has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of atorvastatin calcium tablets at the same time.

- If you take too much atorvastatin calcium tablets or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets are stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium tablets and if you have symptoms of liver problems while you take atorvastatin calcium tablets. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.

- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, tendon problems, memory loss and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of atorvastatin calcium tablets. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

- Store atorvastatin calcium tablets at room temperature, 68 to 77°F (20 to 25°C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep atorvastatin calcium tablets and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information About Atorvastatin Calcium Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium tablets for a condition for which it was not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium acetate, croscarmellose sodium, sodium carbonate, microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

Manufactured By:
Apotex Inc.
Toronto, ON
Canada, M9L 1T9

Manufactured For:
Apotex Corp.
Weston, Florida
33326

Revised: March 2012

Rev. 3

INSIDE PANEL #2

FOLD 1

INSIDE PPI PAD

66 mm
2.598"

NON-PRINTING DIELINE

142 mm
5.5905"

145 mm
5.7085"

287 mm
11.299"

Reference ID: 3118468

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BETTY B TURNER
04/18/2012

JAMES T BARLOW
04/18/2012
Acting Team Leader for Ruby Wu

****LABELING APPROVAL SUMMARY#3****
(Supercedes LBL AP SUM #2 dated 8/30/10)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90548 Date of Submission: November 17, 2011

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

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BASIS OF APPROVAL:

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
80 mg= bottles of 30s, 90s, 500s, and 2500s):

Final print labels acceptable in 11/16/11 e-submission.

Carton (10 x 10): Final print labels acceptable in 11/16/11 e-submission.

Blister (Blister card of 10s): Final print labels acceptable in 5/20/09 e-submission.

Professional Package Insert Labeling: Final printed labeling acceptable in 2/26/2010 e-submission.

Patient Information Sheet: Final printed labeling acceptable in 2/26/2010 e-submission. Apotex submitted a print pad for the patient information.

Revisions needed before full approval: No, could revise the container and carton labels after full approval. However, if this application receives tentative approval because of patent issues, I will notify the firm of the comments below.

<u>CONTAINER and CARTON LABELS:</u>

Add an asterisk after the strength (e.g. 80 mg*) and before " * Each tablet contains atorvastatin..."

SPL

DLDE acceptable as of 8/18/2011 e-submission.

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-056; approved 6/17/09.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

As of November 17, 2011:

Apotex revised their side panel, container labels to state "atorvastatin calcium propylene gycol solvate equivalent to atorvastatin X mg" per chemistry recommendations on 8/18/2011.

Apotex reverted back to the original container labels, stating "atorvastatin calcium equivalent to atorvastatin X mg" per chemistry recommendation on 11/16/2011.

The DESCRIPTION section remains the same: "The drug substance used in atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate... Atorvastatin calcium is a white to off-white solid.."

As of August 30, 2011,

Chemistry has NOT decided if the propylene glycol solvate meets the DS definition in USP. There is an internal discussion within Chemistry. However, as of right now, the labeling and labels are acceptable because the DS is correctly stated as "atorvastatin calcium propylene glycol solvate". If Chemistry decided that the propylene glycol solvate form DOES NOT meet the definition in USP, then Apotex MUST revise their labels.

Email received on 3/4/09

As you might have known "atorvastatin" is (b) (4)

Thus, one can say "atorvastatin calcium equivalent to 10 mg atorvastatin" or "(b) (4) of atorvastatin calcium equivalent to (b) (4)" and technically both are correct.
Thus, from technical perspective, the Apotex labeling is accurate.
However, it is your call if you want the Apotex to change the words similar to RLD.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Wednesday, March 04, 2009 8:56 AM
To: Vaithiyalingam, Sivakumar
Cc: Grace, John F
Subject: Atorvastatin 90-548 (Apotex's atorvastatin)

Siva,

I have a problem with the label of 90-548. Please take a look at the attached pdf file. Apotex's label states:

* Each tablet contains (b) (4) of atorvastatin calcium equivalent to (b) (4).

Lipitor's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

TEVA's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Is Apotex's label accurate? Could Apotex state this because their drug substance is atorvastatin calcium in the form of propylene glycol solvate instead of atorvastatin calcium in the hydrate form. I'm concerned because the label should be consistent between the generic and brand.

Thanks
Ann

Email received on 3/3/09:

Ann,

The RLD is a hydrate whereas the ANDA is a solvate with propylene glycol. Under our current guidance, these drug substances are considered equivalent.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Tuesday, March 03, 2009 1:56 PM
To: Vaithiyalingam, Sivakumar
Cc: Vu, Thuyanh (Ann)
Subject: 90-548 (Apotex's atorvastatin calcium)

The DS in Apotex's atorvastatin is different than the RLD's Lipitor and is this equivalent/acceptable? Thanks Ann

This is Apotex's atorvastatin:

The drug substance used in Atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{68}CaF_2N_4O_{10} * C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:

Lipitor's insert:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, s-056; approved 6/17/09. Supplement provided for the PLR labeling format.

   Please see the email string with the chemist above. I asked the firm to revise the label to state ""Each tablet contains atorvastatin calcium equivalent to YY mg atovastatin" to be consistent with the RLD and other generic manufacturers even though Apotex is technically/chemically correct.

   8/18/2011 AF: Apotex changed the labels. See Chemist Notes above for further information about the solvate form.

   In this amendment, the carton and container labels have been revised to specifically indicate Atorvastatin Calcium Propylene Glycol Solvate as the drug substance. The statement on the container and carton labels has been revised from:

   Each tablet contains atorvastatin calcium equivalent to X mg atorvastatin.
   to:

   Each tablet contains atorvastatin calcium propylene glycol solvate equivalent to X mg of atorvastatin.
   (where X mg is either 10 mg, 20 mg, 40 mg or 80 mg)

   11/16/2011 AF: See Chemist Notes above from further info.

   Apotex changed their container labels back to:

   "Each tablet contains atorvastatin calcium equivalent to X mg of atorvastatin" per advice from Chemistry. The insert remains the same.

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	PIII	Same As
5273995	Dec 28, 2010 ped jun 28, 20011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011* PED	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As, certified in 3/19/09 labeling amendment

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None
I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:calcium acetate, croscramellose sodium, sodium carbonate [redacted], microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose [redacted], polyethylene glycol [redacted], titanium dioxide,

[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.1-original submission]

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T 9 Canada

5. CONTAINER/CLOSURE

- HDPE bottles containing 30 or 90 tablets closed with [redacted] screw caps with a [redacted] desiccant. When originally packed, the bottles are also sealed with a [redacted].
- HDPE bottles containing 500 tablets or greater closed with [redacted] screw caps with a [redacted] desiccant. When originally packed, the bottles are also sealed with a [redacted].
- Blister packs comprised of [redacted] and a [redacted]. Packed in cartons containing 10 strips of 10 tablets (100 tablets total).

6. FINISHED DOSAGE FORM

RLD:

10 mg: coded “PD 155” on one side and “10” on the other

20 mg: coded “PD 156” on one side and “20” on the other

40 mg: coded “PD 157” on one side and “40” on the other

80 mg: coded “PD 158” on one side and “80” on the other

ANDA:

10 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “A10” on the other side.

20 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV20” on the other side.

40 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV40” on the other side.

80 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV80” on the other side.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: DS is compendial ONLY
RLD: store at CRT 20-25°C (68-77°F) [see USP].
ANDA label: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [See USP Controlled Room Temperature]

8. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight container (see USP).

The carton states: “This unit-dose package is not child-resistant”

9. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the propolyne glycol solvate form rather than the trihydrate

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

RLD: 10 mg, 20 mg = bottles of 90s, 5000s and blisters of 100 (10 x 10) unit dose blisters
40 mg: bottles of 90s, 500s, 2500s and blisters of 100 (10 x 10) unit dose blisters
80 mg: bottles of 90s, 500s, 2500s and blisters of 64 (8 x 8) unit dose blisters

ANDA:10 mg, 20 mg = bottles of 30s, 90s, 1000s, 5000s and blisters of 100 (20 mg= violet color, 10 mg= green color)
40 mg= bottles of 30s, 90s, 500s, 1000s, 4000s and blisters of 100 (container color= yellow)
80 mg= bottles of 30s, 90s, , 500s, 2500 and blisters of 100 (container color= red)

Date of Review: November 17, 2011 Date of Submission: November 16, 2011

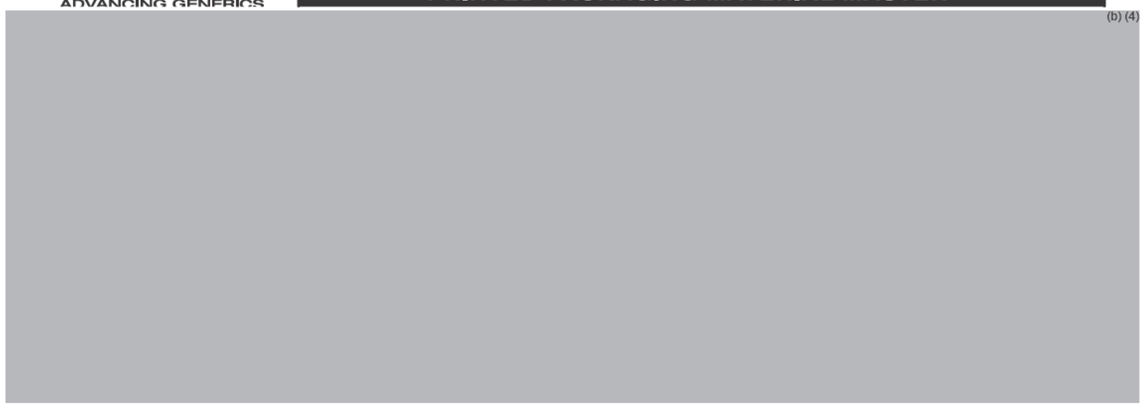
Primary Reviewer: Thuyanh Vu

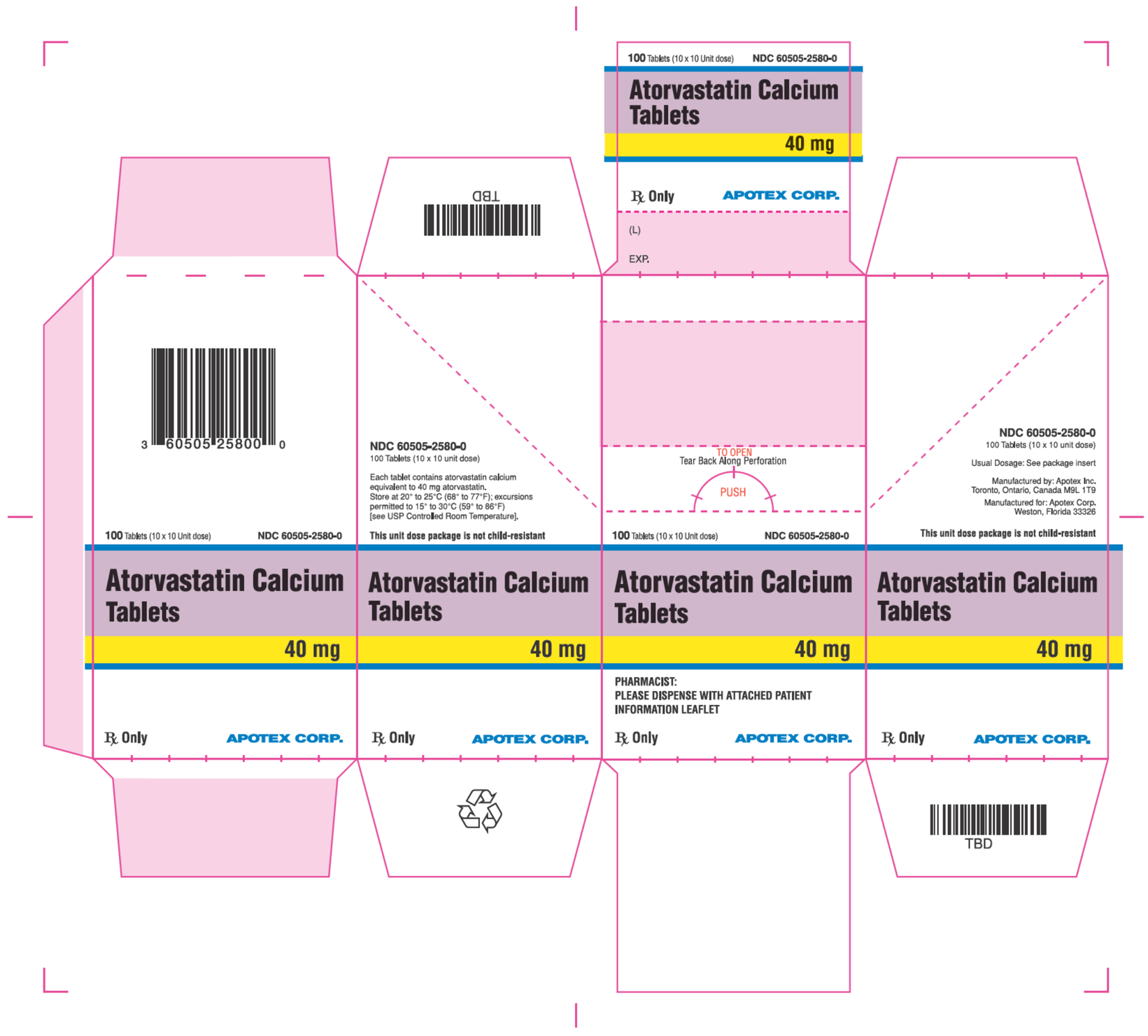
Team Leader: John Grace

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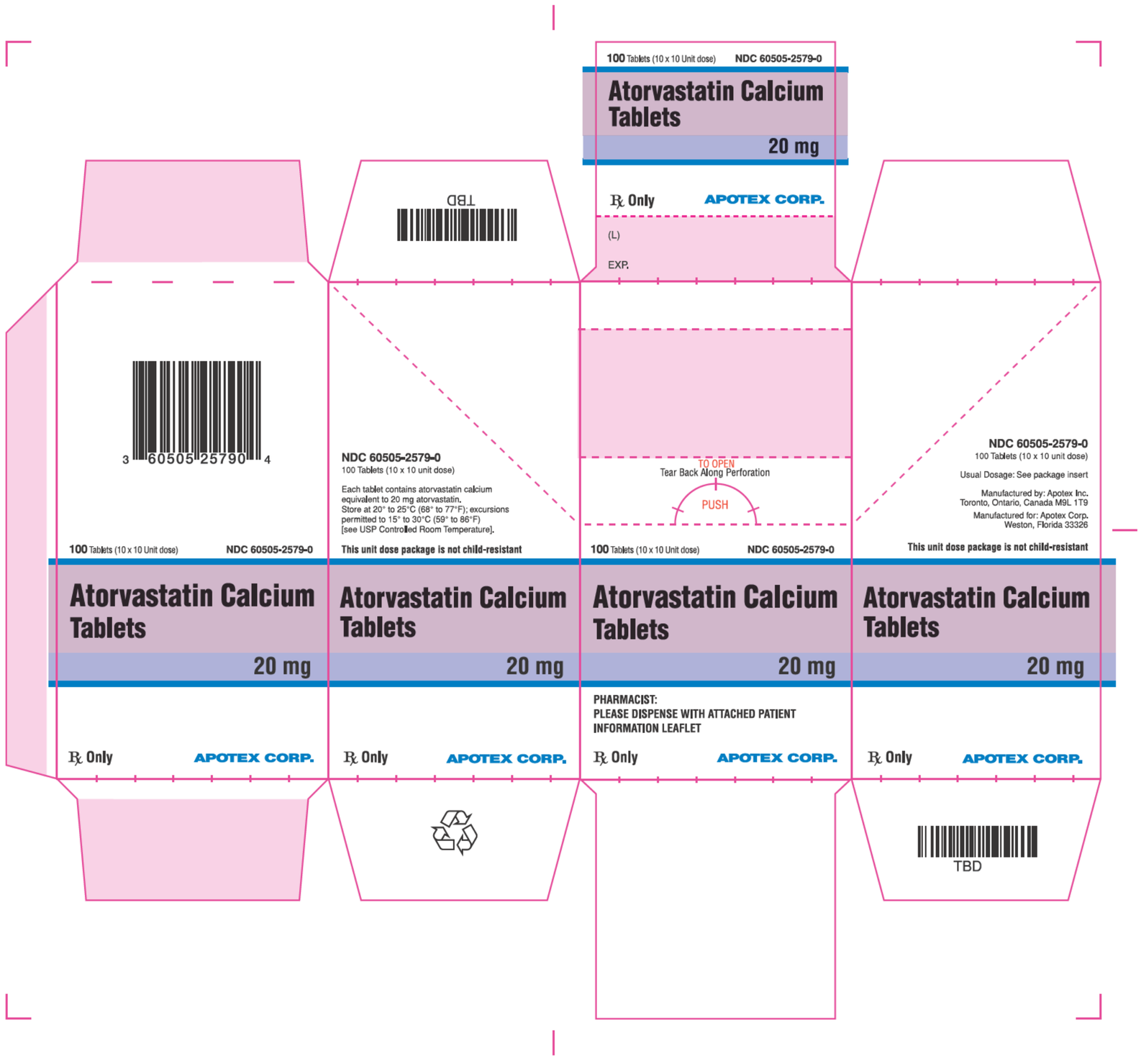


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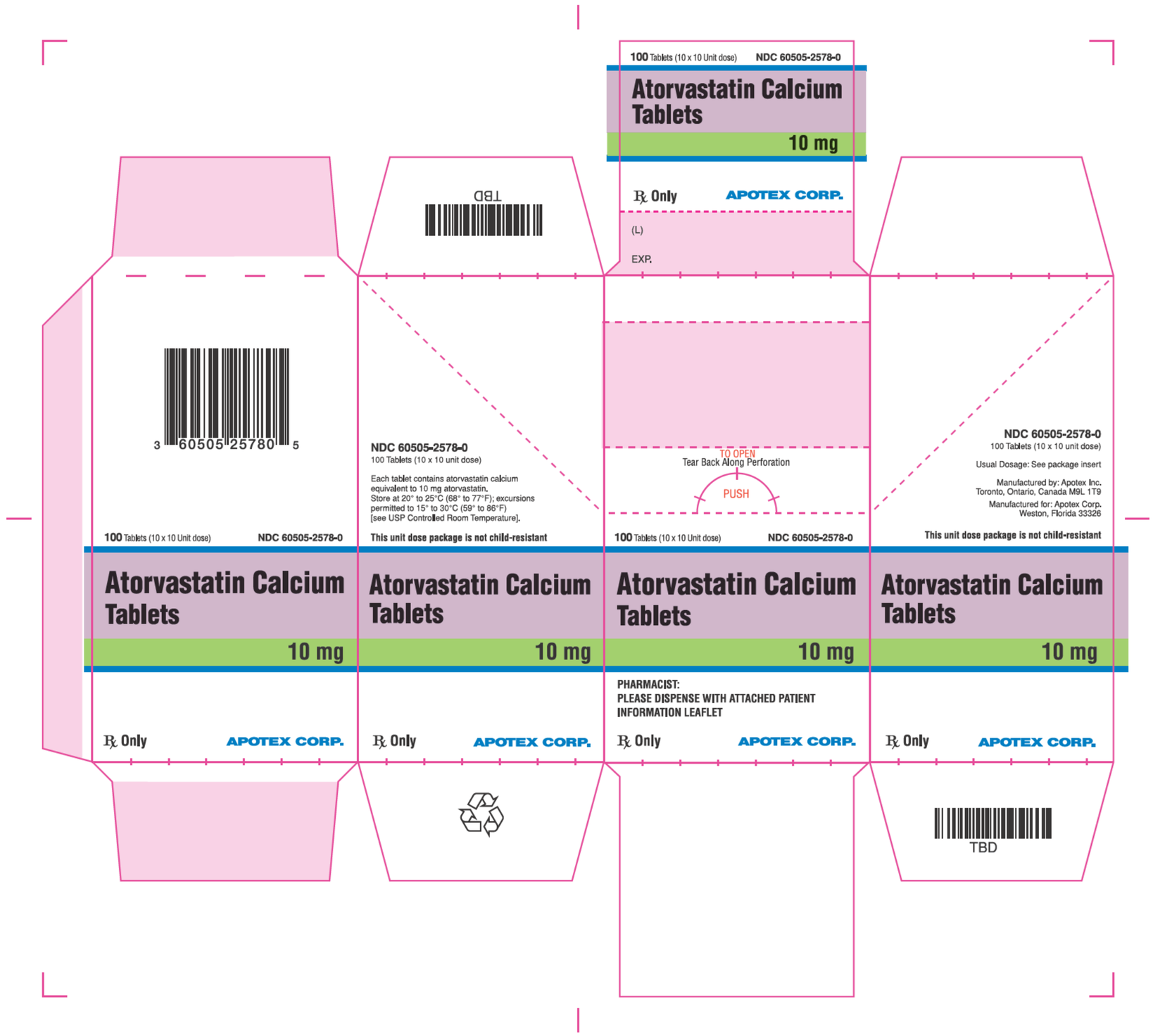


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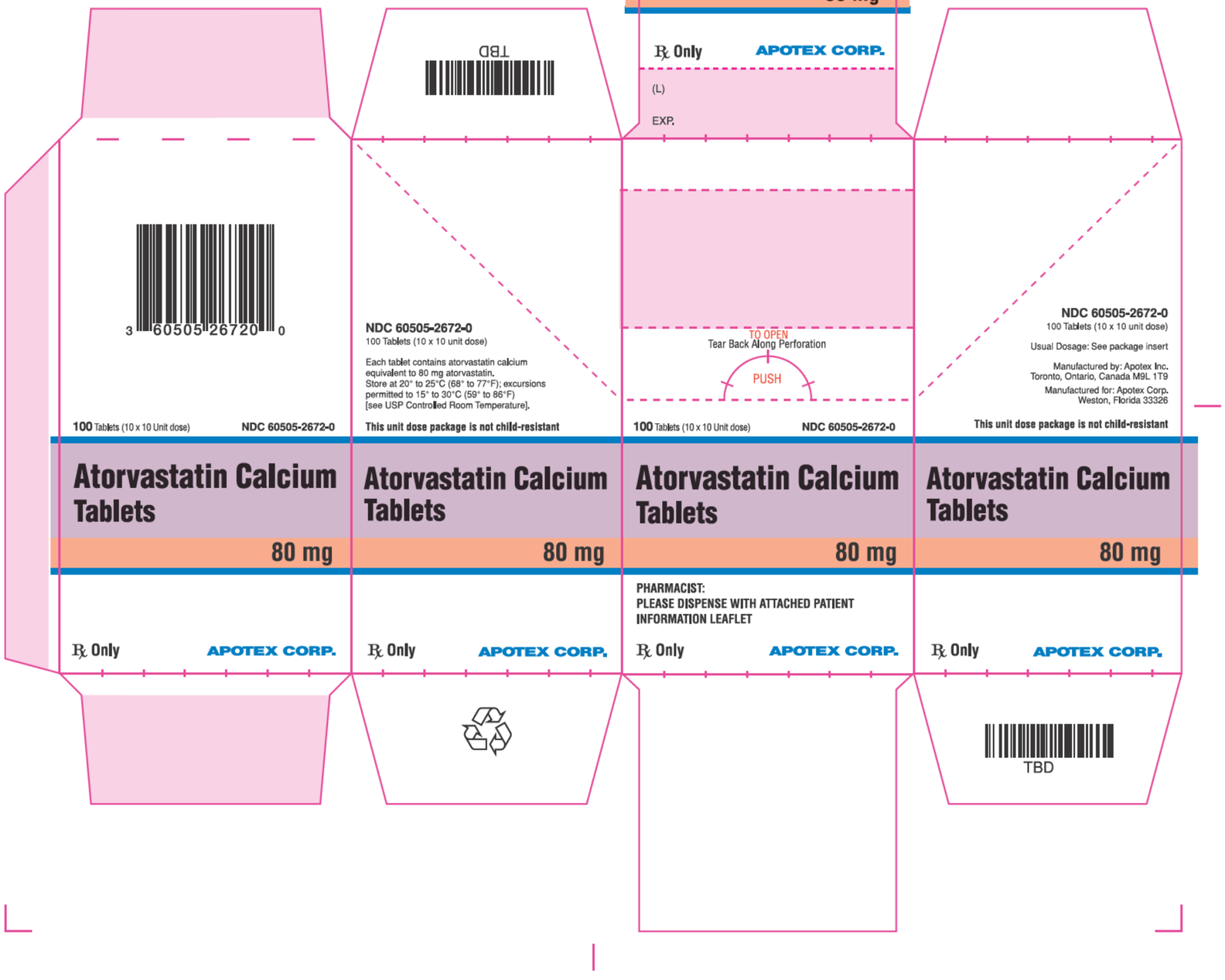


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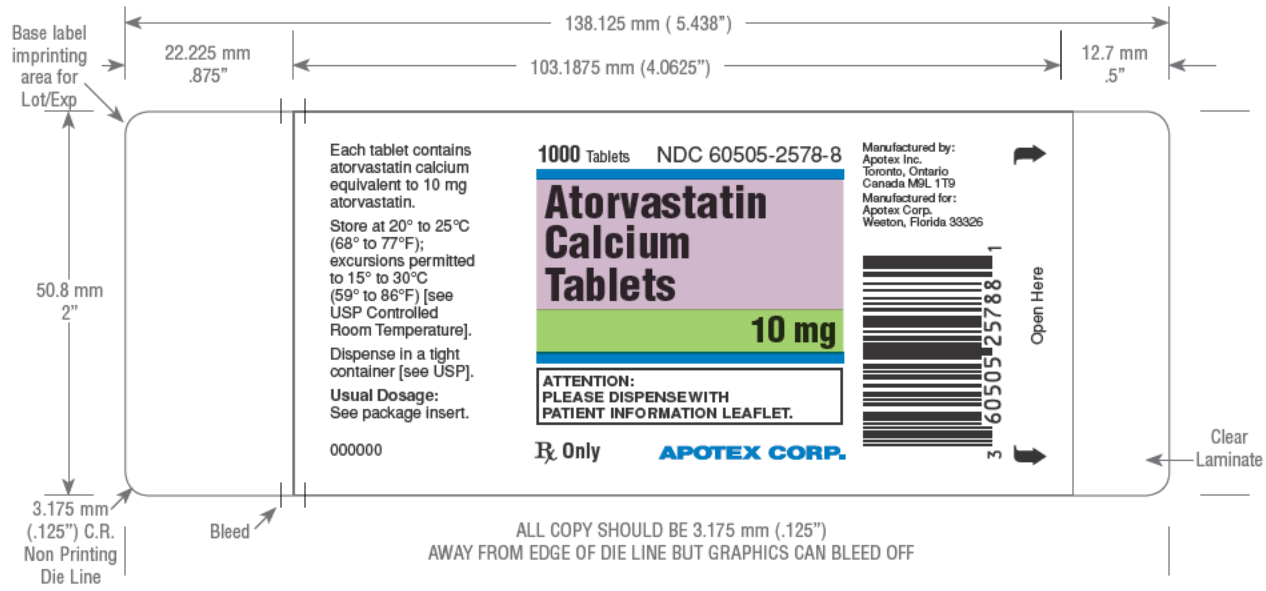
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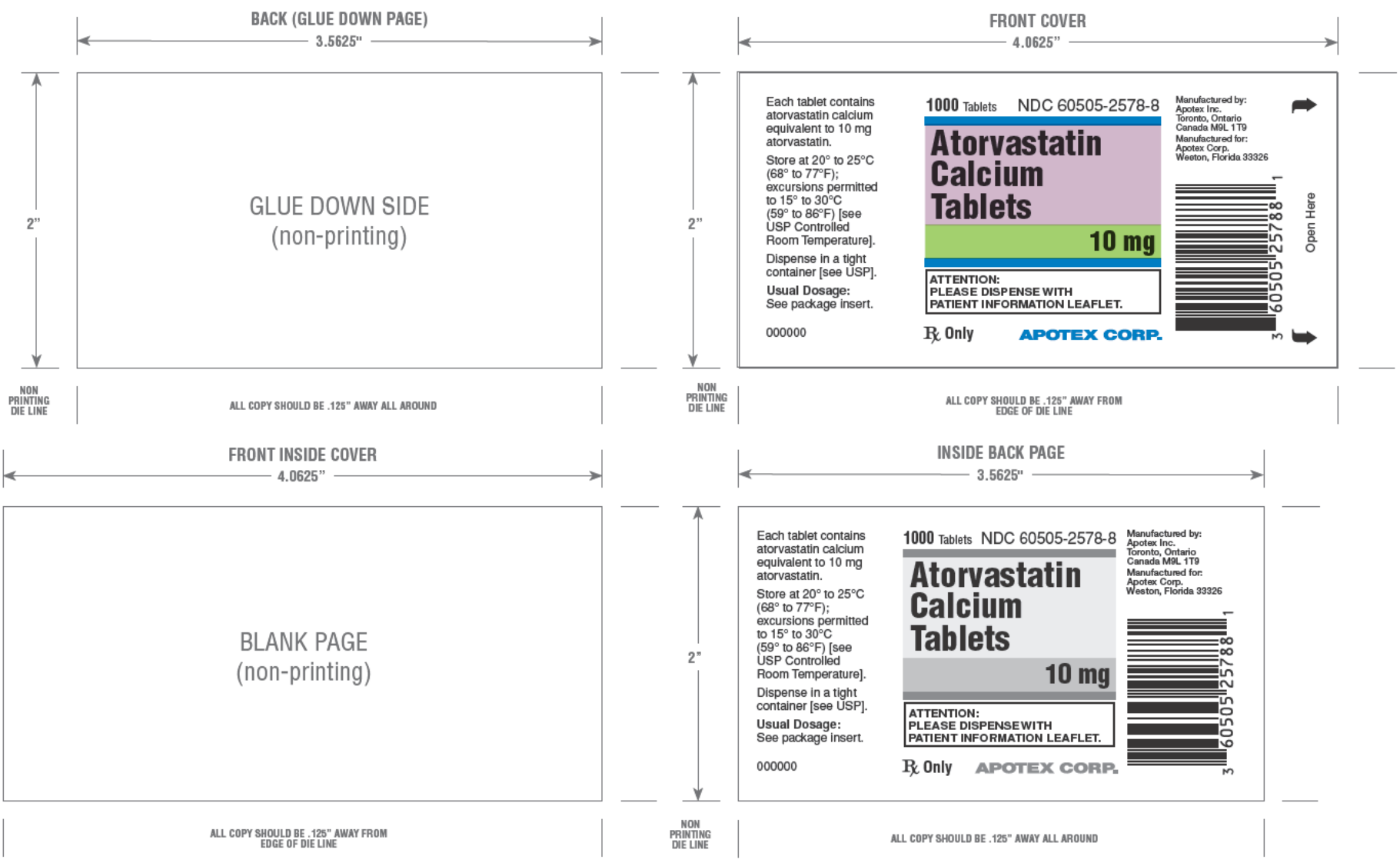
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(b) (4)

COMPOSITE



COVER



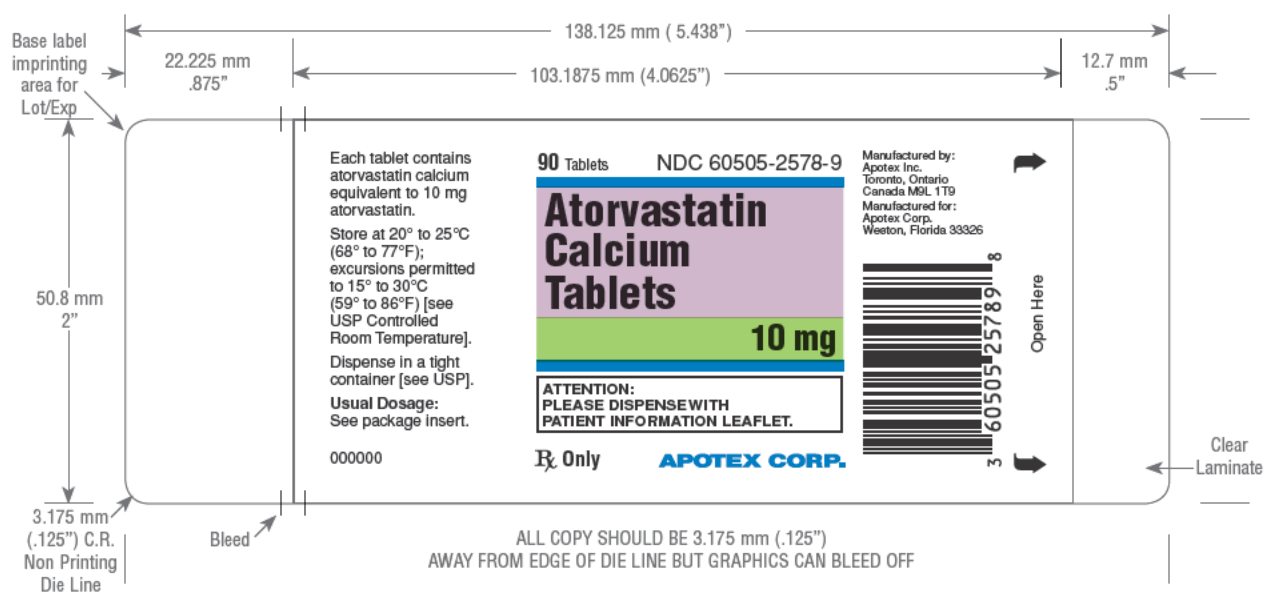
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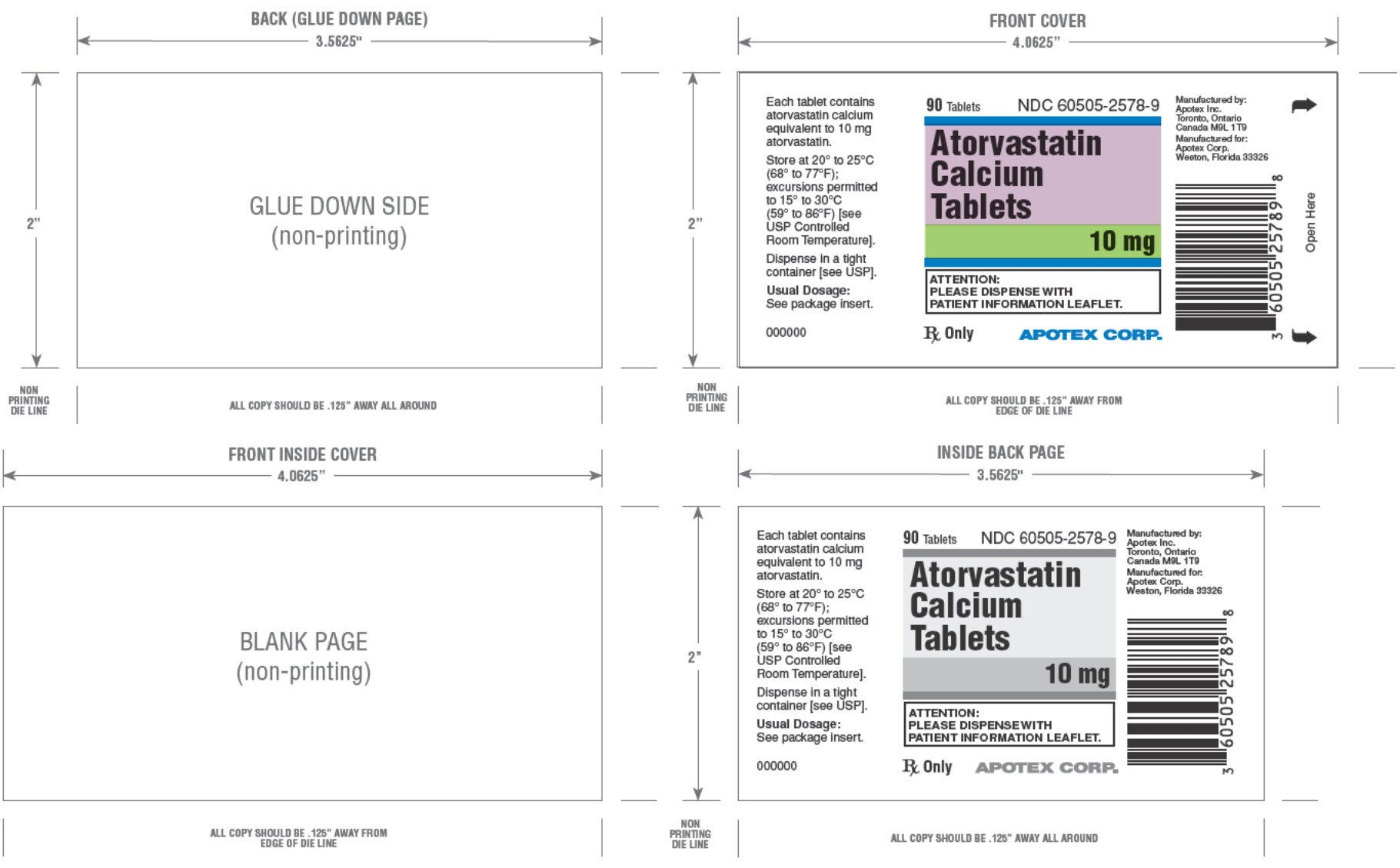
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COMPOSITE



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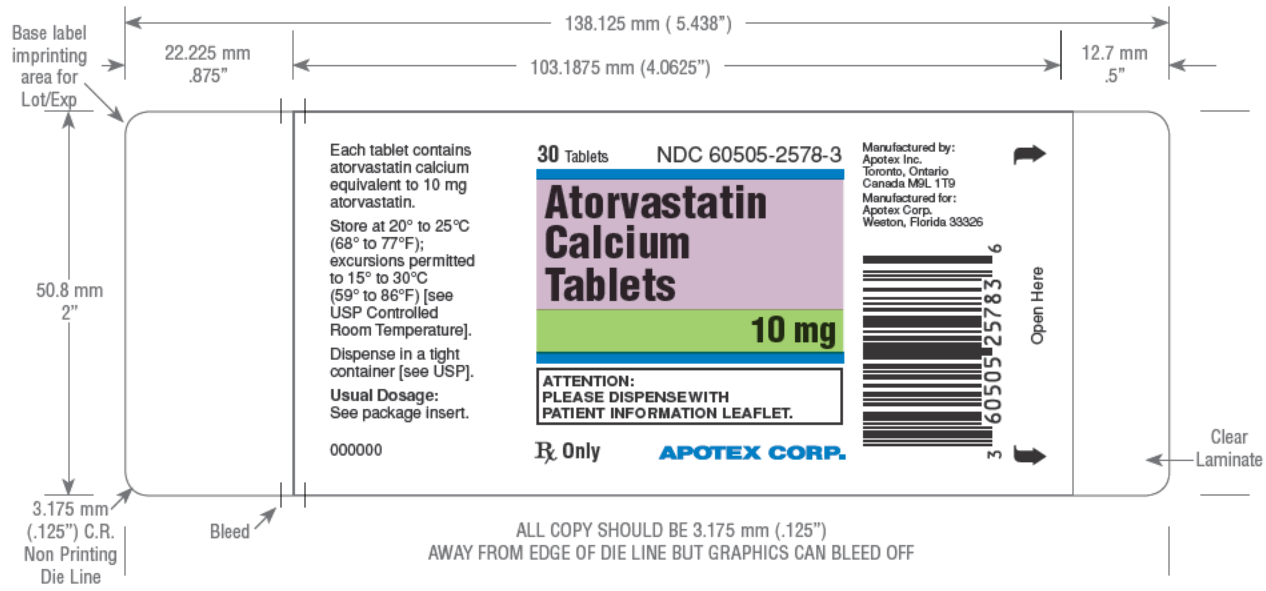
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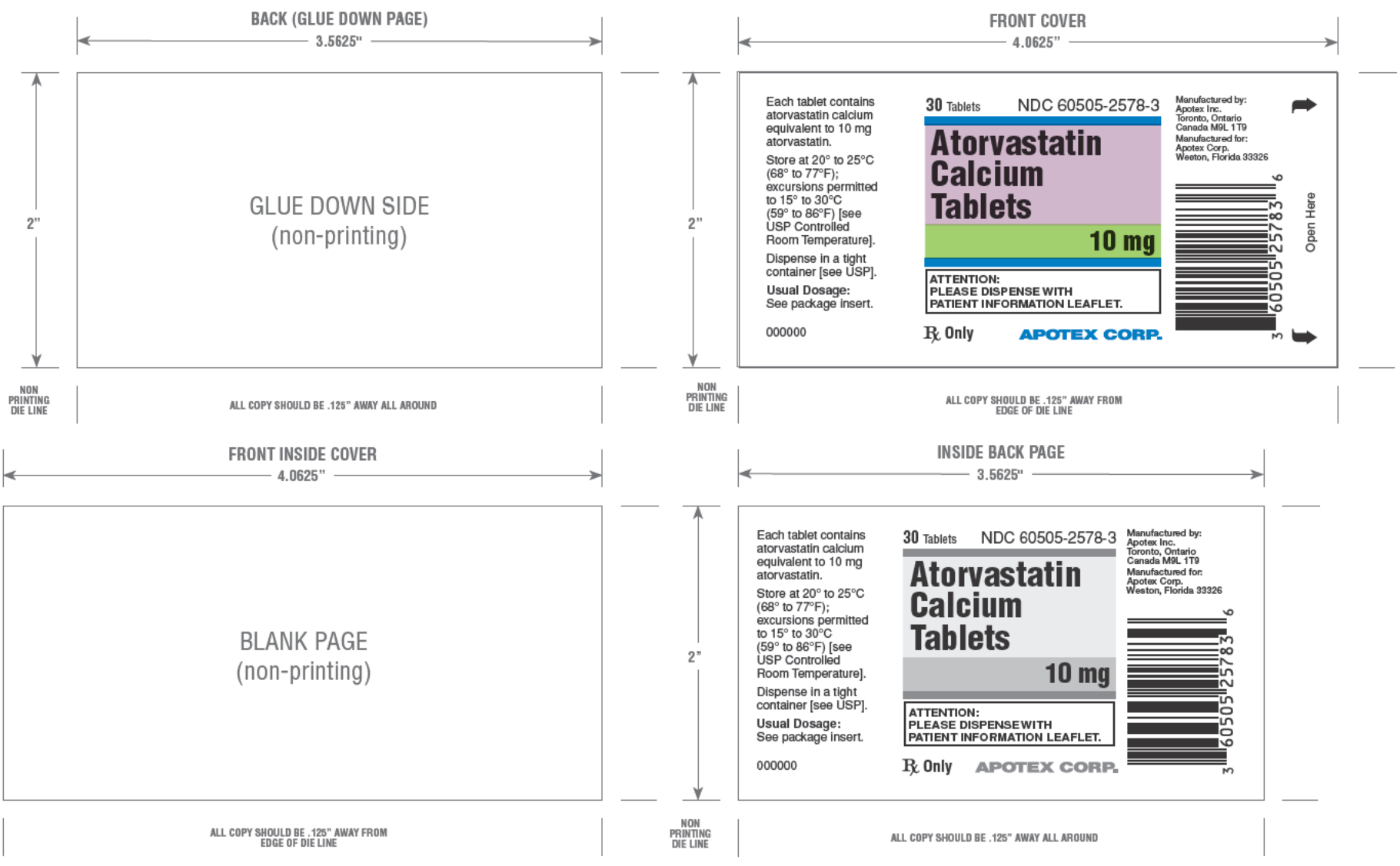
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COMPOSITE



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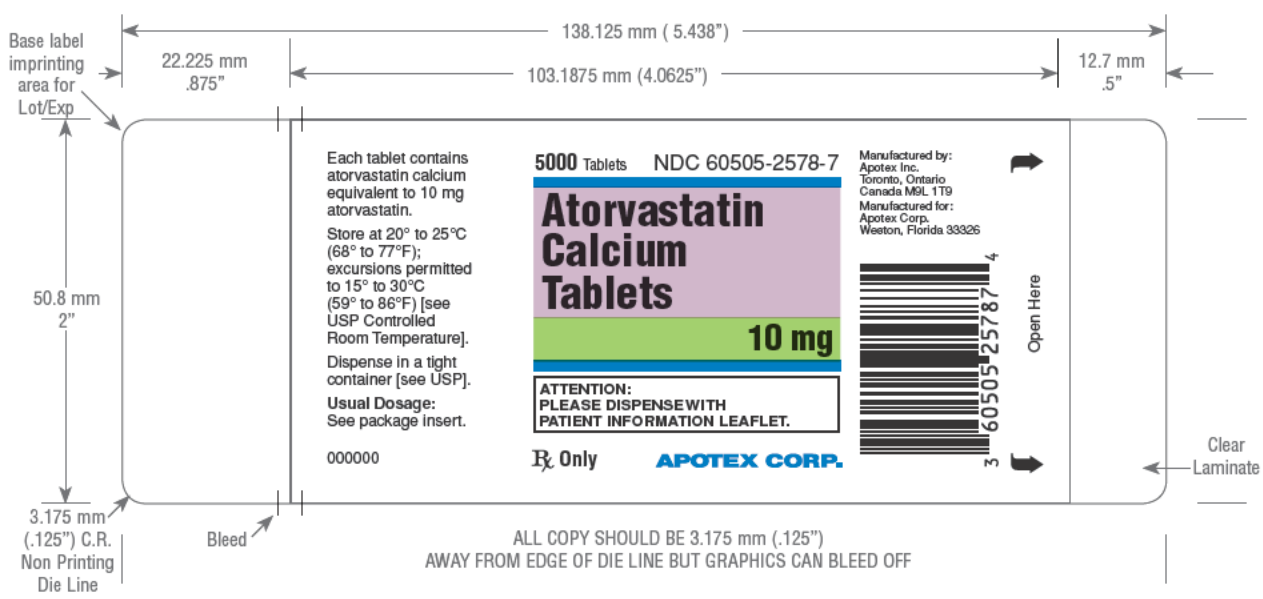
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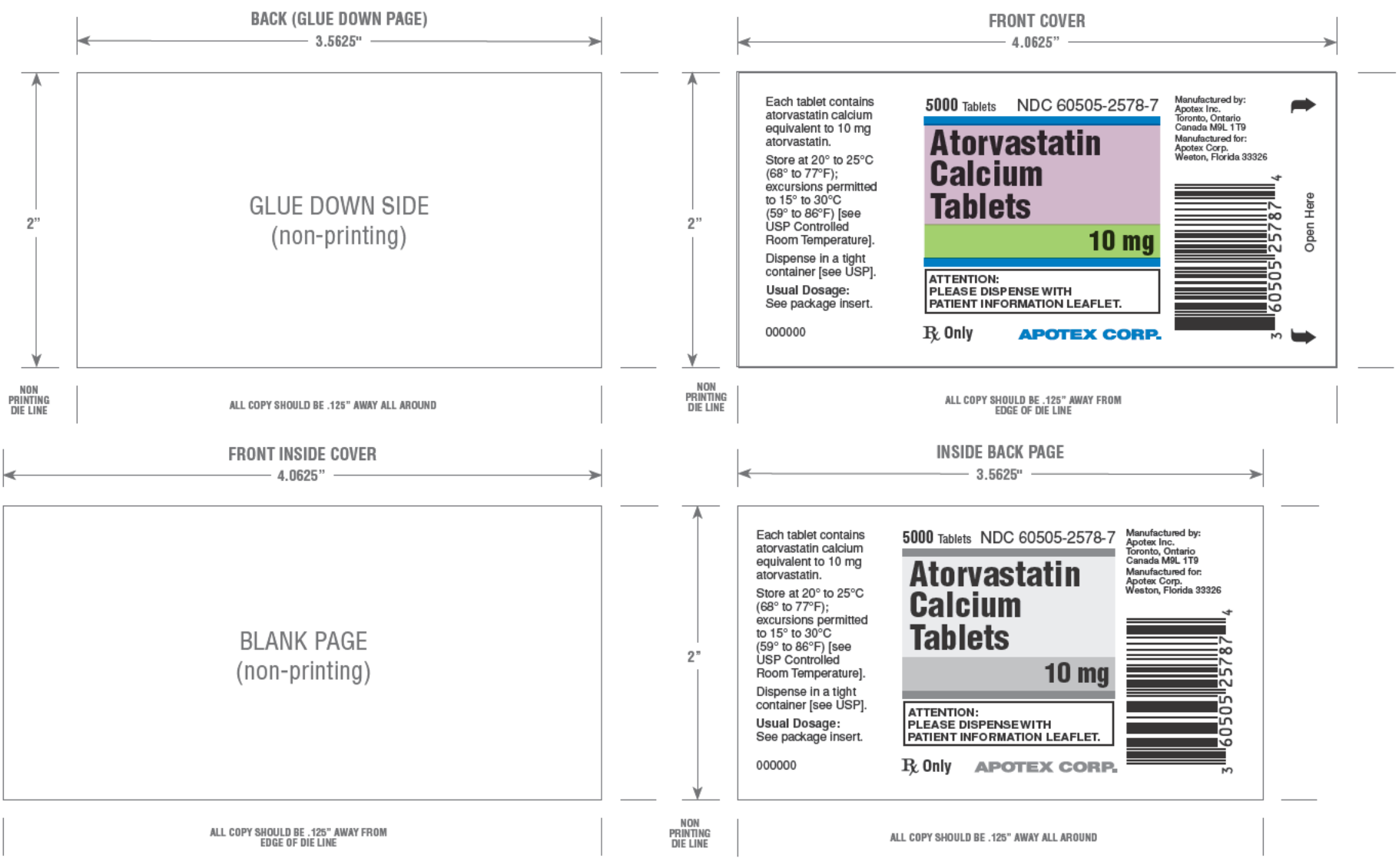
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COMPOSITE



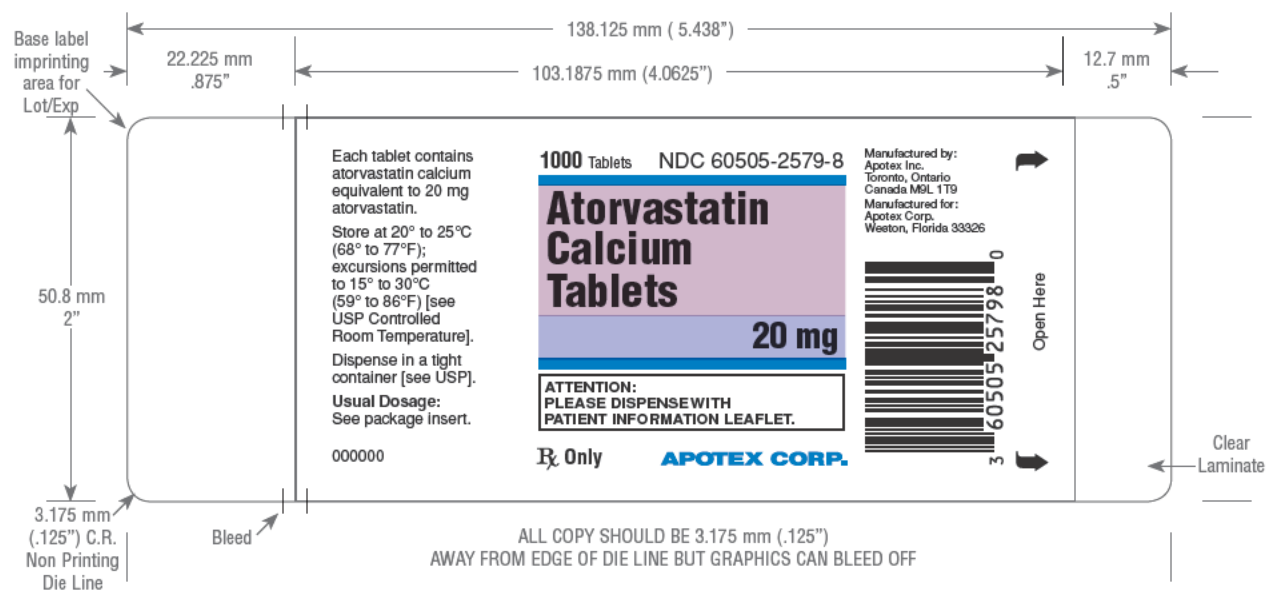
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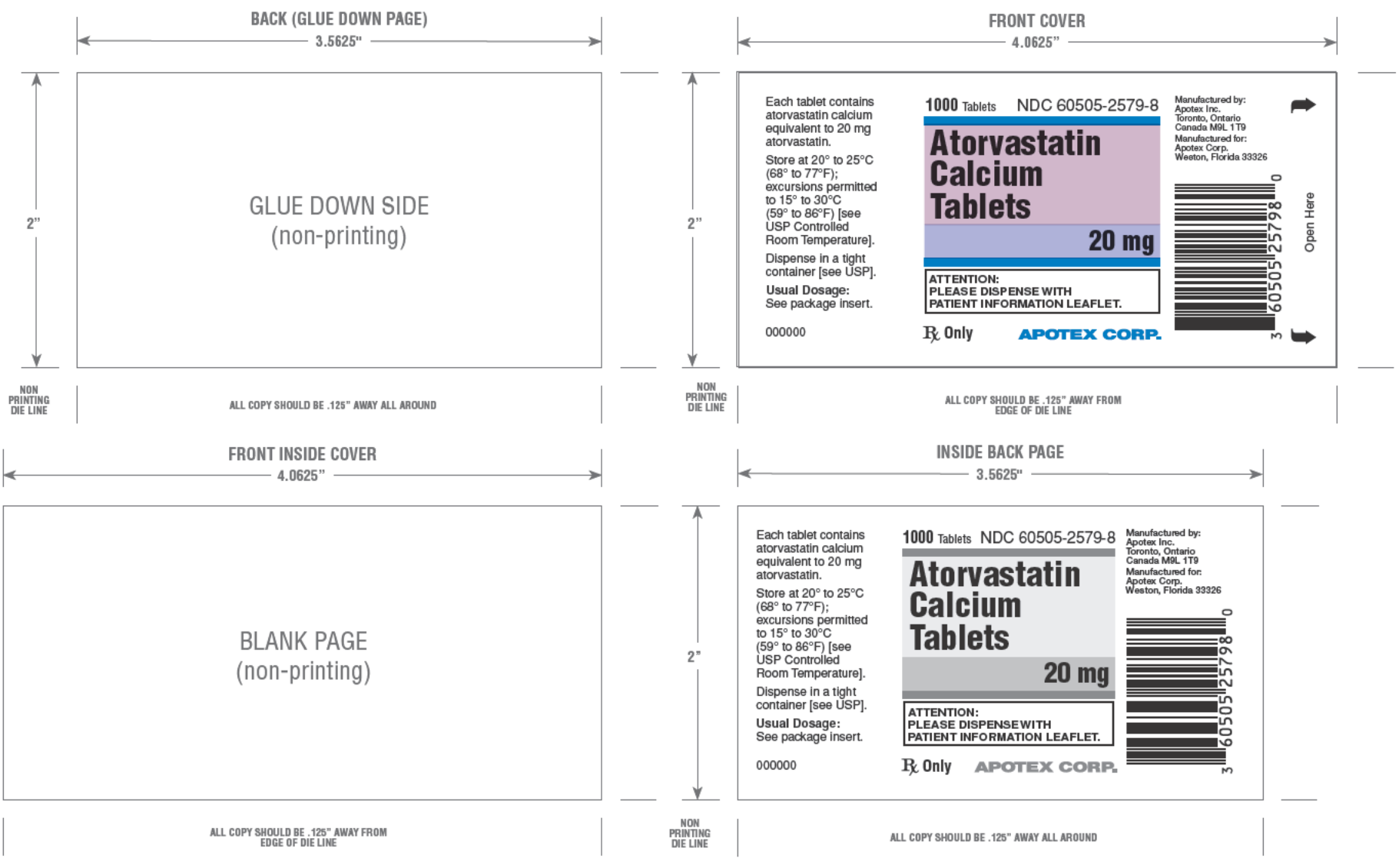
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COMPOSITE



COVER

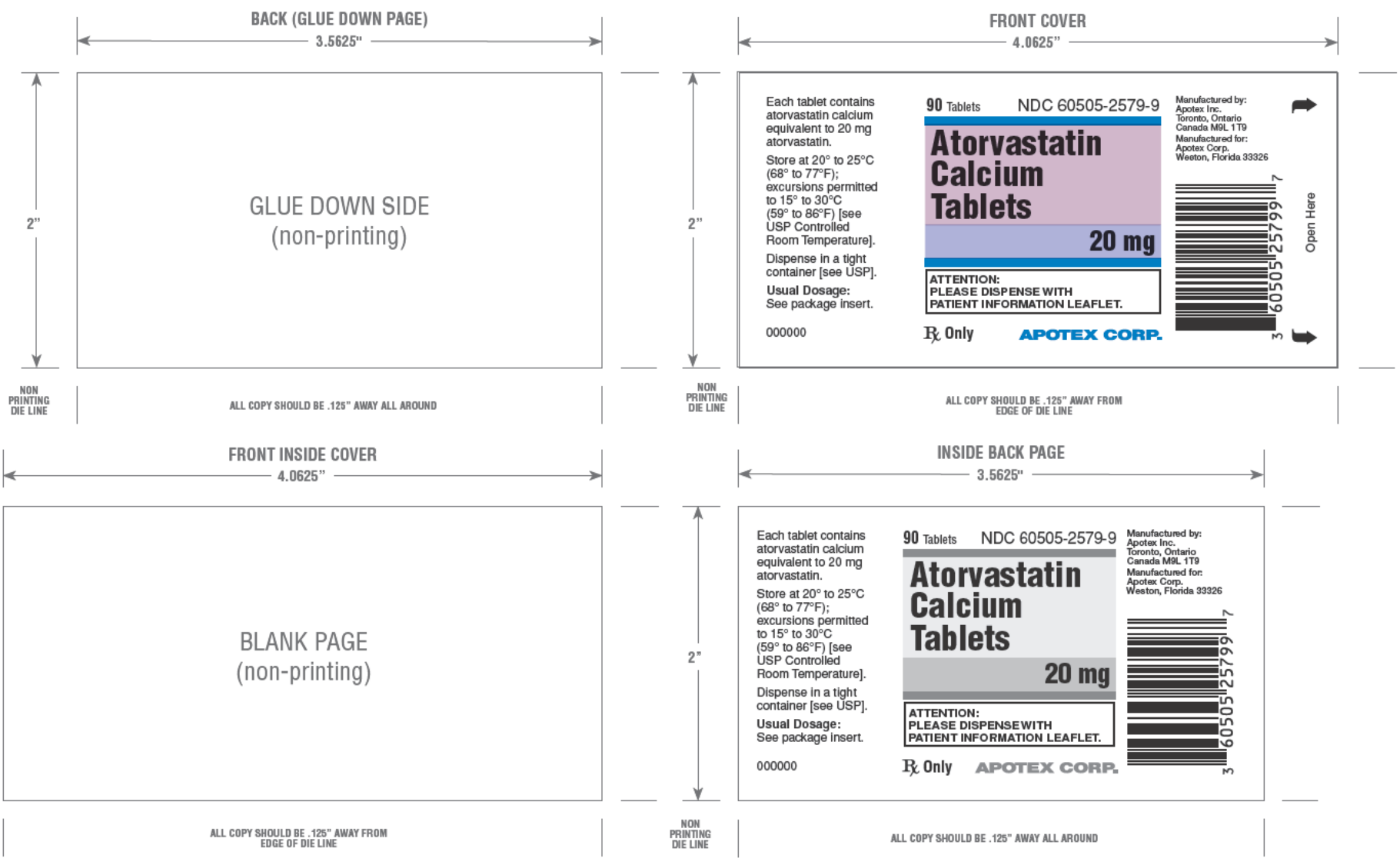


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COMPOSITE



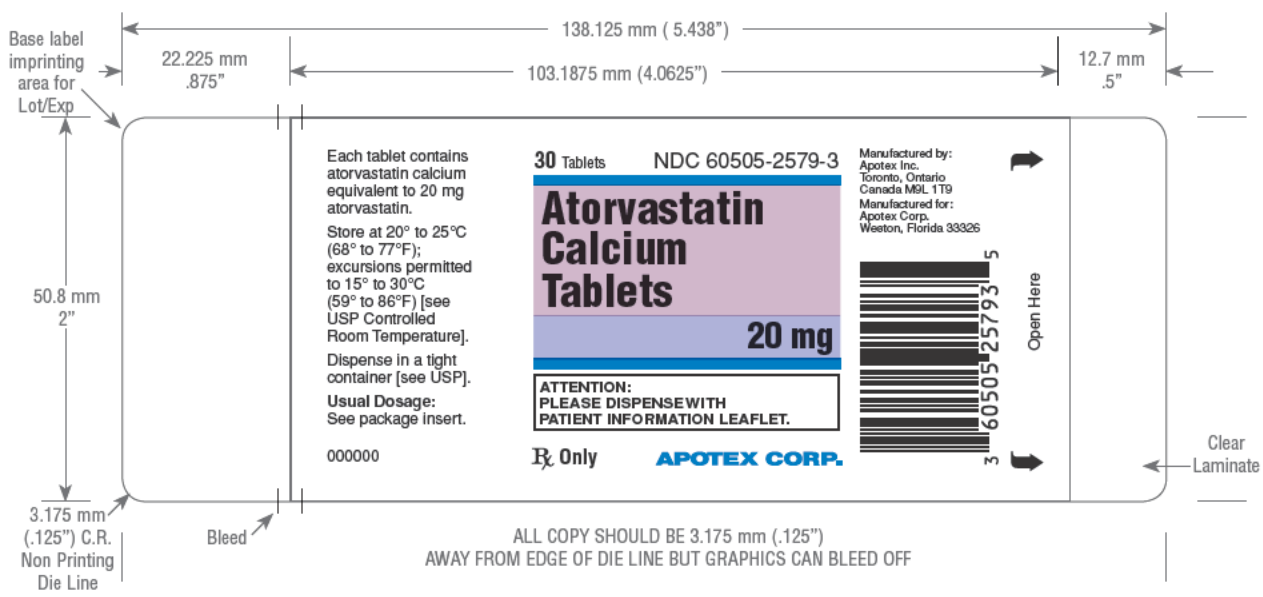
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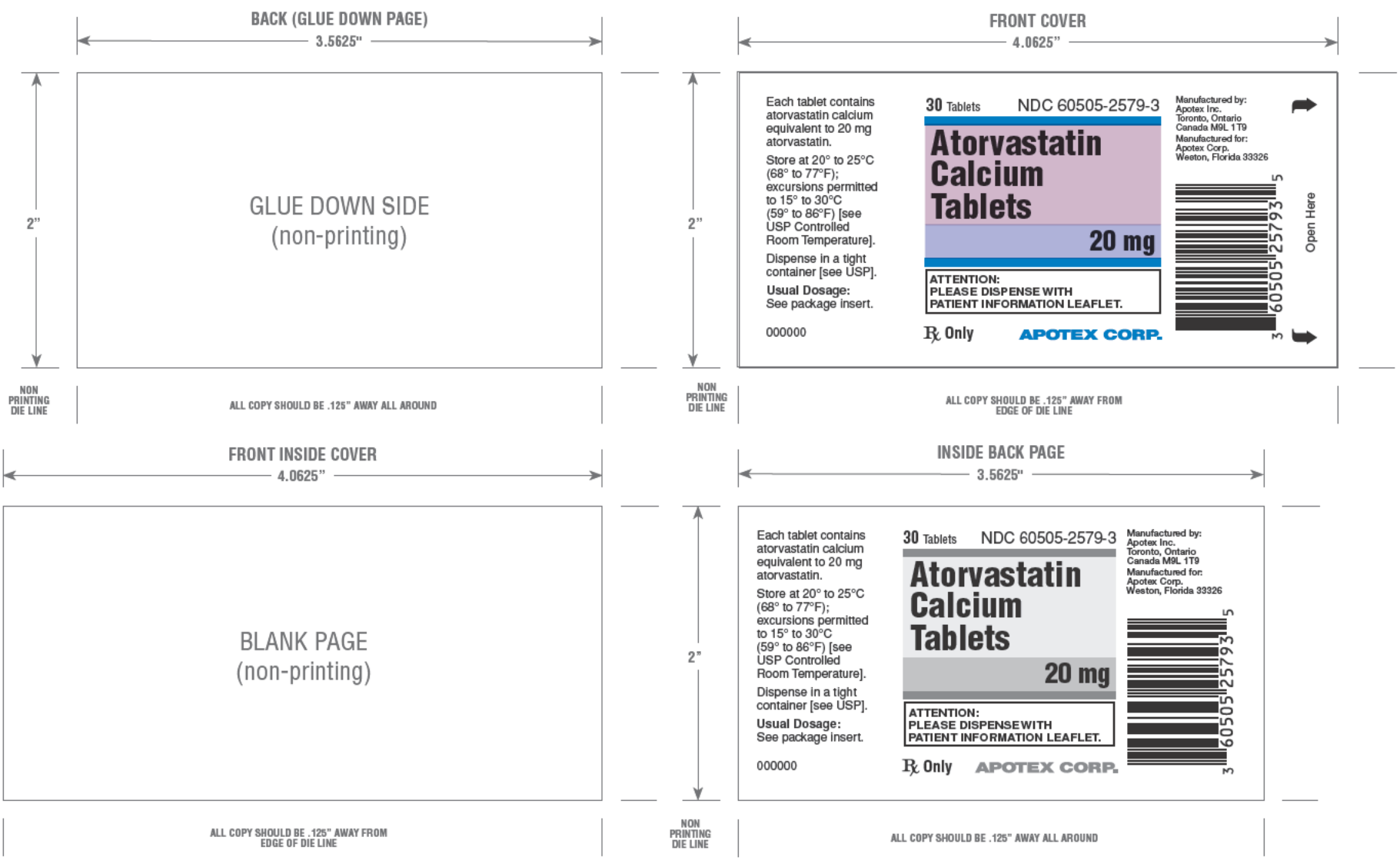
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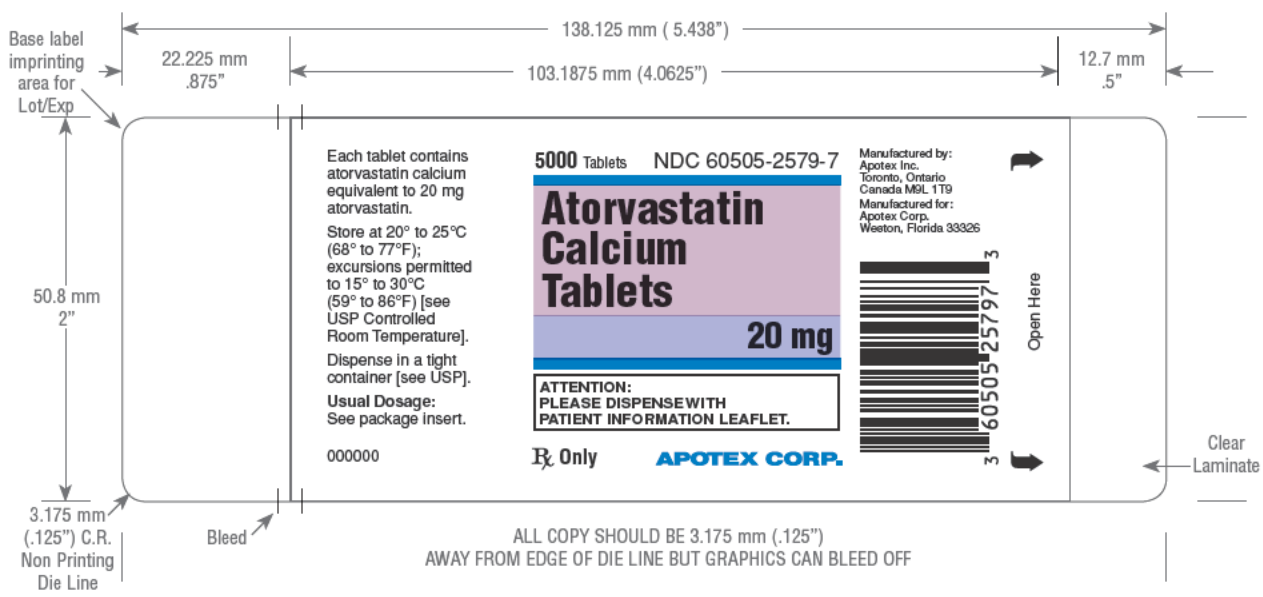
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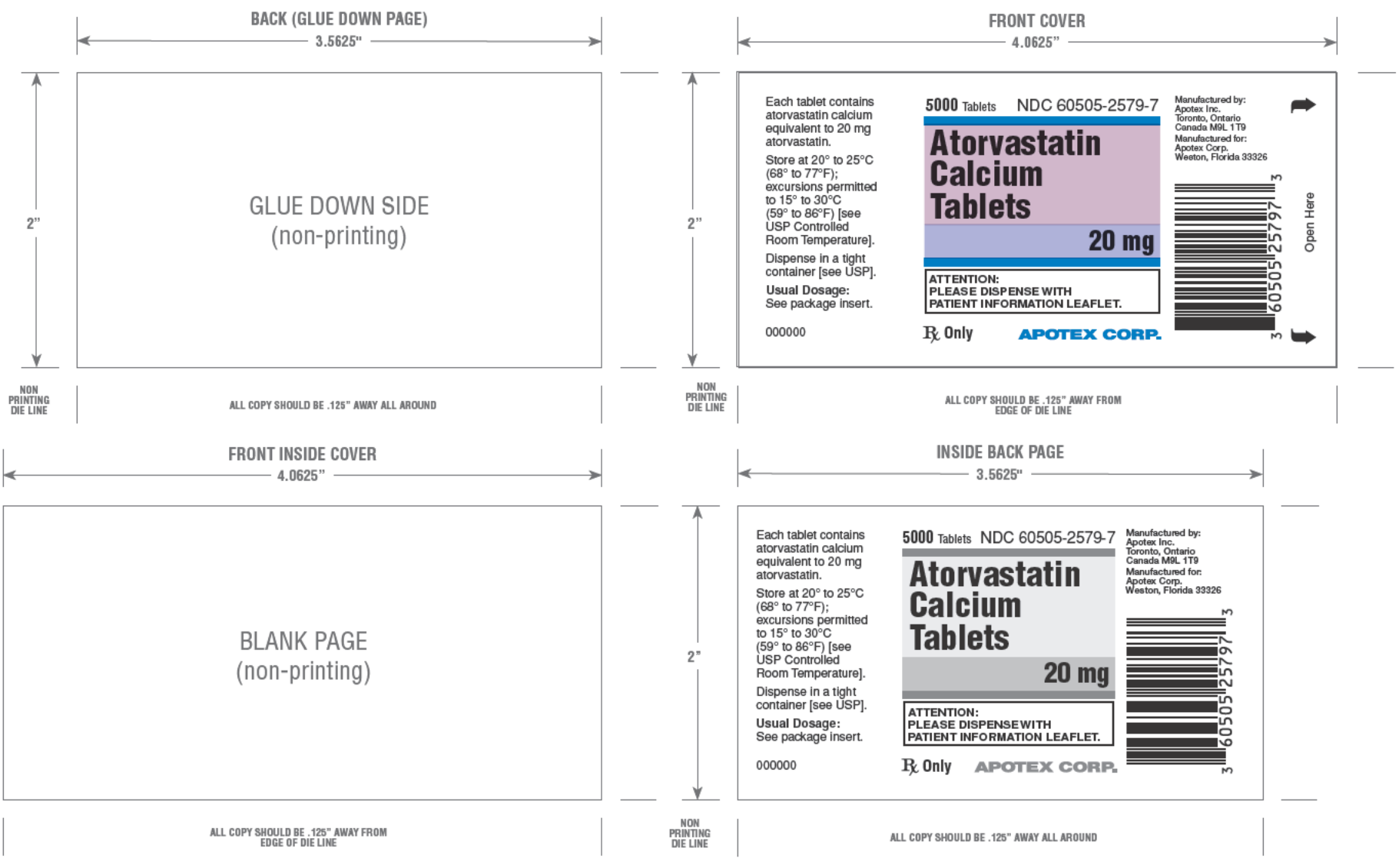
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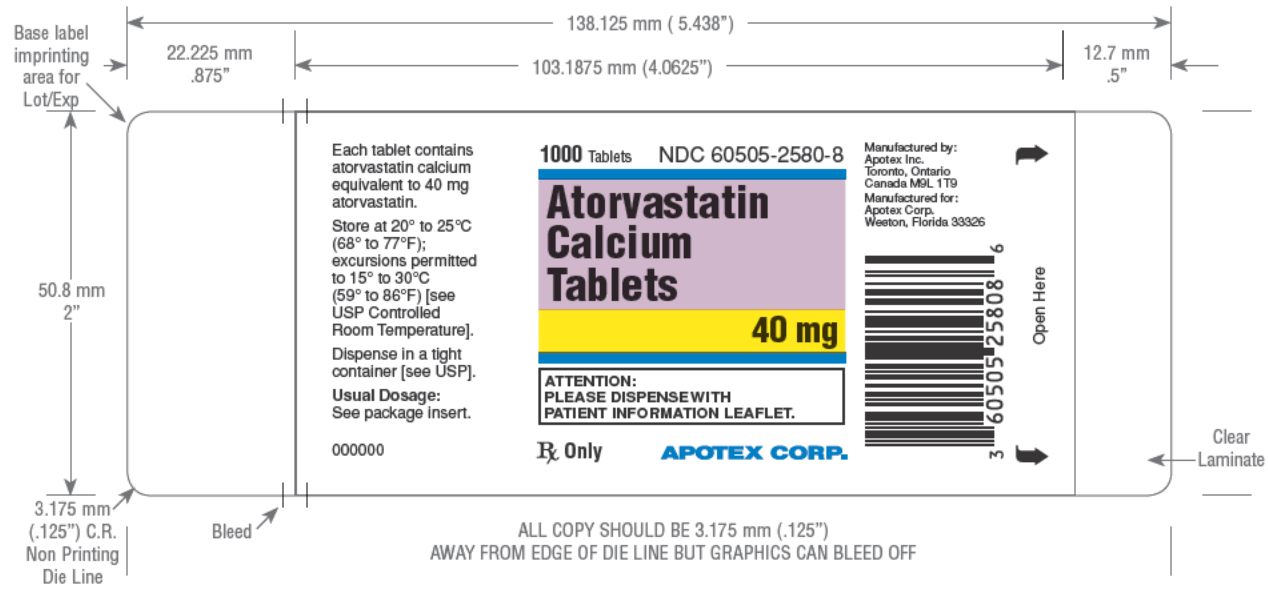
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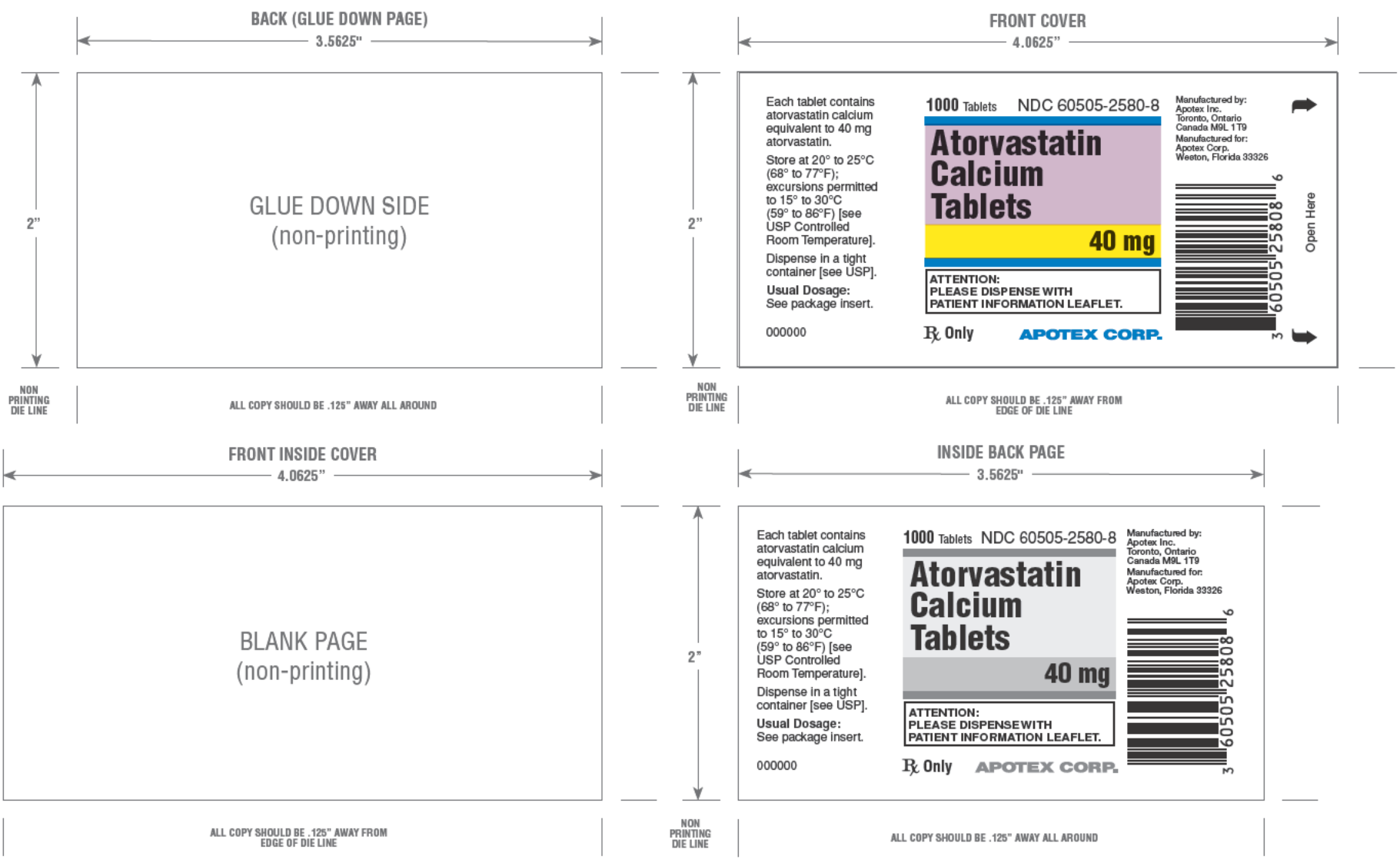
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COMPOSITE



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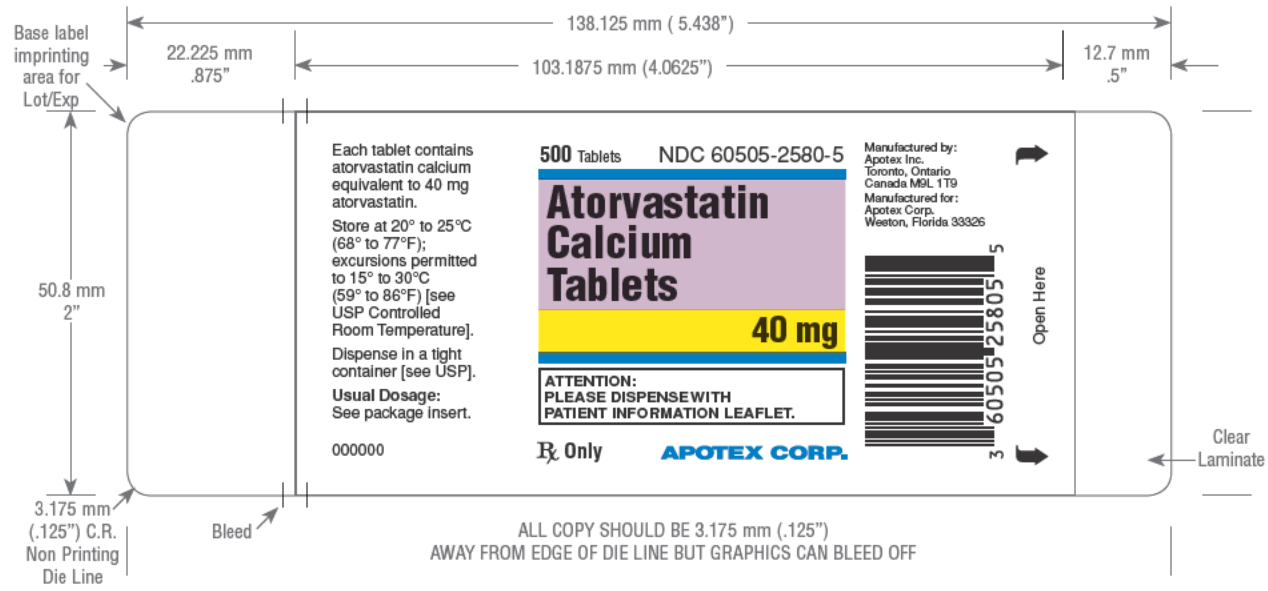


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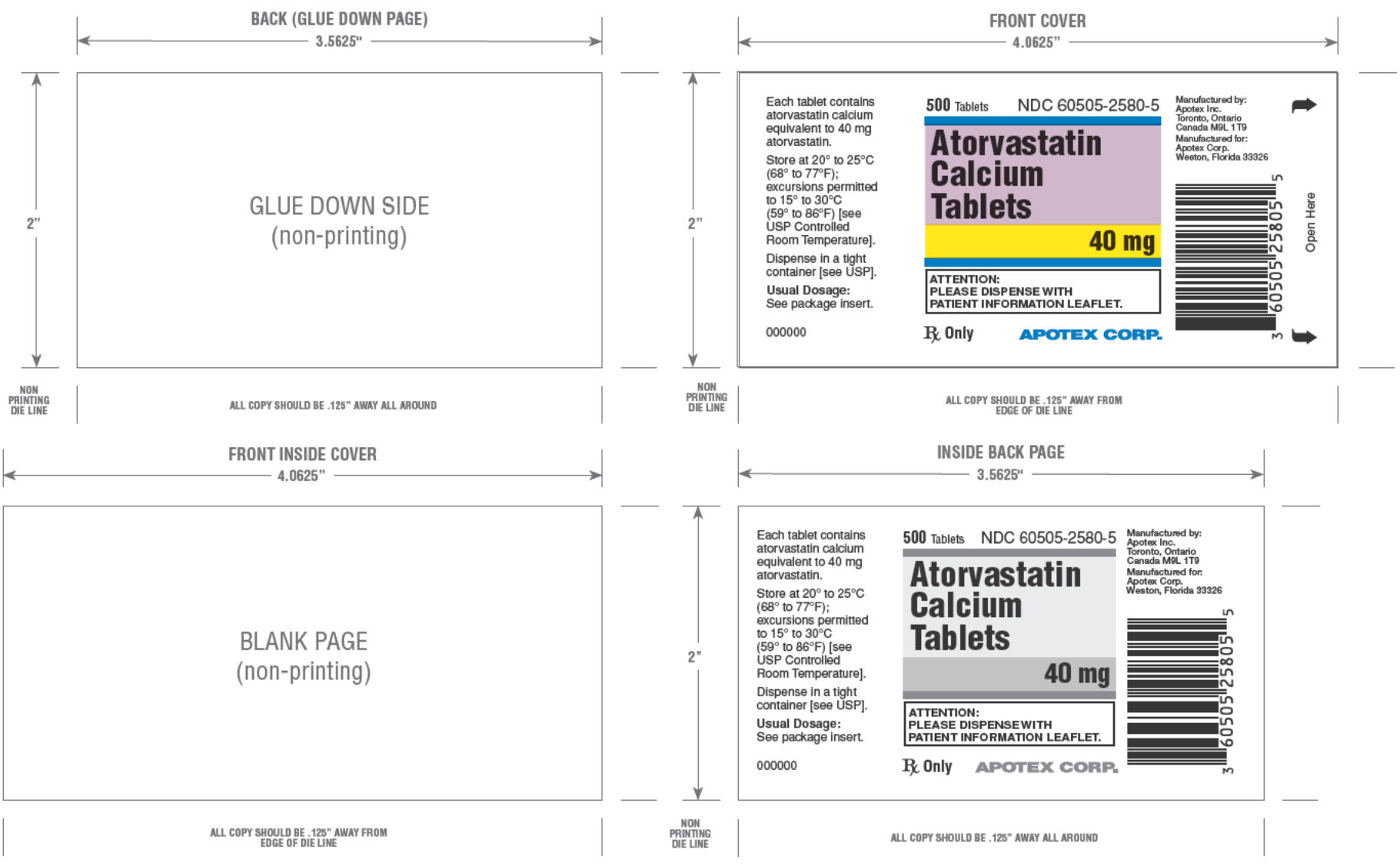
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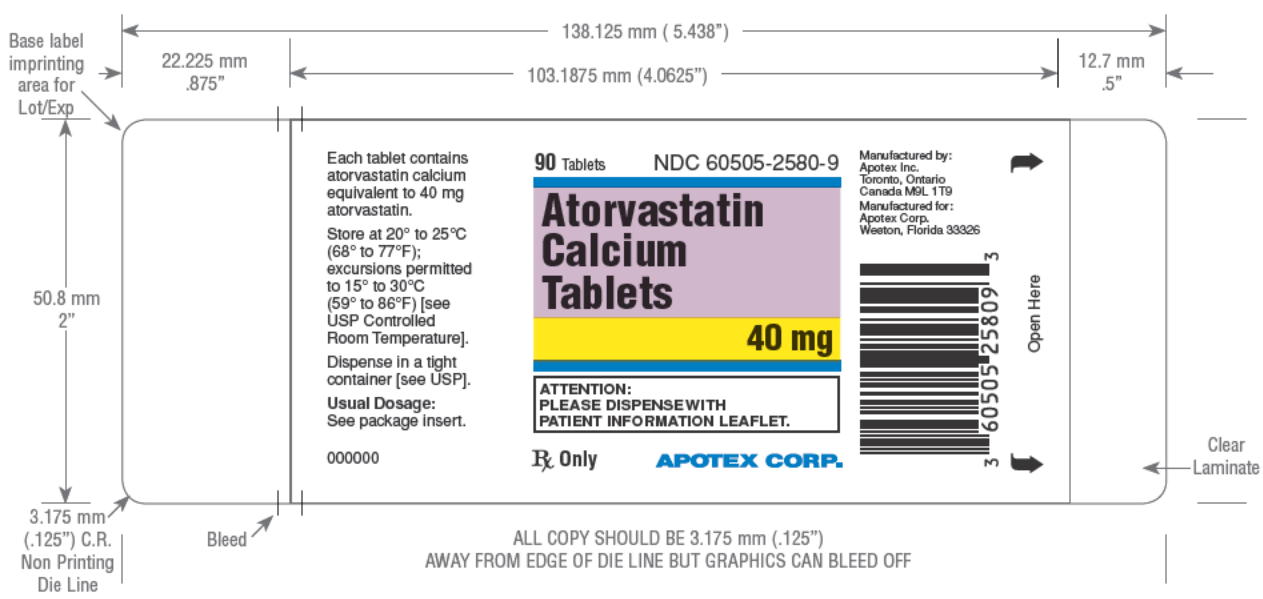


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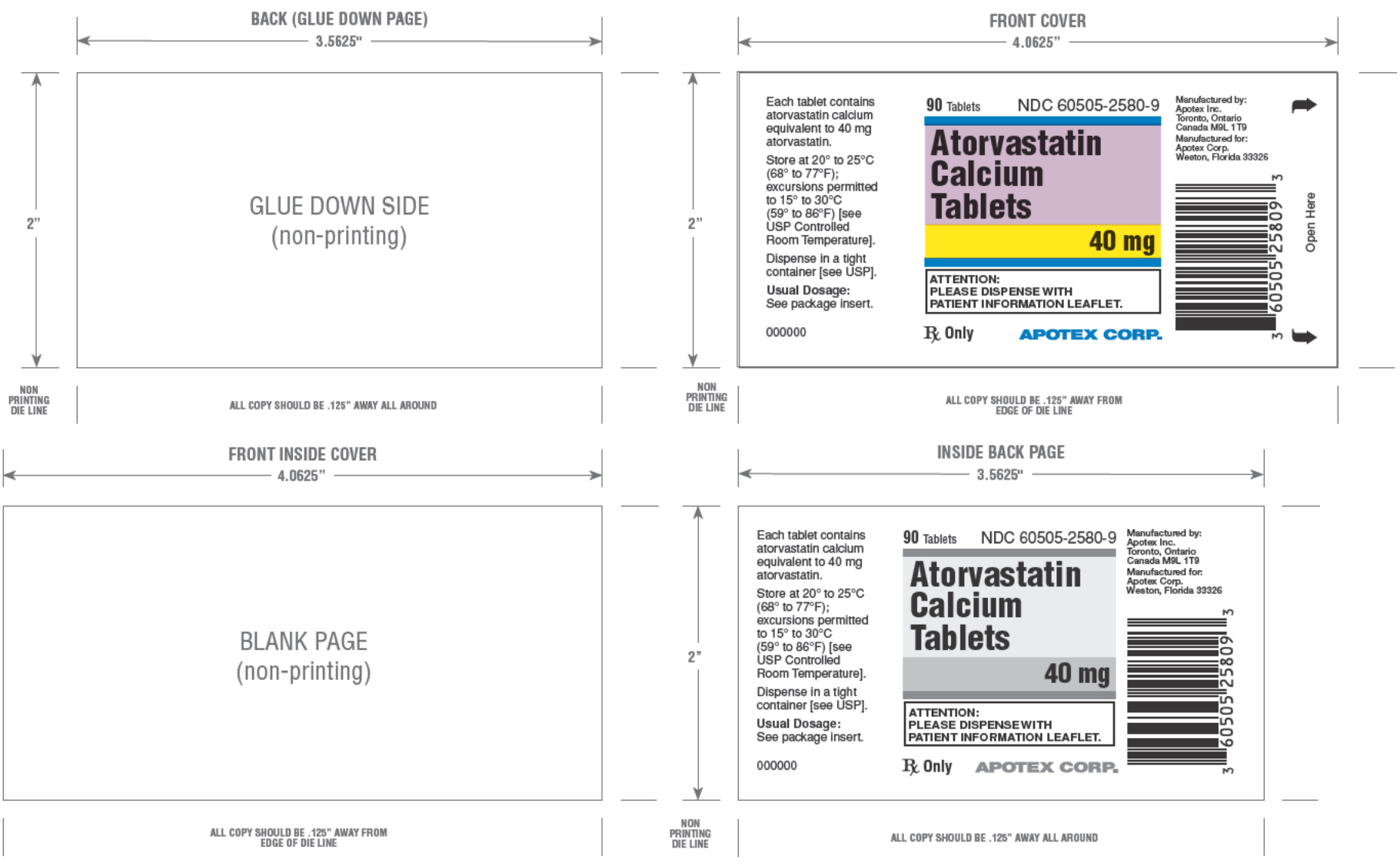


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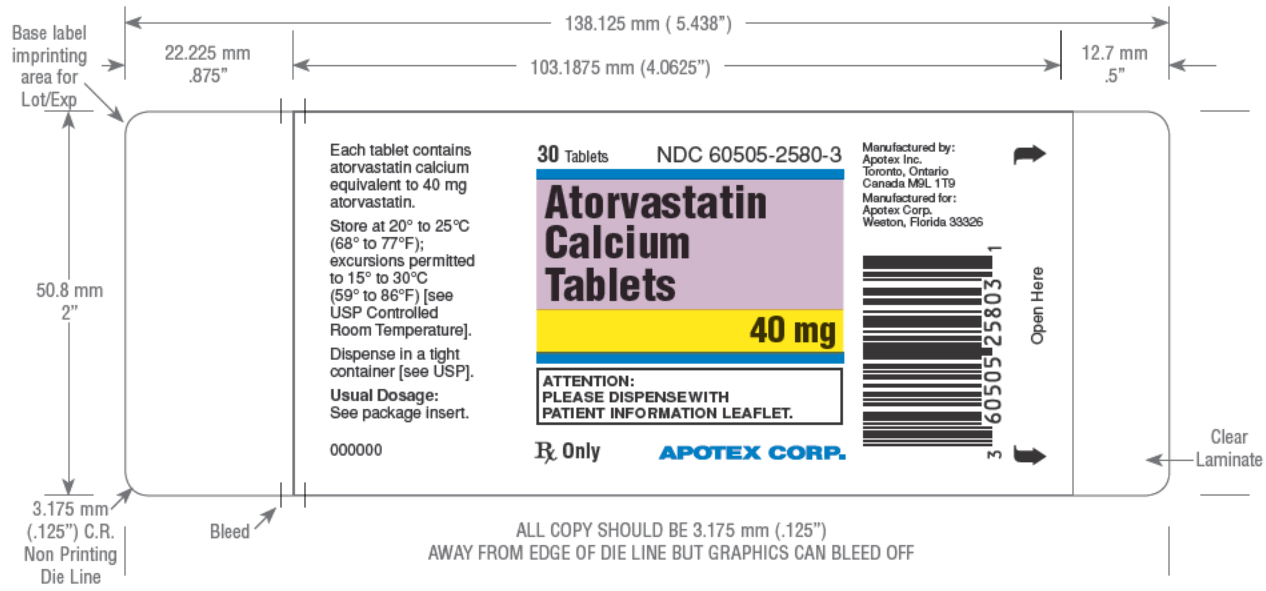
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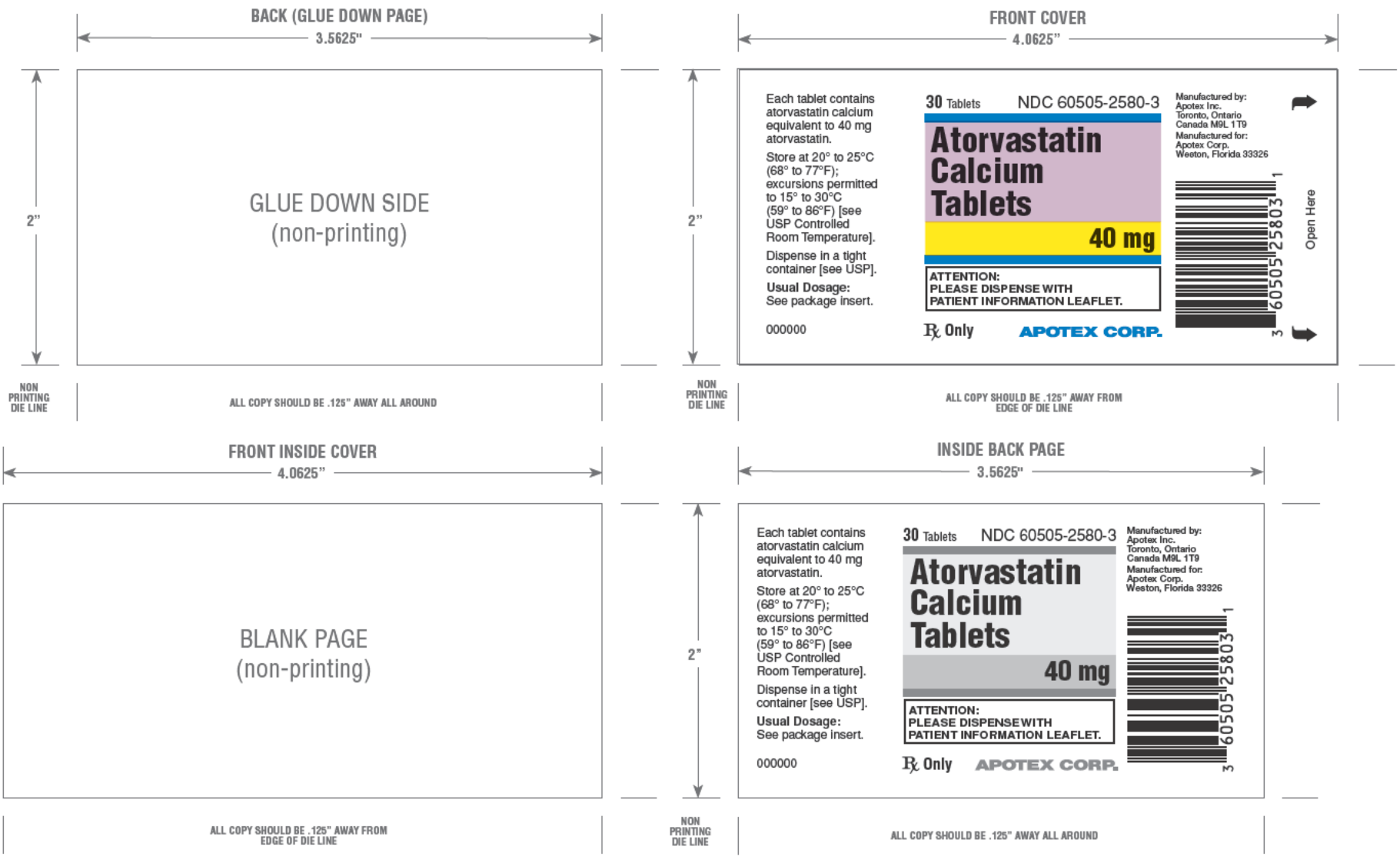
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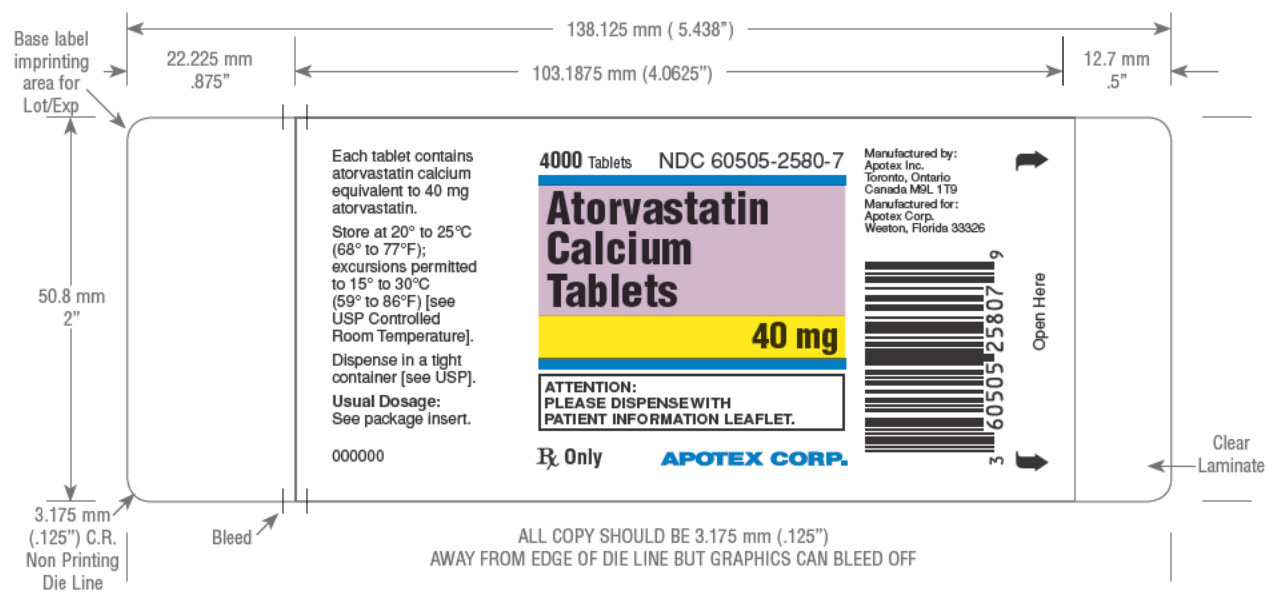


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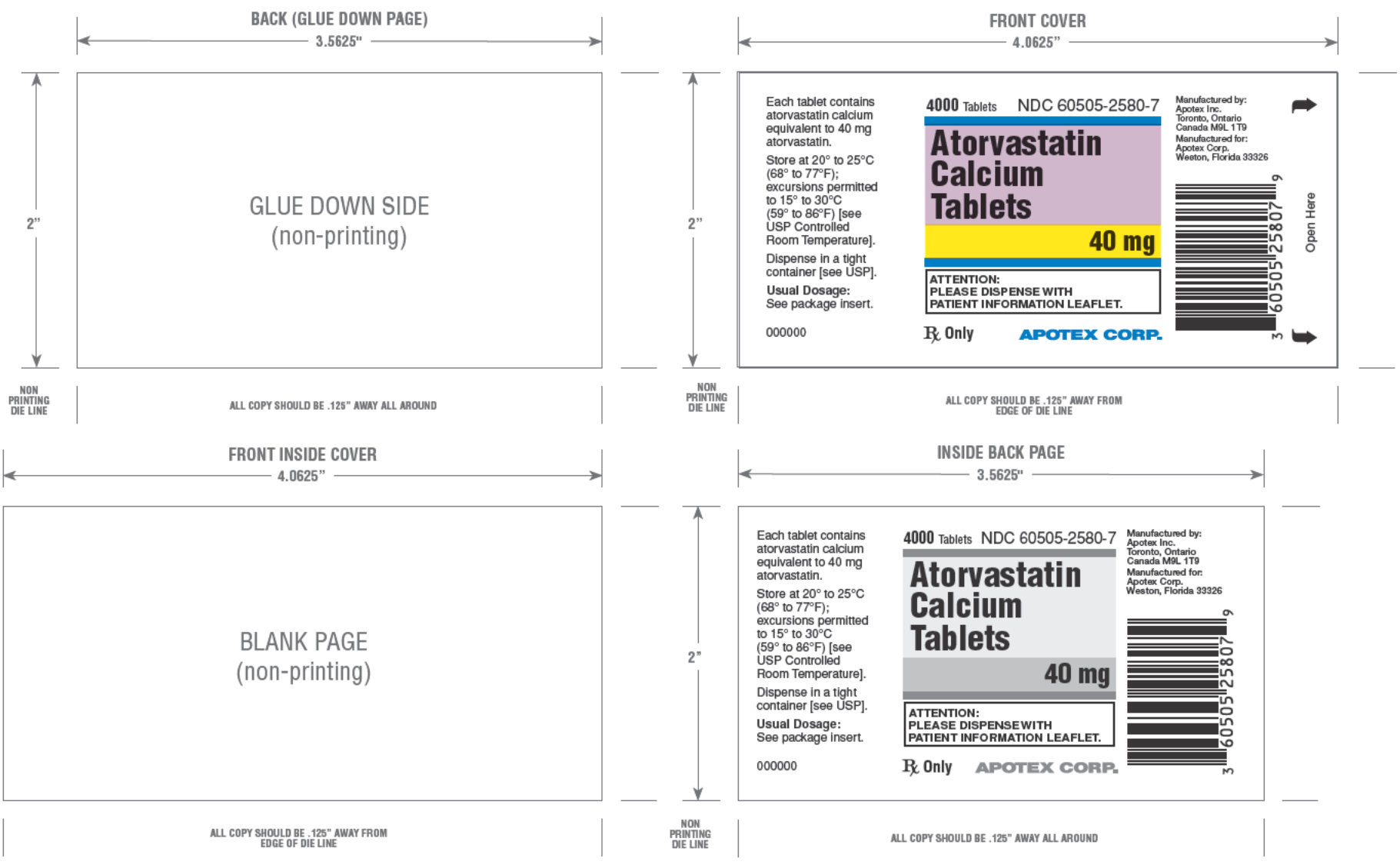
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COMPOSITE



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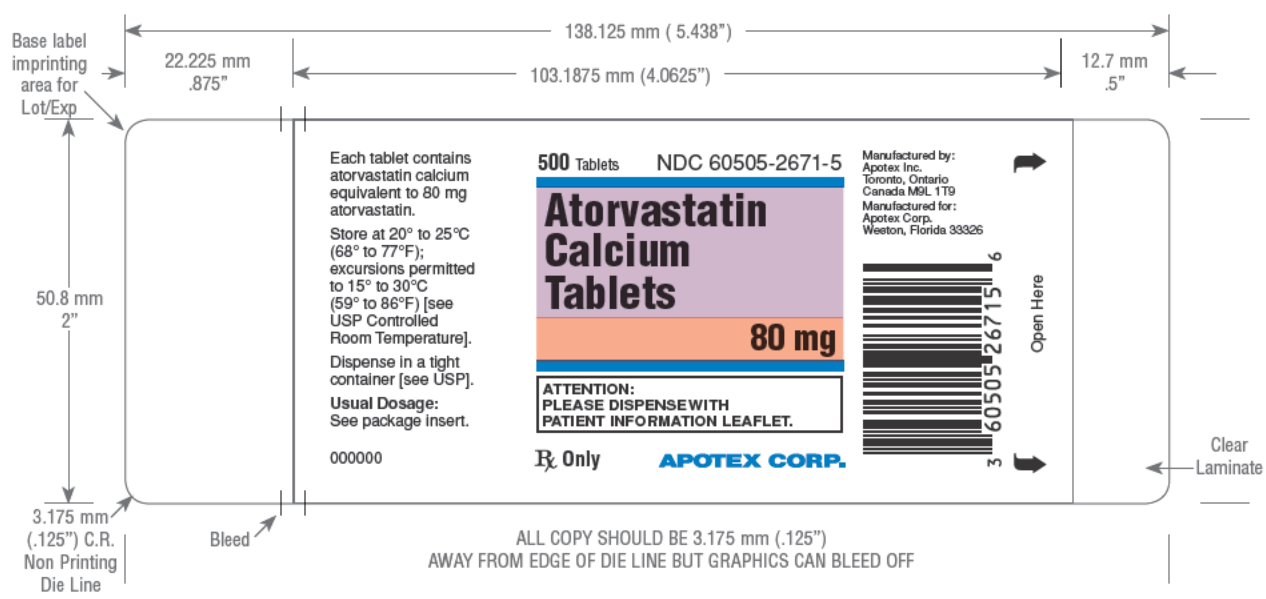
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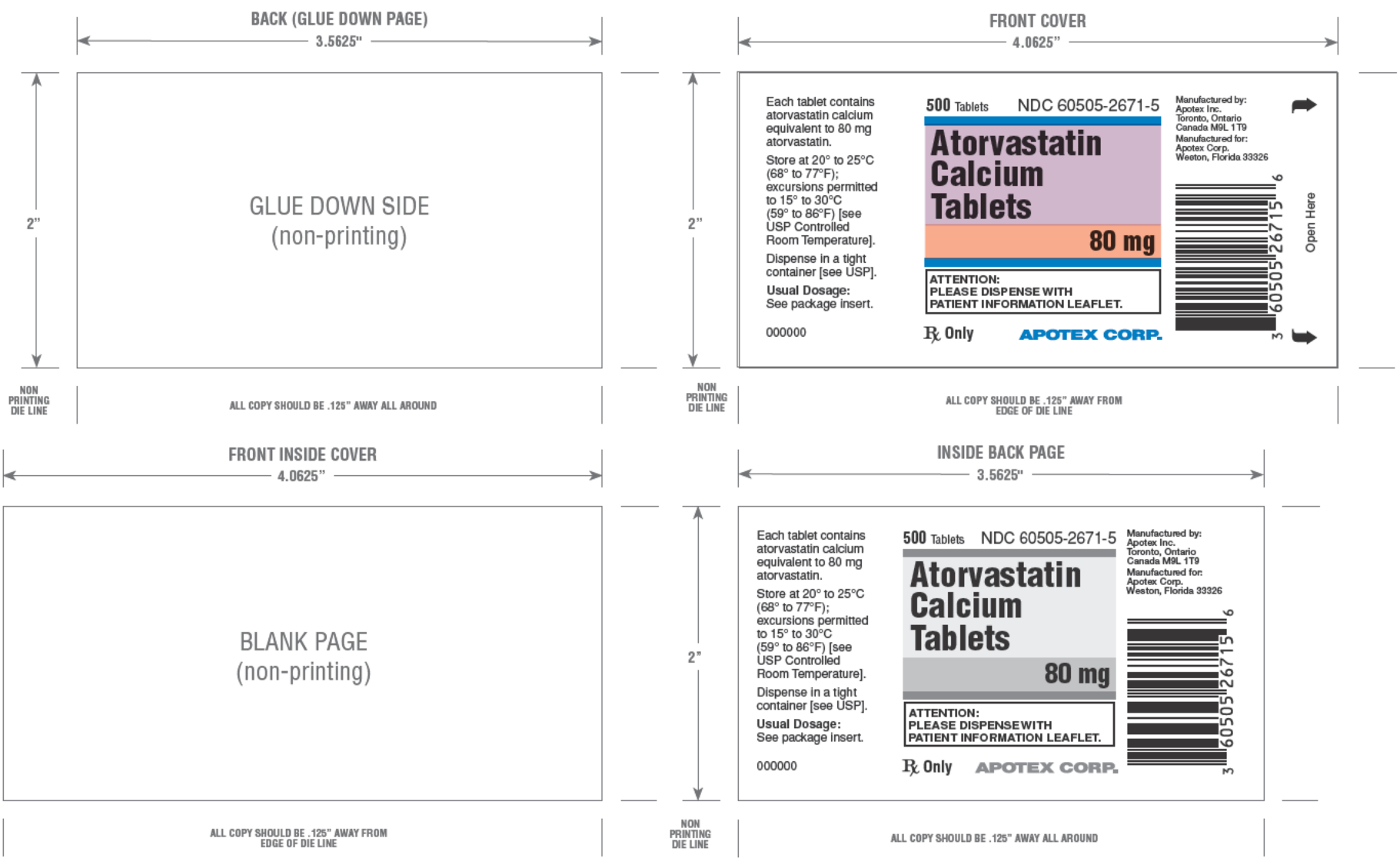
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COMPOSITE



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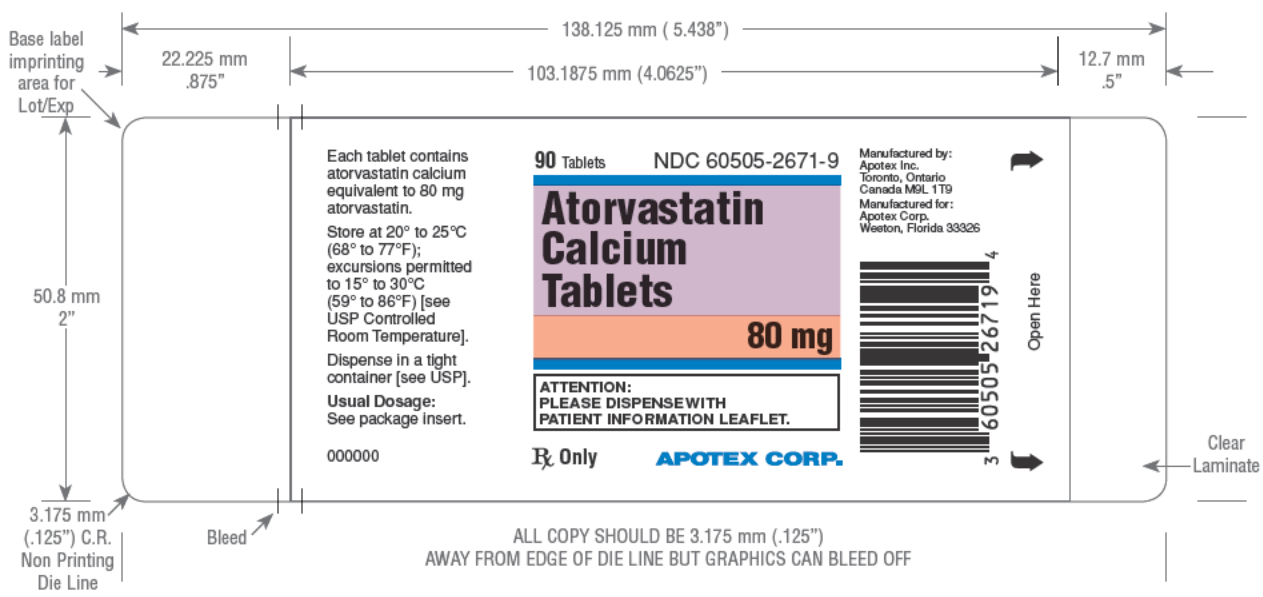
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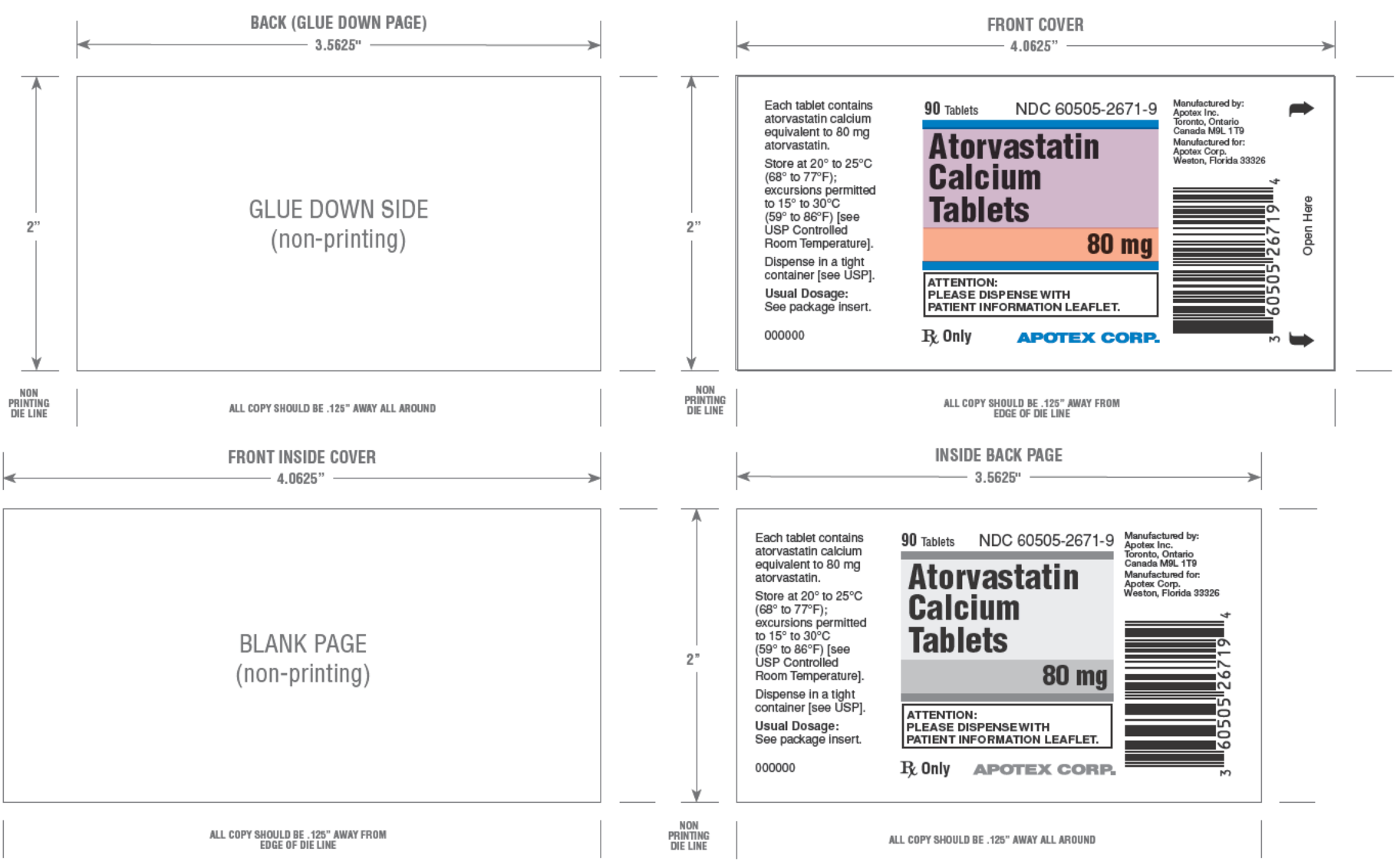
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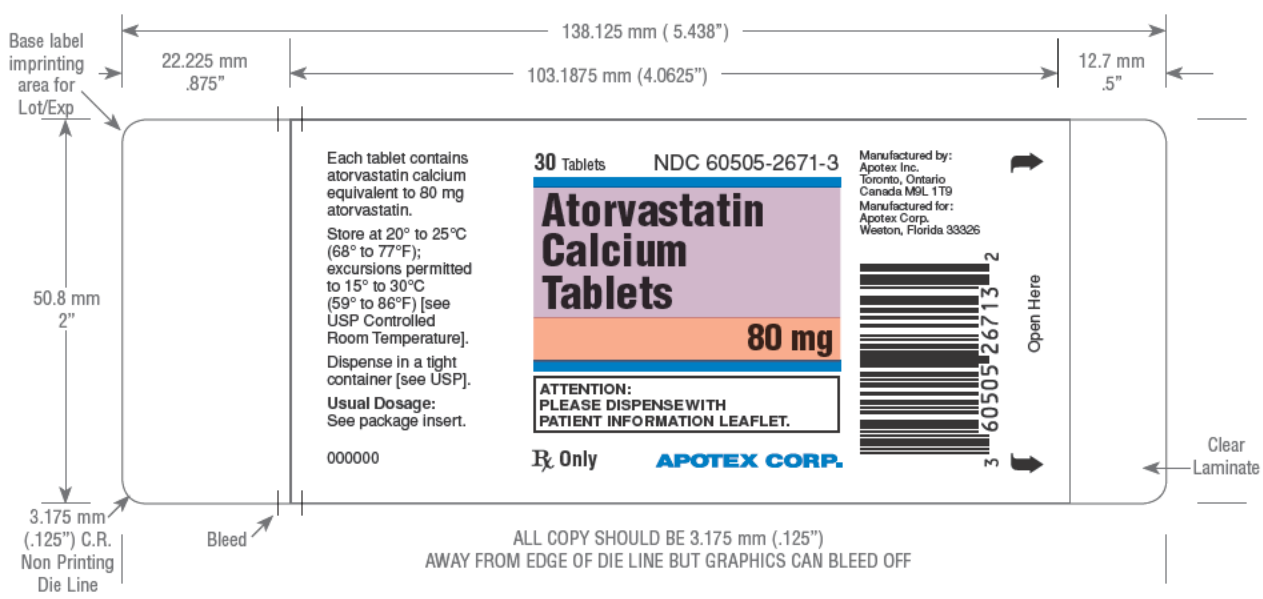
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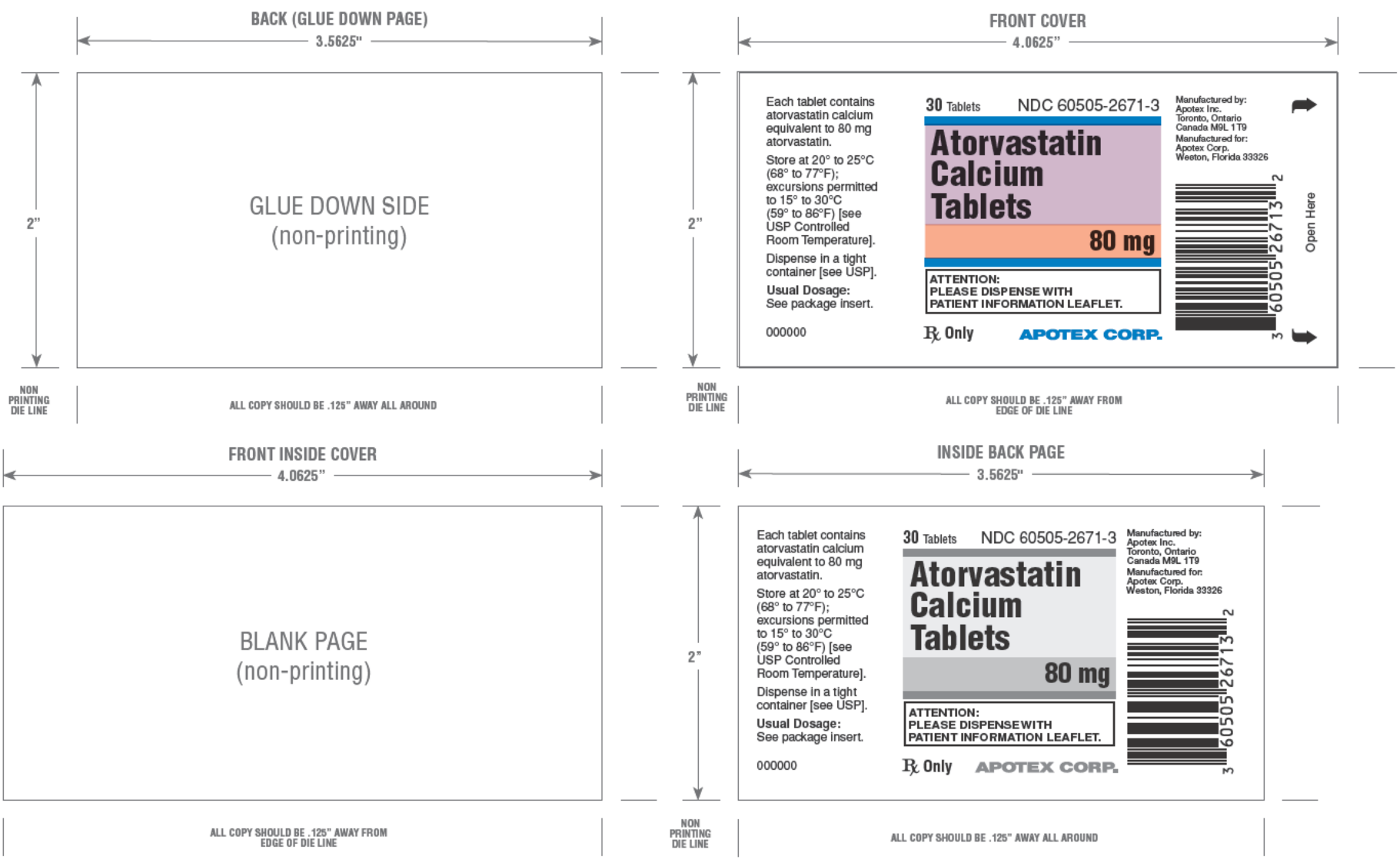
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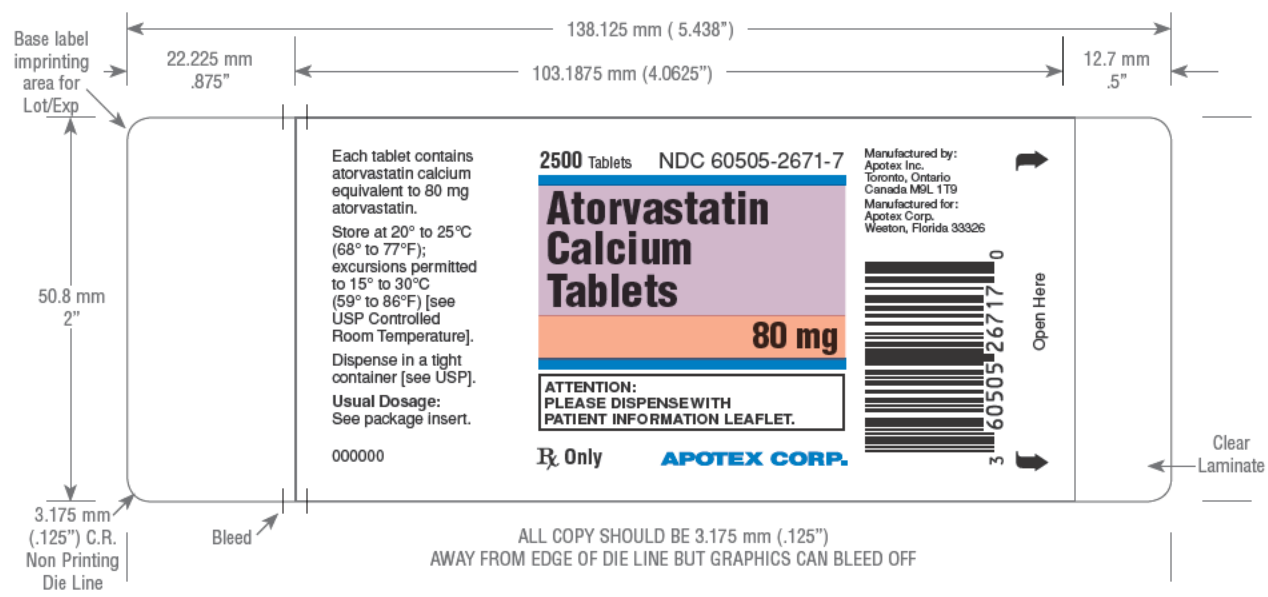
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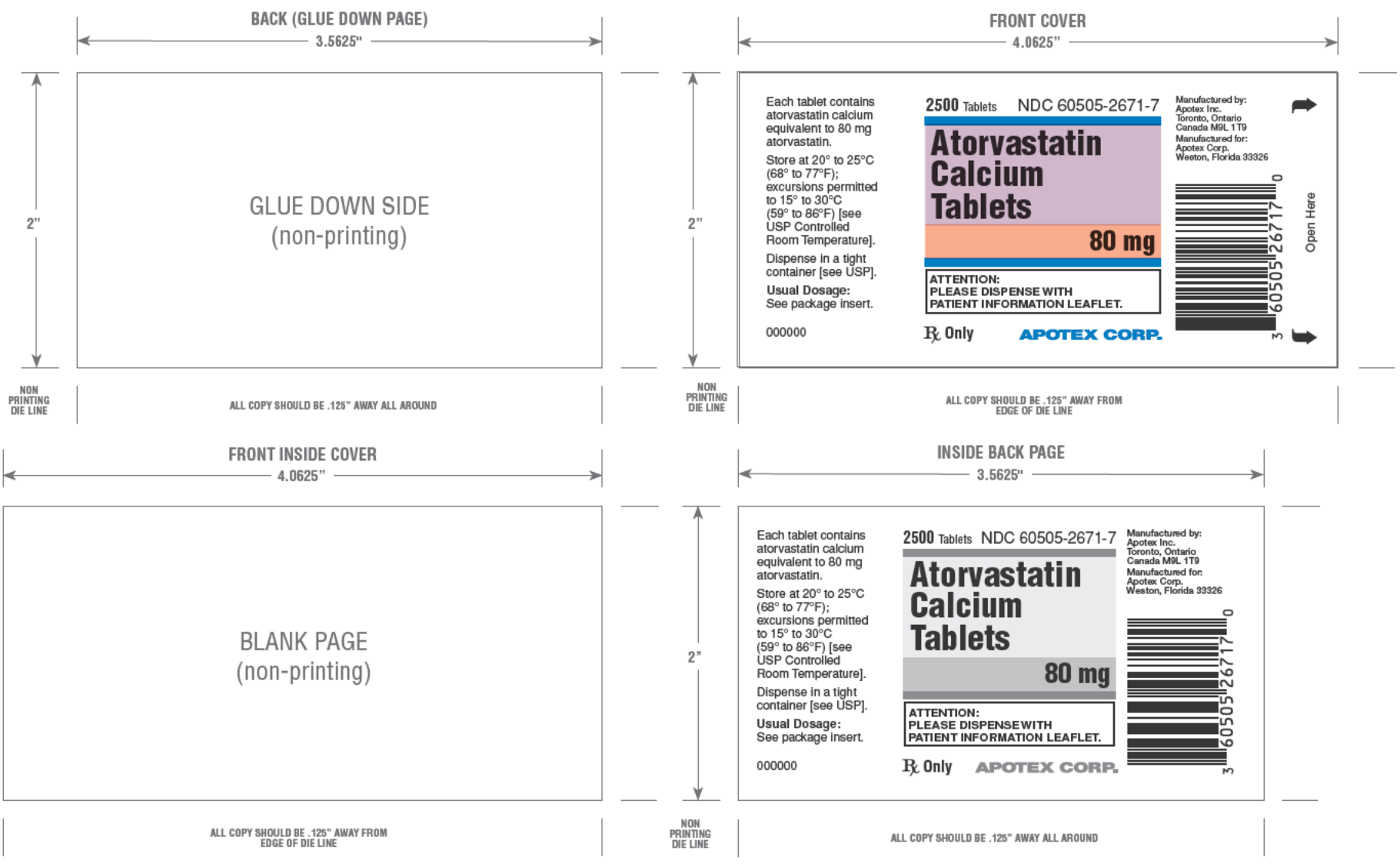
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COMPOSITE



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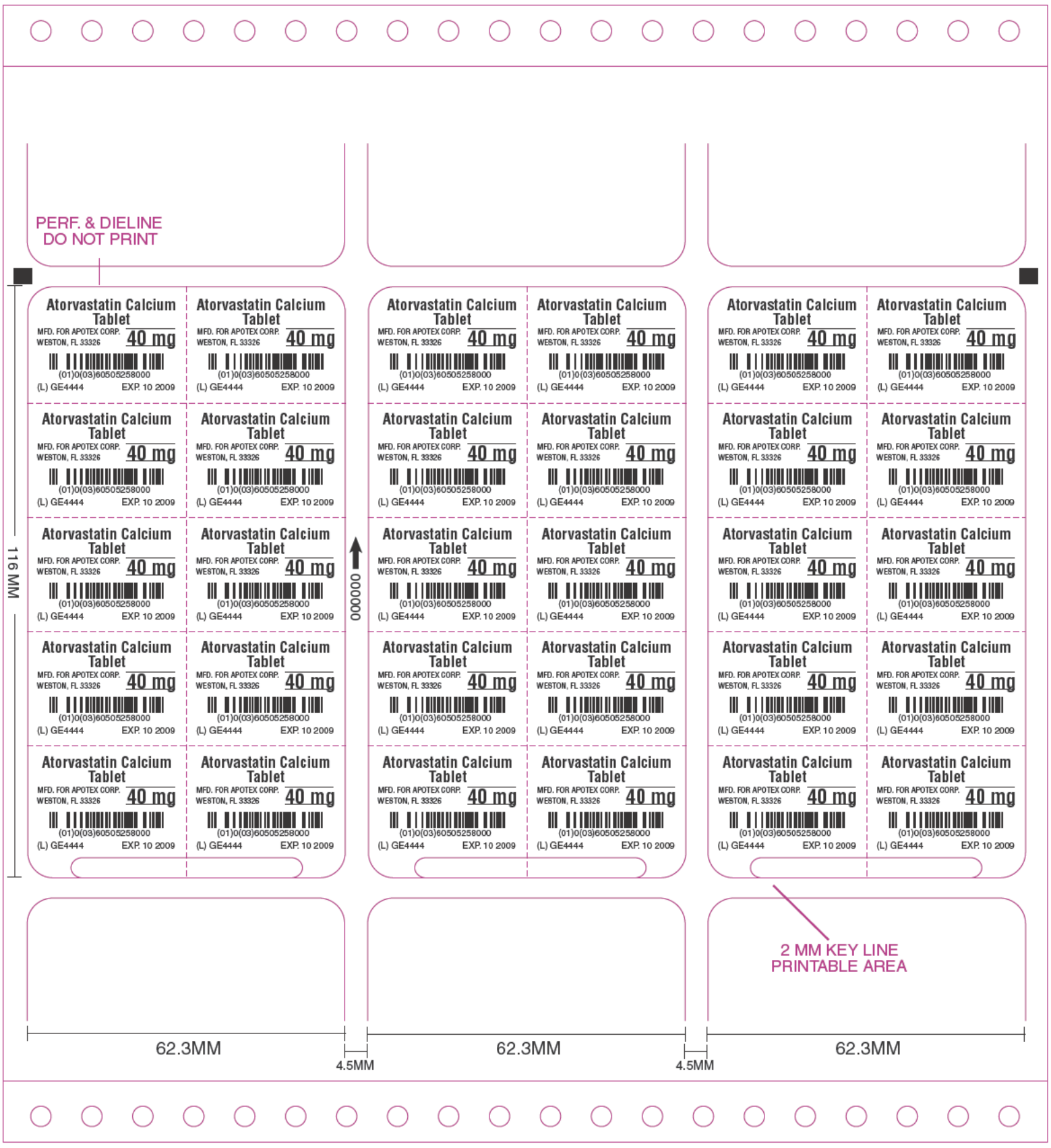


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APOTEX
ADVANCING GENERICS

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Reference ID: 3046267

APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER Copy of

(b) (4)

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PERF. & DIELINE
DO NOT PRINT

116 MM

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Atorvastatin Calcium Tablet
20 mg MFD. FOR APOTEX CORP. WESTON, FL 33326
(01)0(03)60505257904
(L) GE4444 EXP. 10 2009

2 MM KEY LINE
PRINTABLE AREA

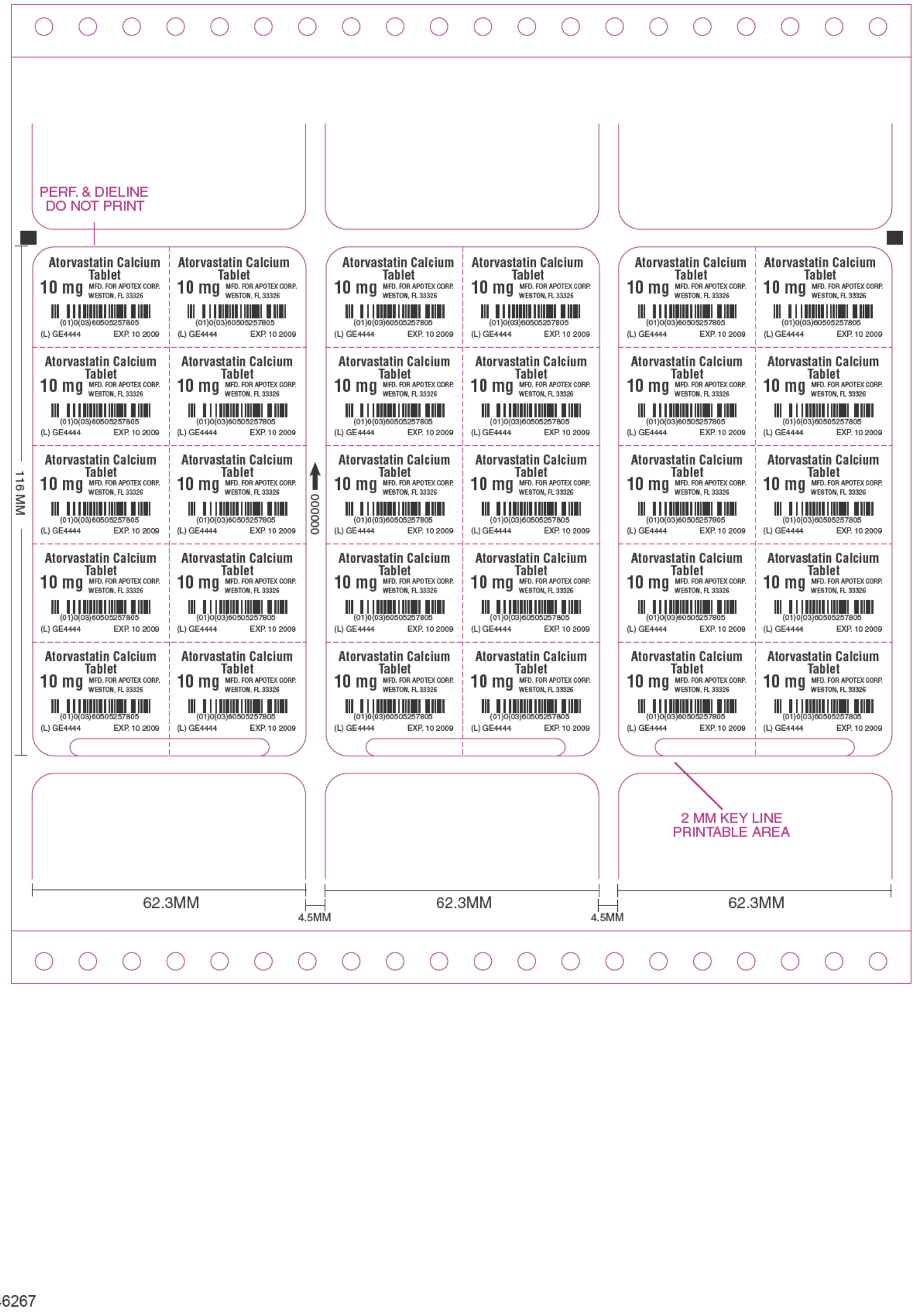
62.3MM 4.5MM 62.3MM 4.5MM 62.3MM

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(b) (4)

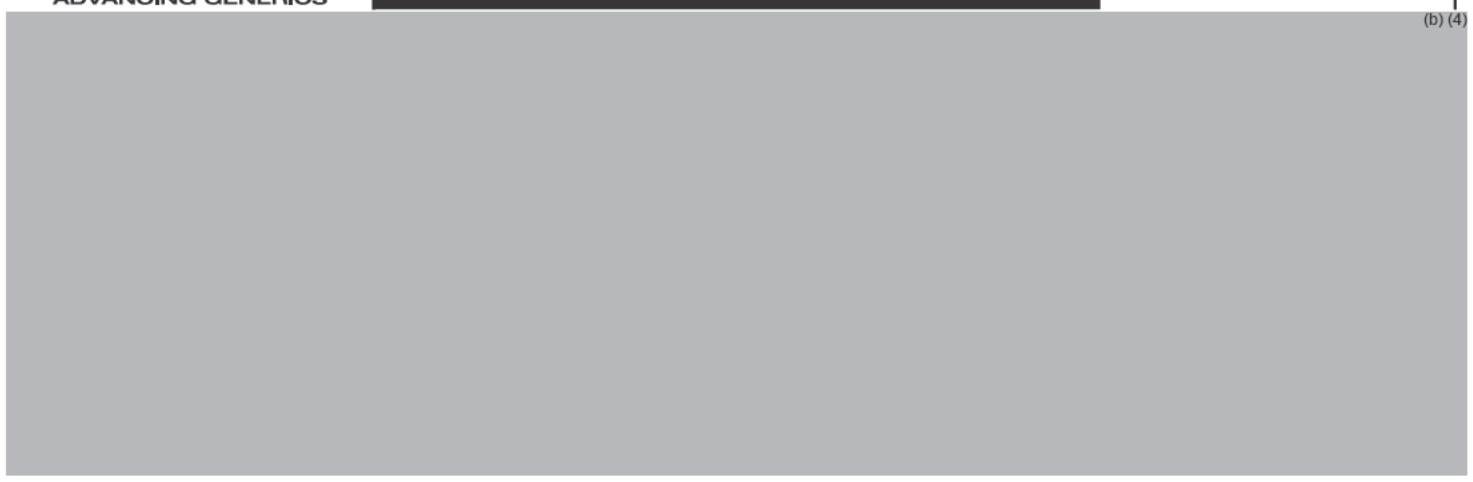


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APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER Copy of

(b) (4)



PERF. & DIELINE
DO NOT PRINT



2 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
11/18/2011

JOHN F GRACE
11/18/2011

****LABELING APPROVAL SUMMARY#2****
(Supercedes LBL AP SUM #1 dated 4/29/10)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90548 Date of Submission: August 18, 2011

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

---

BASIS OF APPROVAL:

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
80 mg= bottles of 30s, 90s, 500s, and 2500s):

Final print labels acceptable in 8/18/2011 e-submission.

Carton (10 x 10): Final print labels acceptable in 8/18/2011 e-submission.

Blister (Blister card of 10s): Final print labels acceptable in 5/20/09 e-submission.

Professional Package Insert Labeling: Final printed labeling acceptable in 2/26/2010 e-submission.

Patient Information Sheet: Final printed labeling acceptable in 2/26/2010 e-submission. Apotex submitted a print pad for the patient information.

Revisions needed before full approval: No, could revise the container and carton labels after full approval. However, if this application receives tentative approval because of patent issues, I will notify the firm of the comments below.

<u>CONTAINER and CARTON LABELS:</u>

Add an asterisk after the strength (e.g. 80 mg*) and before " * Each tablet contains atorvastatin..."

SPL

DLDE acceptable as of 8/18/2011 e-submission.

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-056; approved 6/17/09.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

As of August 30, 2011,

Chemistry has NOT decided if the propylene glycol solvate meets the DS definition in USP. There is an internal discussion within Chemistry. However, as of right now, the labeling and labels are acceptable because the DS is correctly stated as "atorvastatin calcium propylene glycol solvate". If Chemistry decided that the propylene glycol solvate form DOES NOT meet the definition in USP, then Apotex MUST revise their labels.

Email received on 3/4/09

As you might have known "atorvastatin" is (b) (4)
Thus, one can say "atorvastatin calcium equivalent to 10 mg atorvastatin" or (b) (4) of atorvastatin calcium equivalent to (b) (4)" and technically both are correct.
Thus, from technical perspective, the Apotex labeling is accurate.
However, it is your call if you want the Apotex to change the words similar to RLD.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Wednesday, March 04, 2009 8:56 AM

To: Vaithiyalingam, Sivakumar
Cc: Grace, John F
Subject: Atorvastatin 90-548 (Apotex's atorvastatin)

Siva,

I have a problem with the label of 90-548. Please take a look at the attached pdf file. Apotex's label states:

* Each tablet contains (b) (4) of atorvastatin calcium equivalent to (b) (4)

Lipitor's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

TEVA's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Is Apotex's label accurate? Could Apotex state this because their drug substance is atorvastatin calcium in the form of propylene glycol solvate instead of atorvastatin calcium in the hydrate form. I'm concerned because the label should be consistent between the generic and brand.

Thanks
Ann

Email received on 3/3/09:

Ann,

The RLD is a hydrate whereas the ANDA is a solvate with propylene glycol. Under our current guidance, these drug substances are considered equivalent.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Tuesday, March 03, 2009 1:56 PM
To: Vaithiyalingam, Sivakumar
Cc: Vu, Thuyanh (Ann)
Subject: 90-548 (Apotex's atorvastatin calcium)

The DS in Apotex's atorvastatin is different than the RLD's Lipitor and is this equivalent/acceptable? Thanks Ann

This is Apotex's atorvastatin:

The drug substance used in Atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{68}CaF_2N_4O_{10} * C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:

Lipitor's insert:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, ð-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, s-056; approved 6/17/09. Supplement provided for the PLR labeling format.

   Please see the email string with the chemist above. I asked the firm to revise the label to state ""Each tablet contains atorvastatin calcium equivalent to YY mg atovastatin" to be consistent with the RLD and other generic manufacturers even though Apotex is technically/chemically correct.

   8/18/2011 AF: Apotex changed the labels. See Chemist Notes above for further information about the solvate form.

   In this amendment, the carton and container labels have been revised to specifically indicate Atorvastatin Calcium Propylene Glycol Solvate as the drug substance. The statement on the container and carton labels has been revised from:

   Each tablet contains atorvastatin calcium equivalent to X mg atorvastatin.
   to:

   Each tablet contains atorvastatin calcium propylene glycol solvate equivalent to X mg of atorvastatin.
   (where X mg is either 10 mg, 20 mg, 40 mg or 80 mg)

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	PIII	Same As
5273995	Dec 28, 2010 ped jun 28, 20011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA	IV	Same As

			AND METHOD FOR TREATING HYPERLIPIDEMIA		
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011* PED	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As, certified in 3/19/09 labeling amendment

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None
I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:calcium acetate, croscramellose sodium, sodium carbonate (b) (4) microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose (b) (4), polyethylene glyco (b) (4), titanium dioxide,

[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.1-original submission]

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T 9 Canada

5. CONTAINER/CLOSURE

- HDPE bottles containing 30 or 90 tablets closed with [redacted] screw caps with a [redacted] desiccant. When originally packed, the bottles are also sealed with a [redacted].

- HDPE bottles containing 500 tablets or greater closed with [redacted] screw caps with a [redacted] desiccant. When originally packed, the bottles are also sealed with a [redacted].

- Blister packs comprised of [redacted] and a [redacted]. Packed in cartons containing 10 strips of 10 tablets (100 tablets total).

6. FINISHED DOSAGE FORM

RLD:

10 mg: coded "PD 155" on one side and "10" on the other

20 mg: coded "PD 156" on one side and "20" on the other

40 mg: coded "PD 157" on one side and "40" on the other

80 mg: coded "PD 158" on one side and "80" on the other

ANDA:

10 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "A10" on the other side.

20 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "ATV20" on the other side.

40 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "ATV40" on the other side.

80 mg: white, oval, biconvex film-coated tablets. Engraved "APO" on one side, "ATV80" on the other side.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: DS is compendial ONLY
RLD: store at CRT 20-25°C (68-77°F) [see USP].
ANDA label: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [See USP Controlled Room Temperature]

8. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight container (see USP).

The carton states: "This unit-dose package is not child-resistant"

9. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the propolyne glycol solvate form rather than the trihydrate

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

RLD: 10 mg, 20 mg = bottles of 90s, 5000s and blisters of 100 (10 x 10) unit dose blisters
40 mg: bottles of 90s, 500s, 2500s and blisters of 100 (10 x 10) unit dose blisters
80 mg: bottles of 90s, 500s, 2500s and blisters of 64 (8 x 8) unit dose blisters

ANDA: 10 mg, 20 mg = bottles of 30s, 90s, 1000s, 5000s and blisters of 100 (20 mg= violet color, 10 mg= green color)
40 mg= bottles of 30s, 90s, 500s, 1000s, 4000s and blisters of 100 (container color= yellow)
80 mg= bottles of 30s, 90s, , 500s, 2500 and blisters of 100 (container color= red)

Date of Review: August 30, 2011 Date of Submission: August 18, 2011

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

32 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
08/30/2011

JOHN F GRACE
08/30/2011

LABELING APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-548 Date of Submission: February 26, 2010

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

---

BASIS OF APPROVAL:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
80 mg= bottles of 30s, 90s, 500s, and 2500s):

Final print labels acceptable in 2/26/2010 e-submission.

Carton (10 x 10): Final print labels acceptable in 2/26/10 e-submission.

Blister (Blister card of 10s): Final print labels acceptable in 5/20/09 e-submission.

Professional Package Insert Labeling: Final printed labeling acceptable in 2/26/2010 e-submission.

Patient Information Sheet: Final printed labeling acceptable in 2/26/2010 e-submission. Apotex submitted a print pad for the patient information.

Revisions needed before full approval: No, could revise the container and carton labels after full approval. However, if this application receives tentative approval because of patent issues, I will notify the firm of the comments below.

<u>CONTAINER and CARTON LABELS:</u>

Add an asterisk after the strength (e.g. 80 mg*) and before " * Each tablet contains atorvastatin..."

<u>SPL</u>

Unable to open the SPL file submitted in the 2/26/2010 e-submission. Need to send a SPL file with next labeling amendment.

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-056; approved 6/17/09.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

E

mail received on 3/4/09

As you might have known "atorvastatin" is (b) (4)
Thus, one can say "atorvastatin calcium equivalent to 10 mg atorvastatin" or (b) (4) of atorvastatin calcium equivalent to (b) (4)" and technically both are correct.
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Exclusivity Data For NDA 20702			
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I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None

I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[original submission]

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The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:calcium acetate, croscramellose sodium, sodium carbonate [(b) (4)], microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose [(b) (4)], polyethylene glycol [(b) (4)], titanium dioxide,

[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.1-original submission]

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T 9 Canada

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- HDPE bottles containing 30 or 90 tablets closed with [(b) (4)] screw caps with a [(b) (4)] desiccant. When originally packed, the bottles are also sealed with a [(b) (4)].
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7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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RLD: store at CRT 20-25°C (68-77°F) [see USP].
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The carton states: “This unit-dose package is not child-resistant”

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RLD: Not scored
ANDA: Not scored

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RLD: 10 mg, 20 mg = bottles of 90s, 5000s and blisters of 100 (10 x 10) unit dose blisters
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40 mg= bottles of 30s, 90s, 500s, 1000s, 4000s and blisters of 100 (container color= yellow)
80 mg= bottles of 30s, 90s, , 500s, 2500 and blisters of 100 (container color= red)

Date of Review: April 27, 2010 Date of Submission: February 26, 2010

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

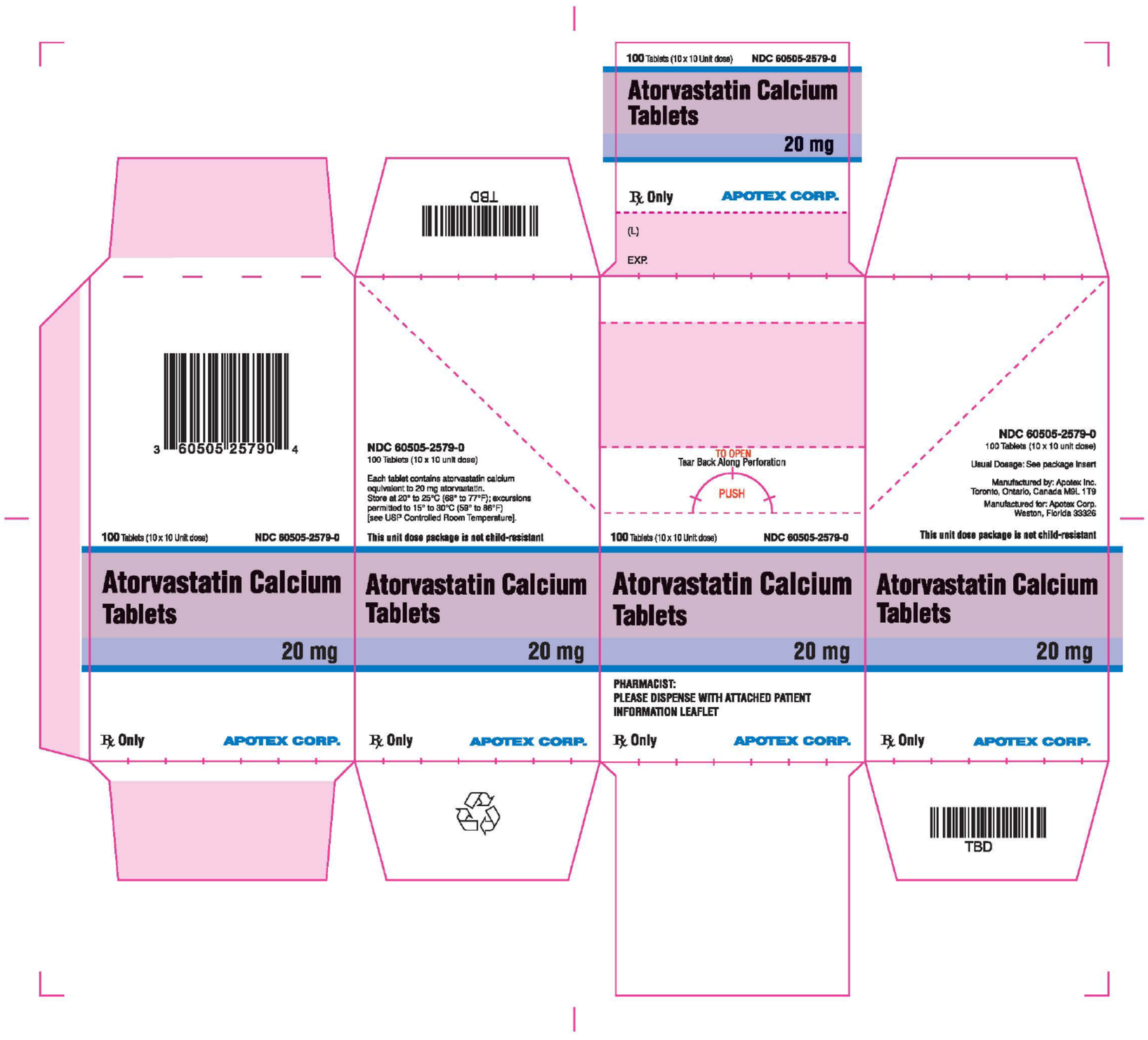
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APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

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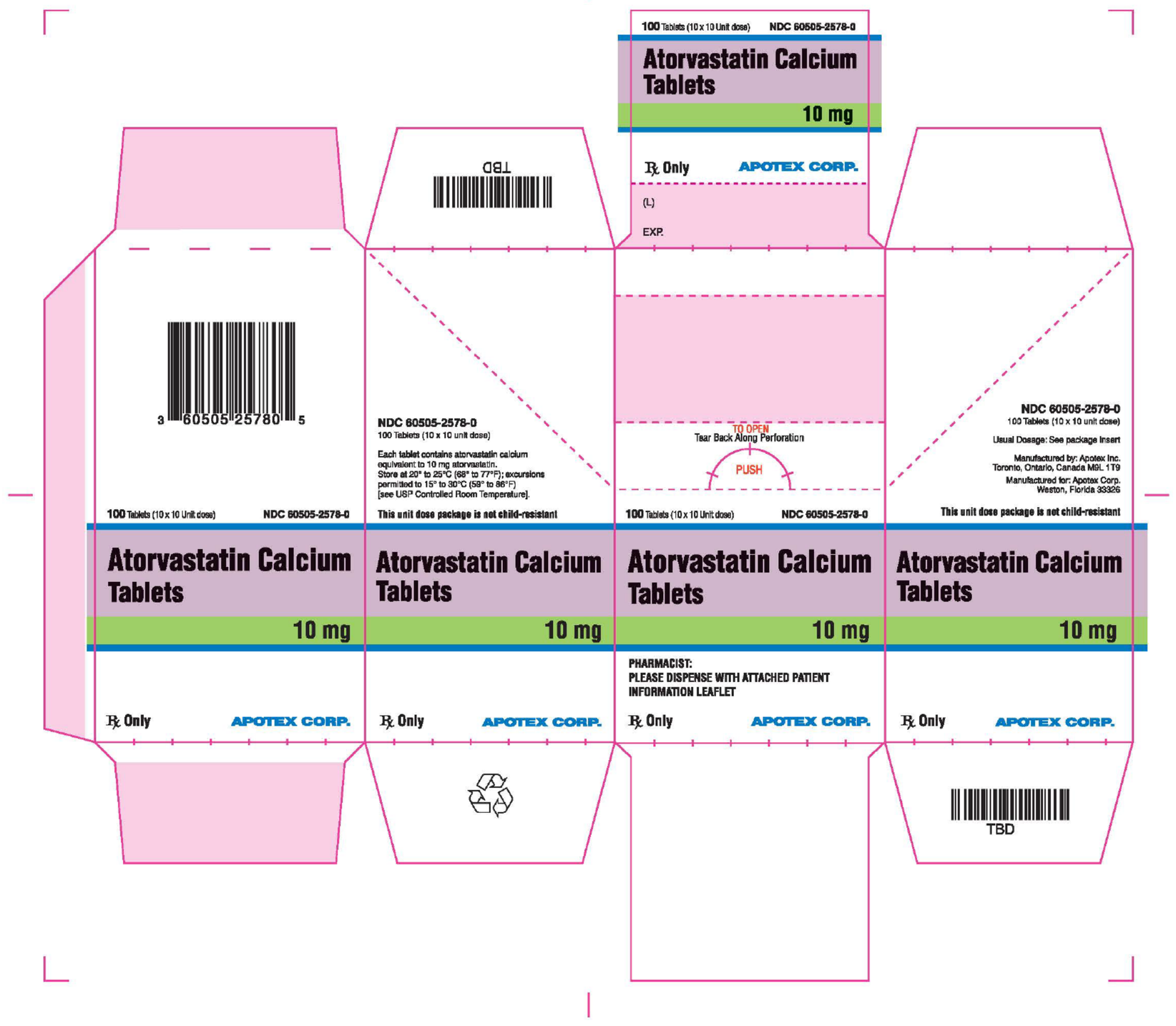


APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

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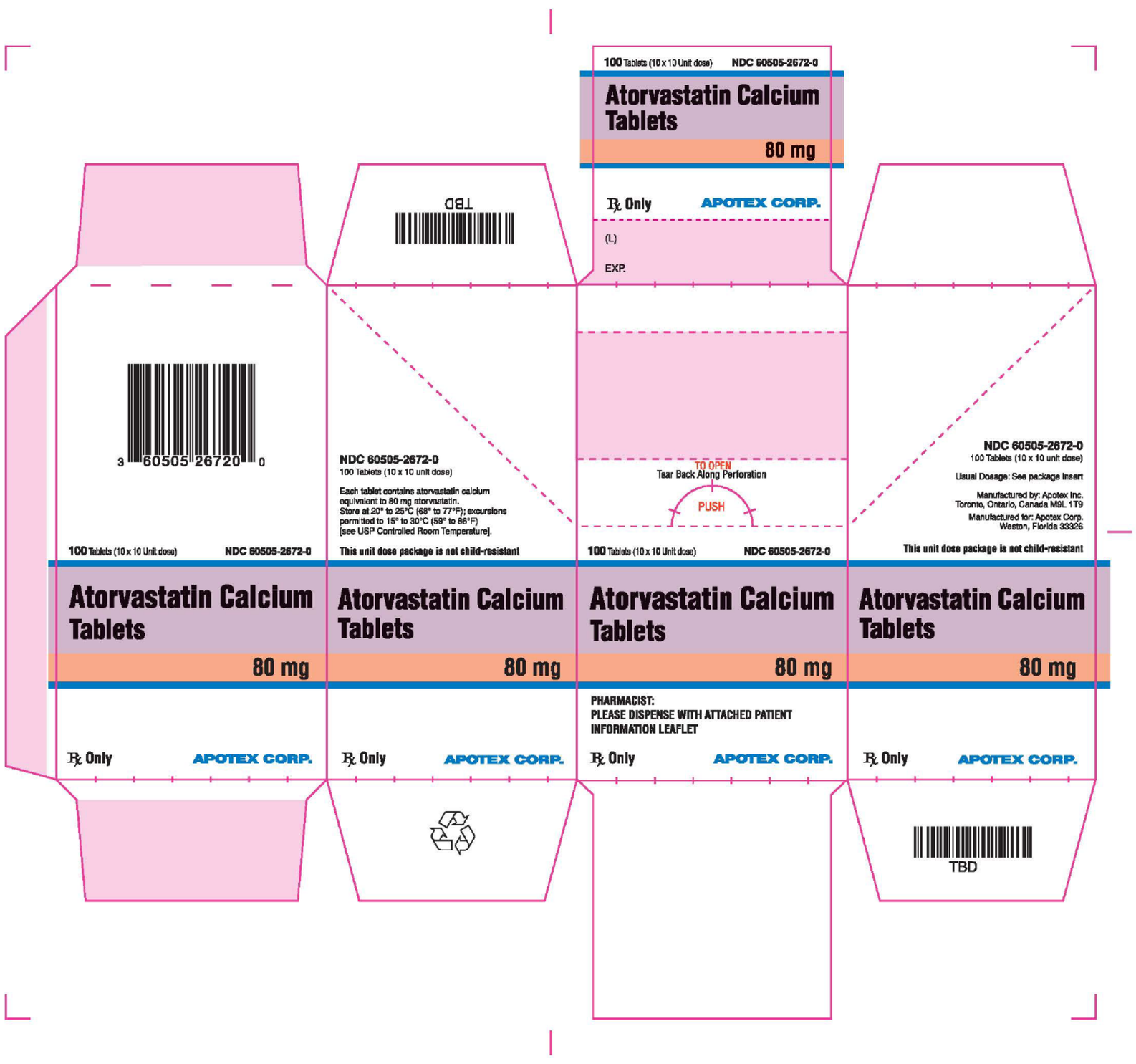


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ADVANCING GENERICS

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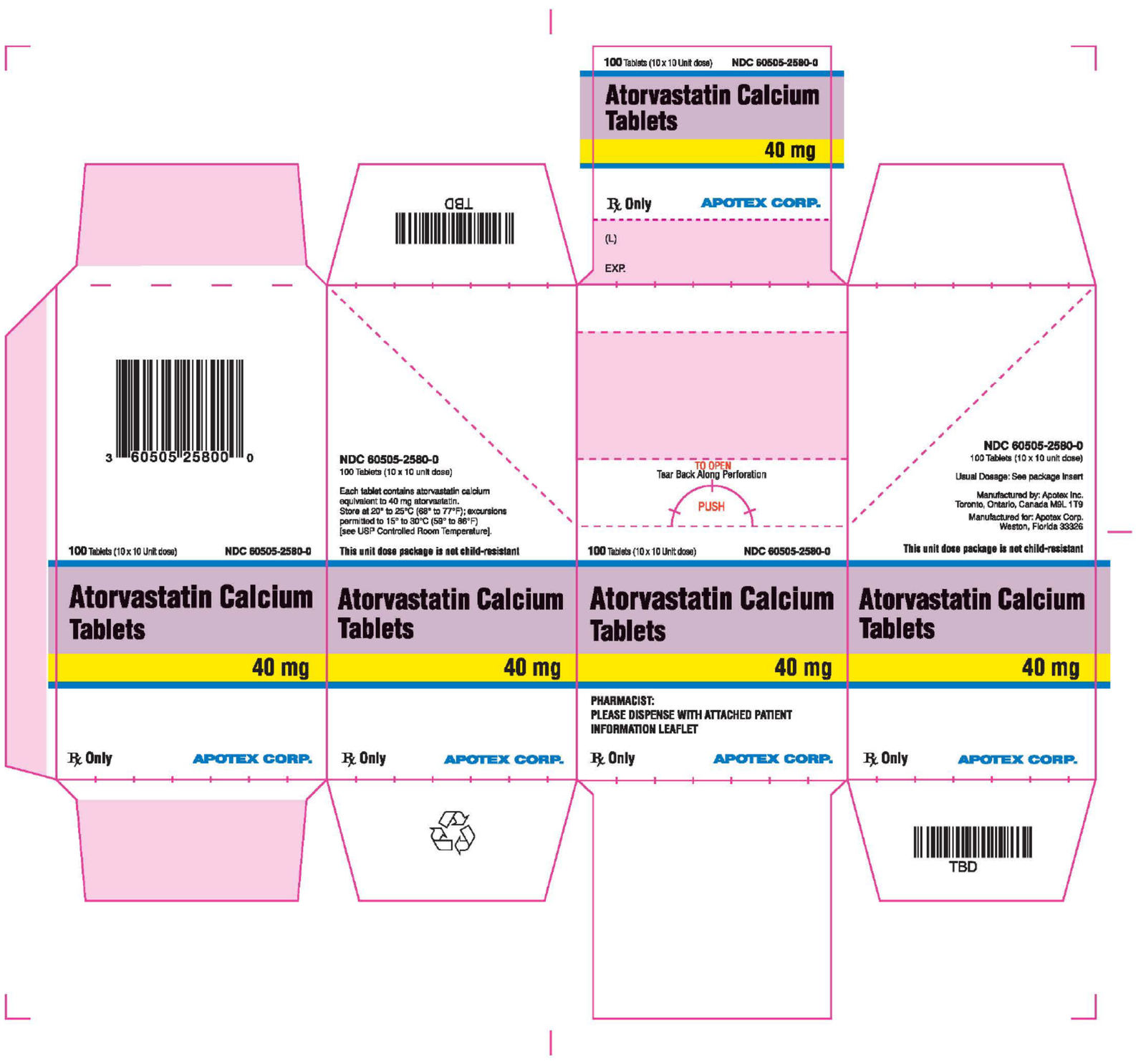


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ADVANCING GENERICS

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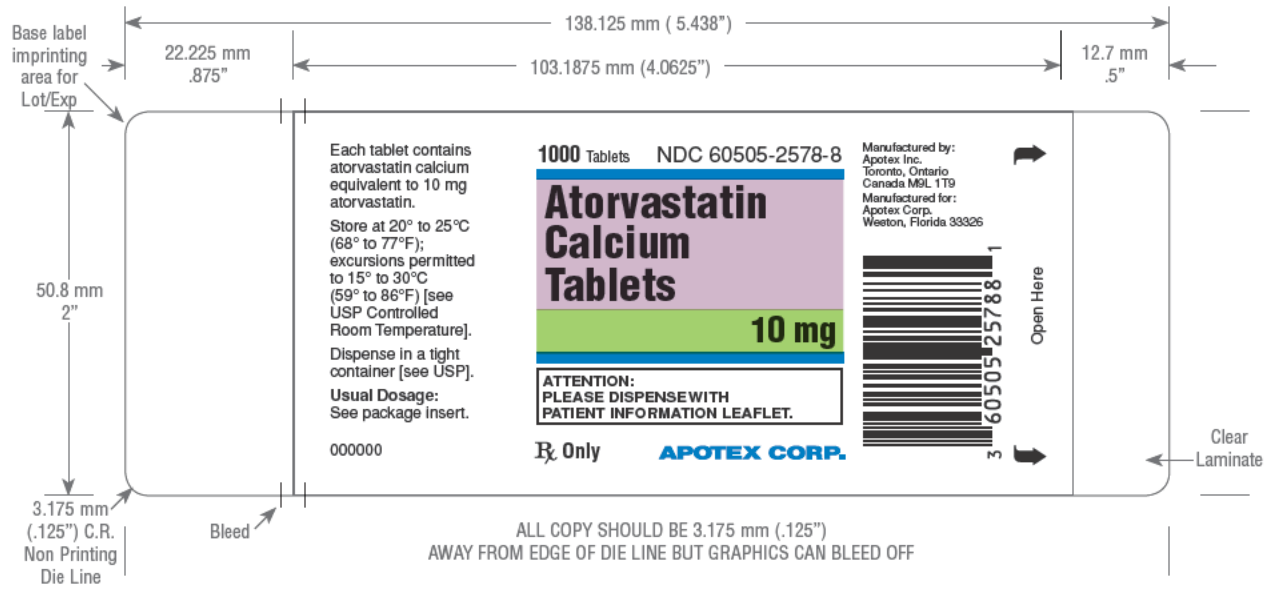
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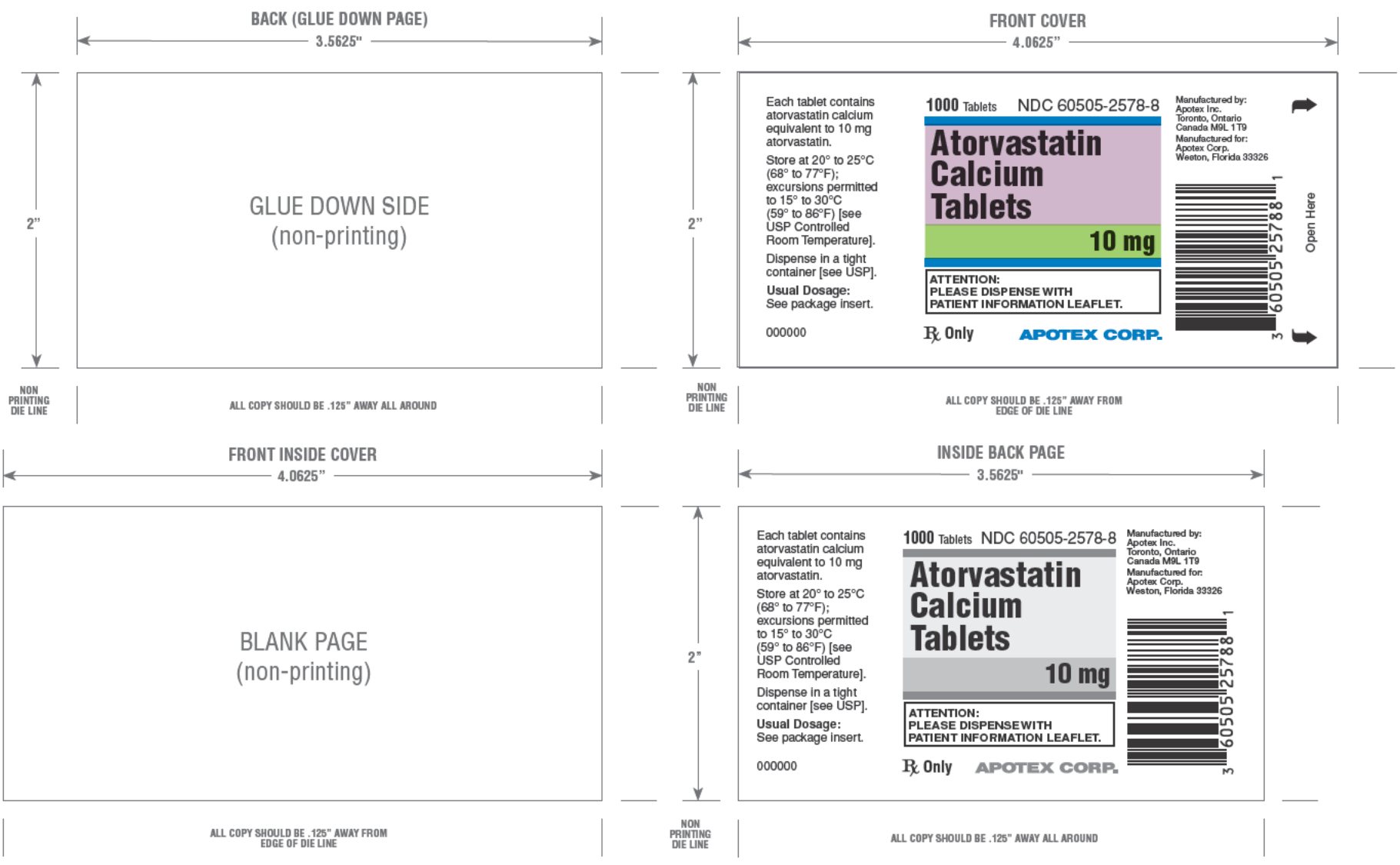
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COMPOSITE



COVER



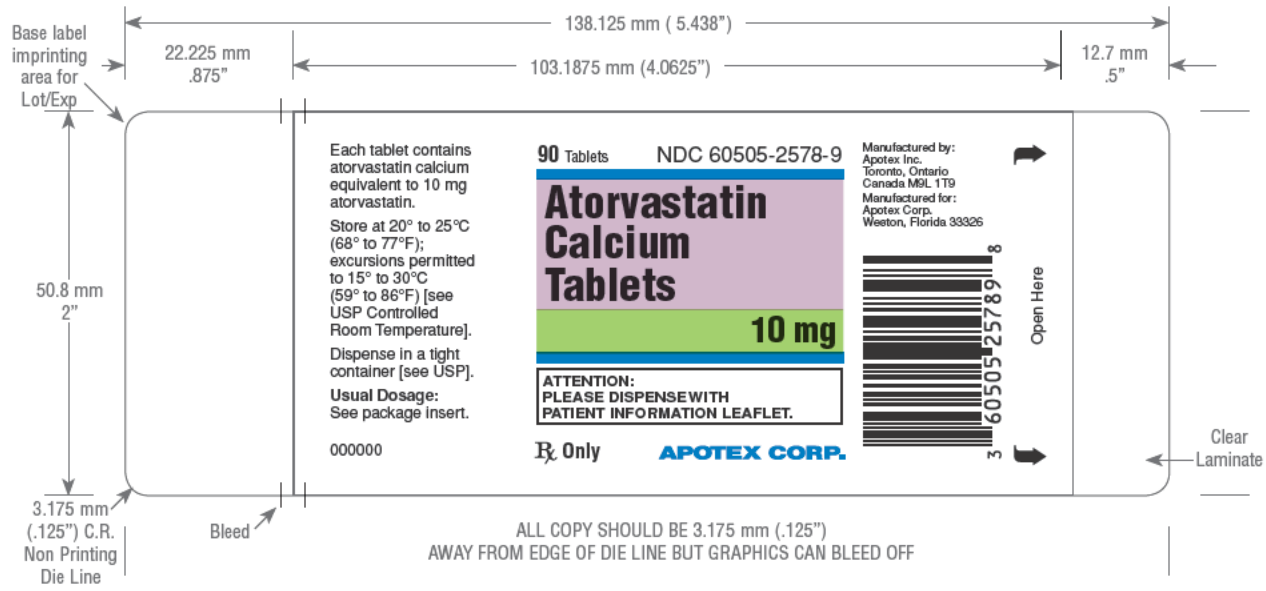
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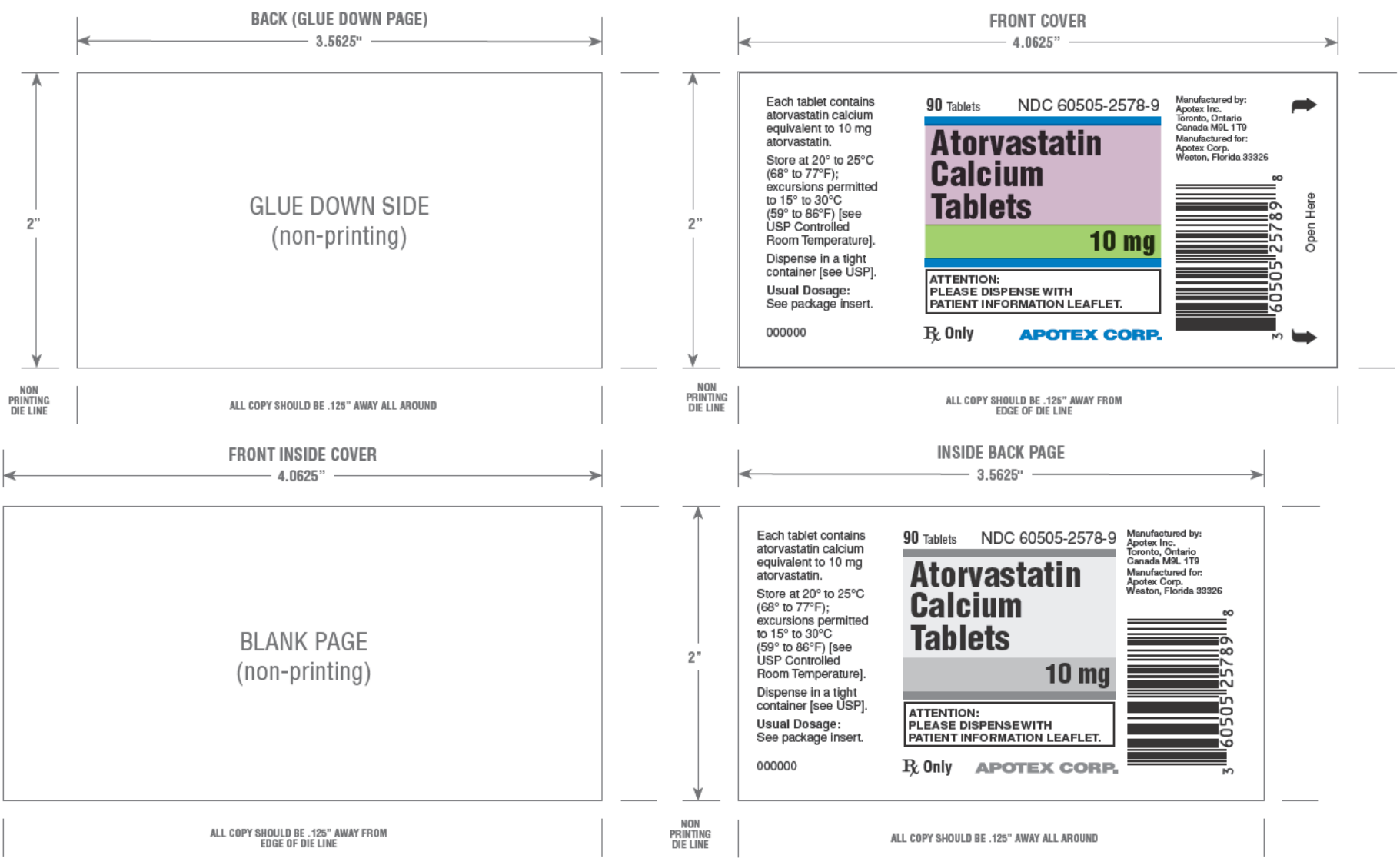
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COMPOSITE



COVER



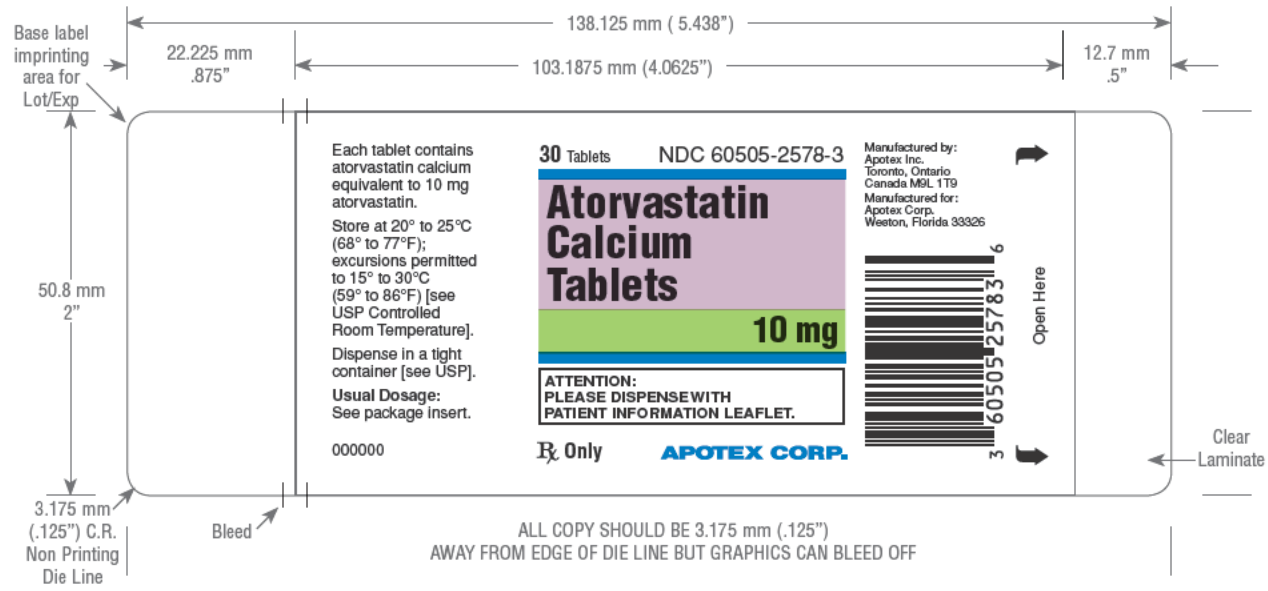
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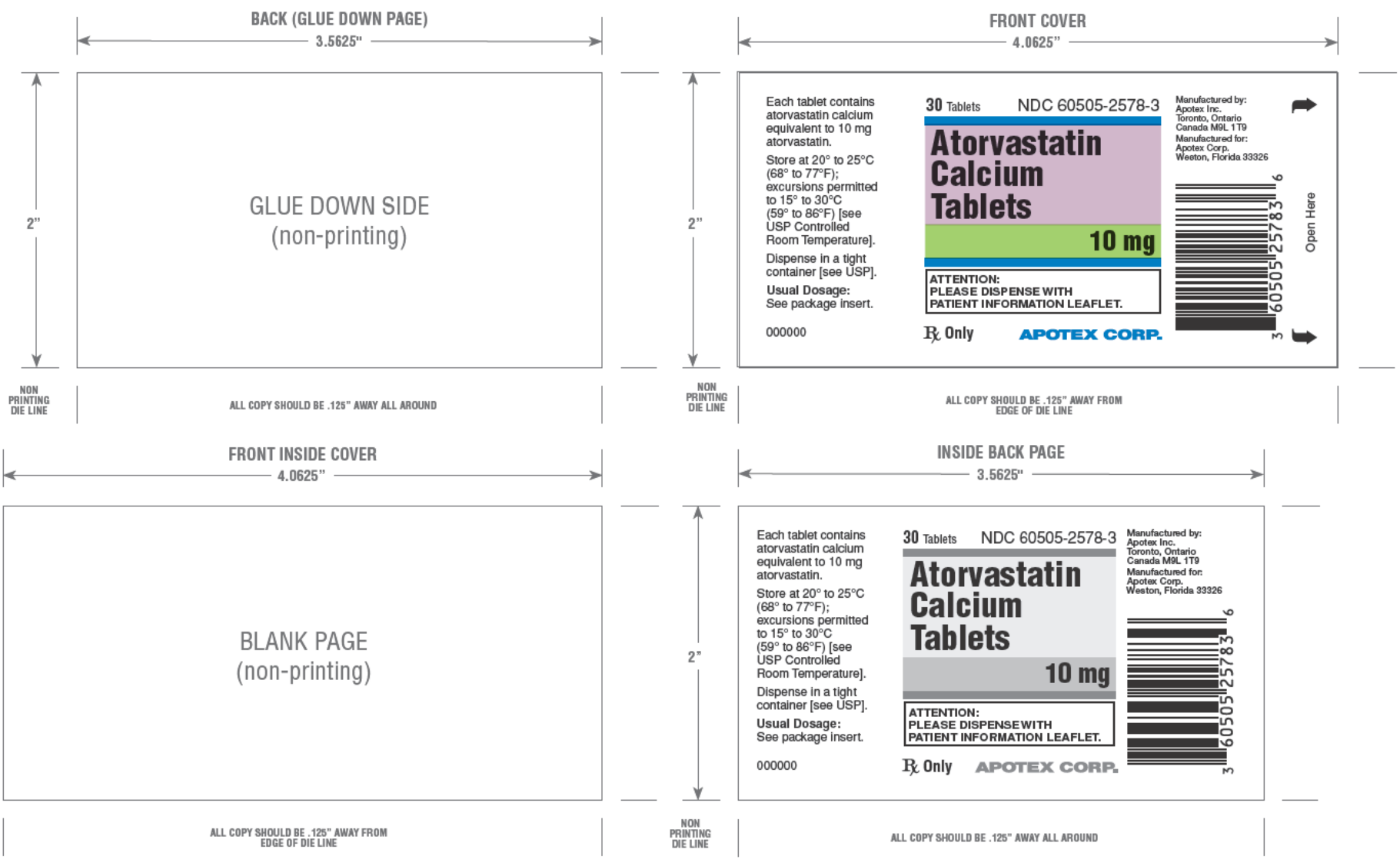
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COMPOSITE



COVER



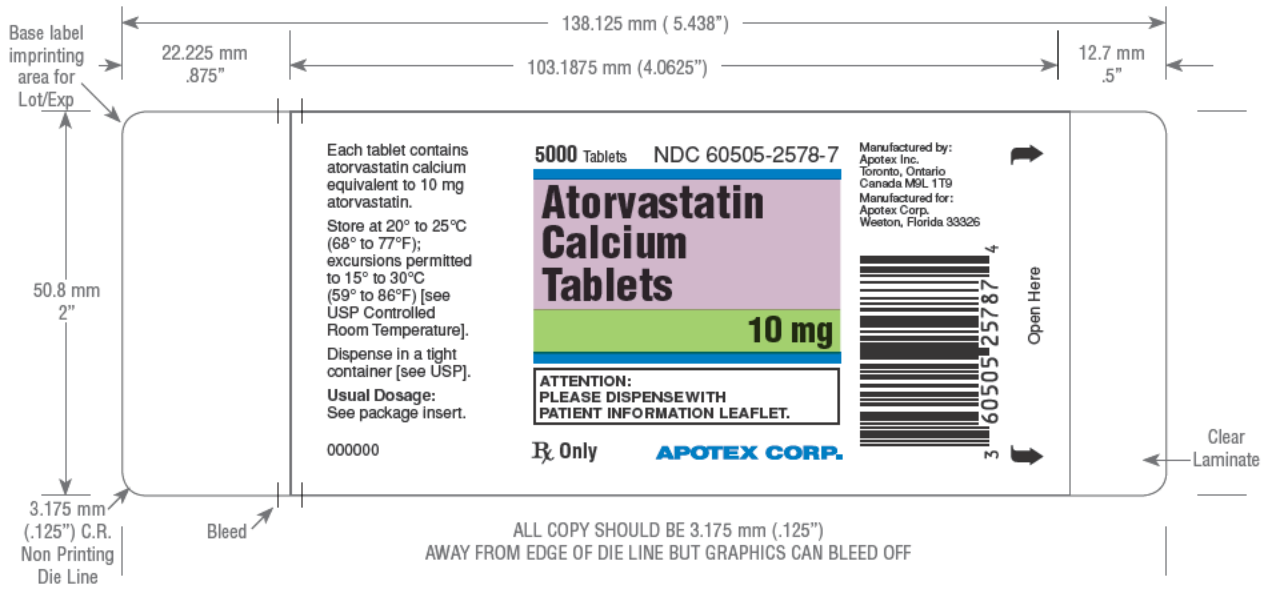
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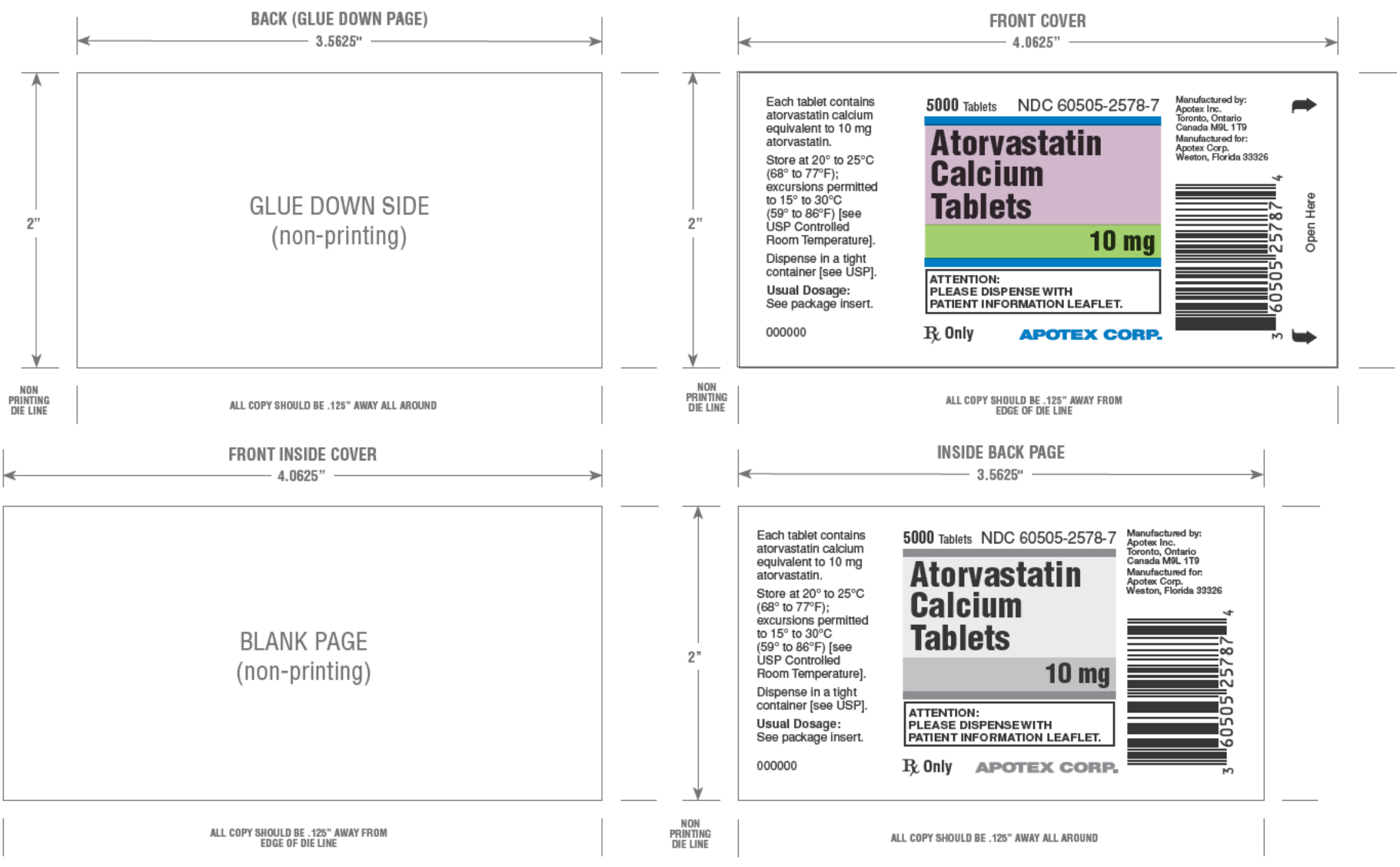
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[redacted]

COMPOSITE



COVER

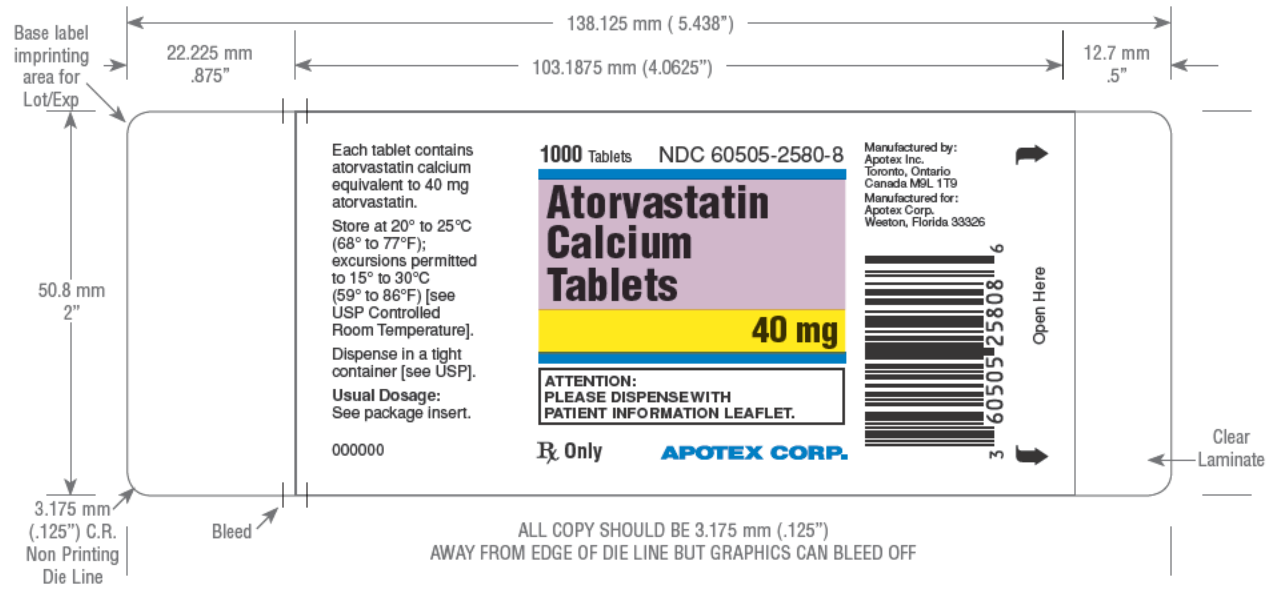


APOTEX
ADVANCING GENERICS

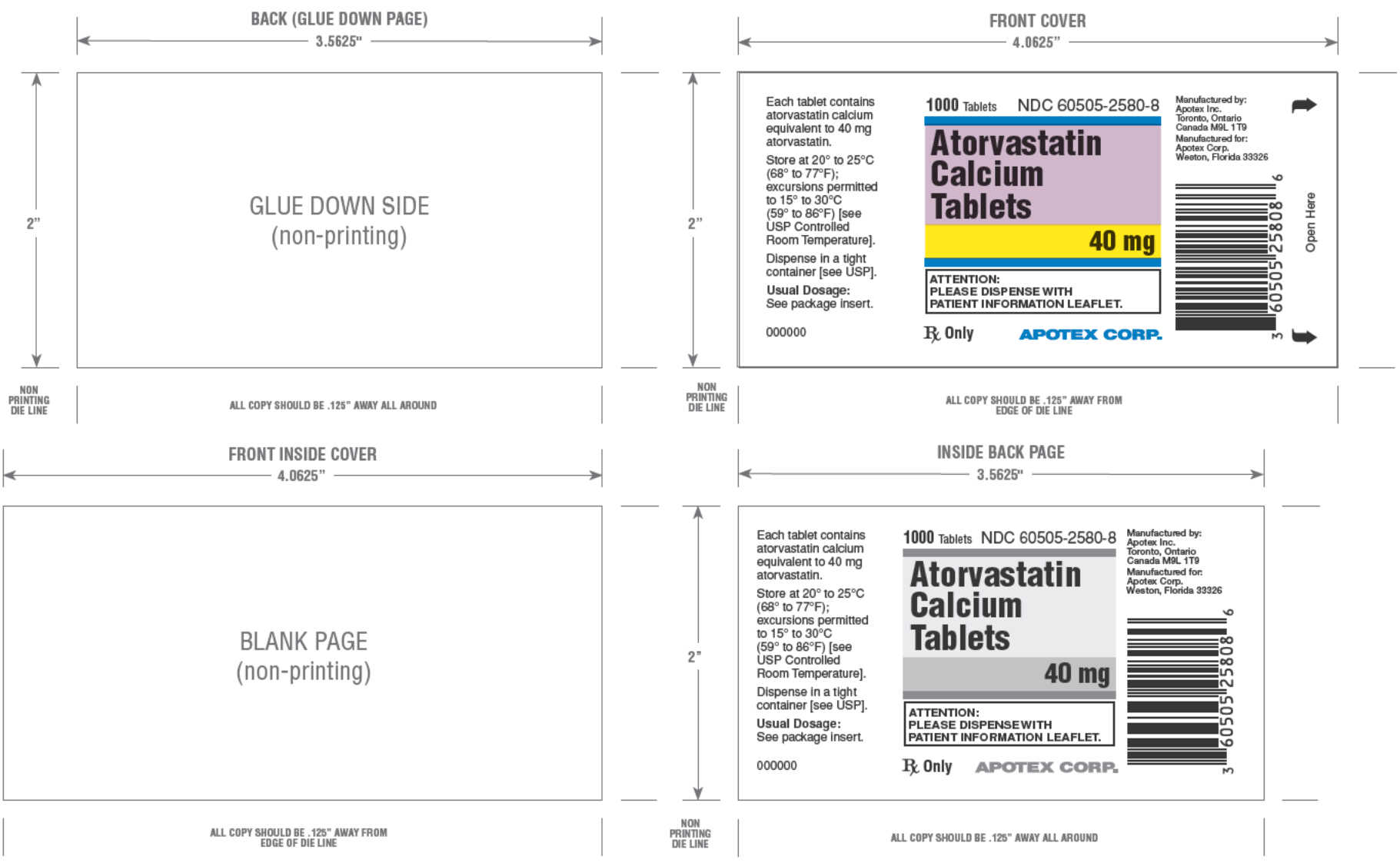
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(b) (4)

COMPOSITE



COVER

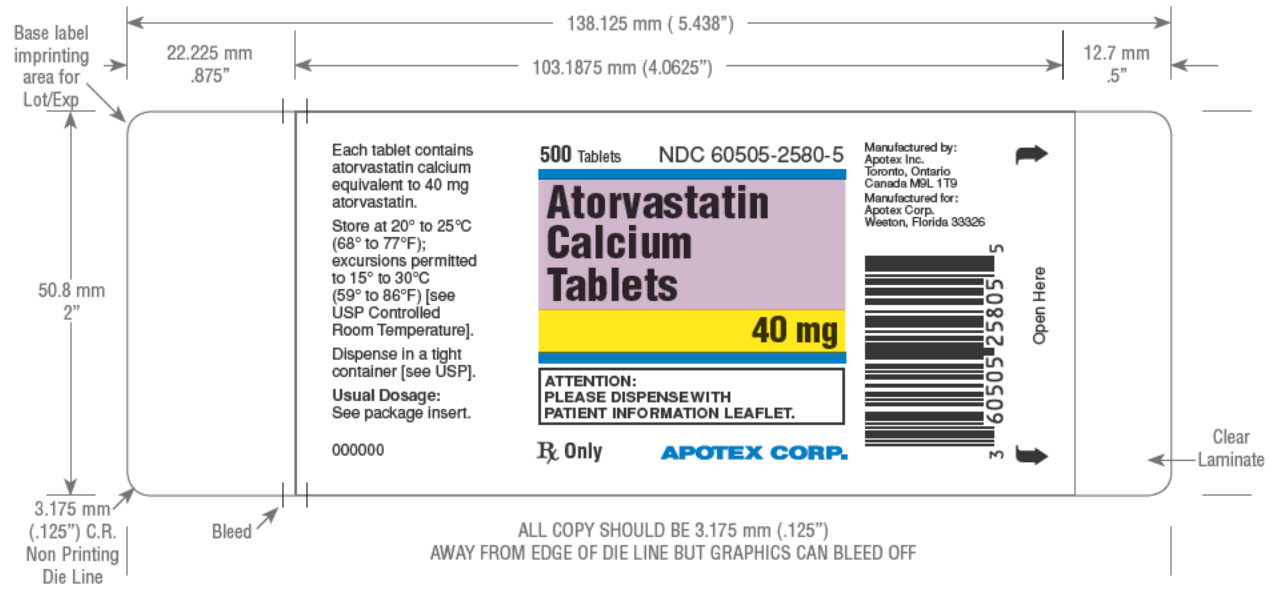


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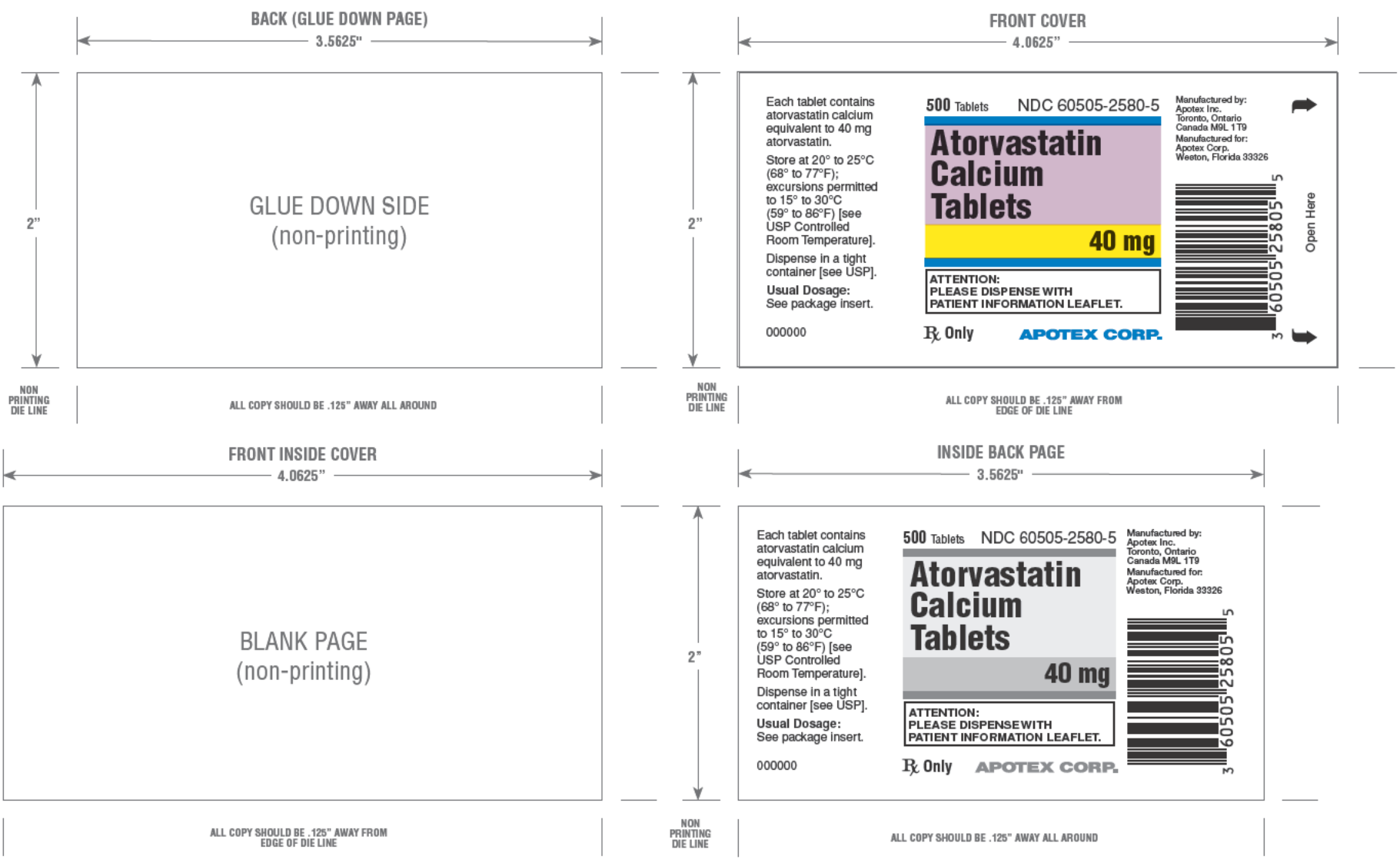
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(b) (4)

COMPOSITE



COVER



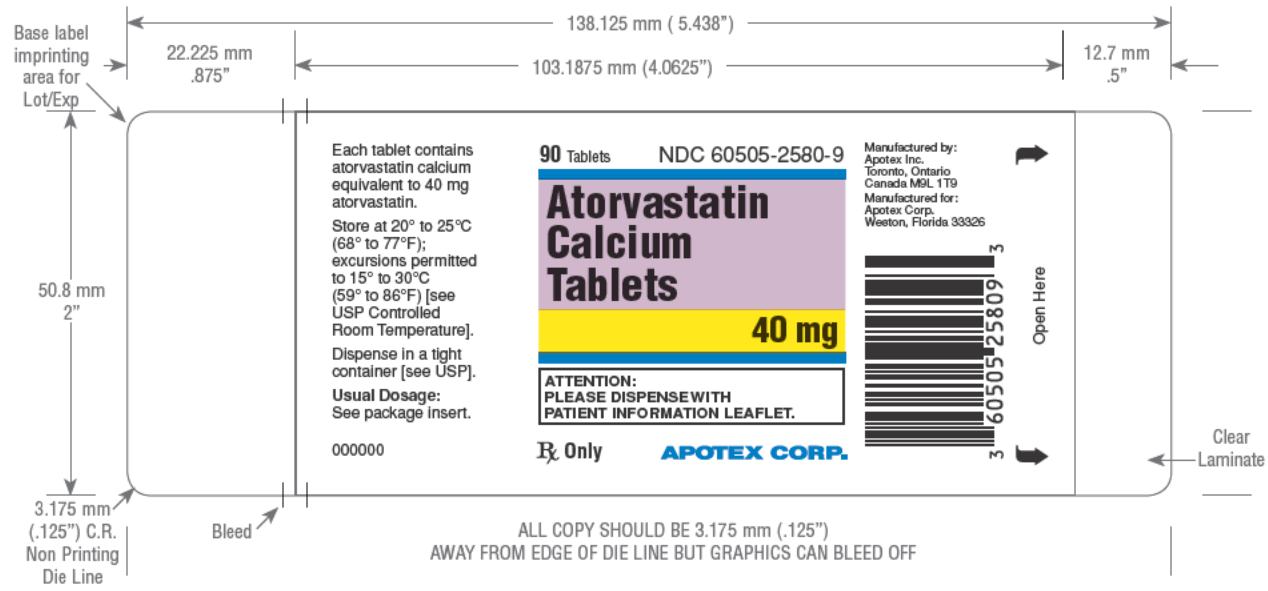
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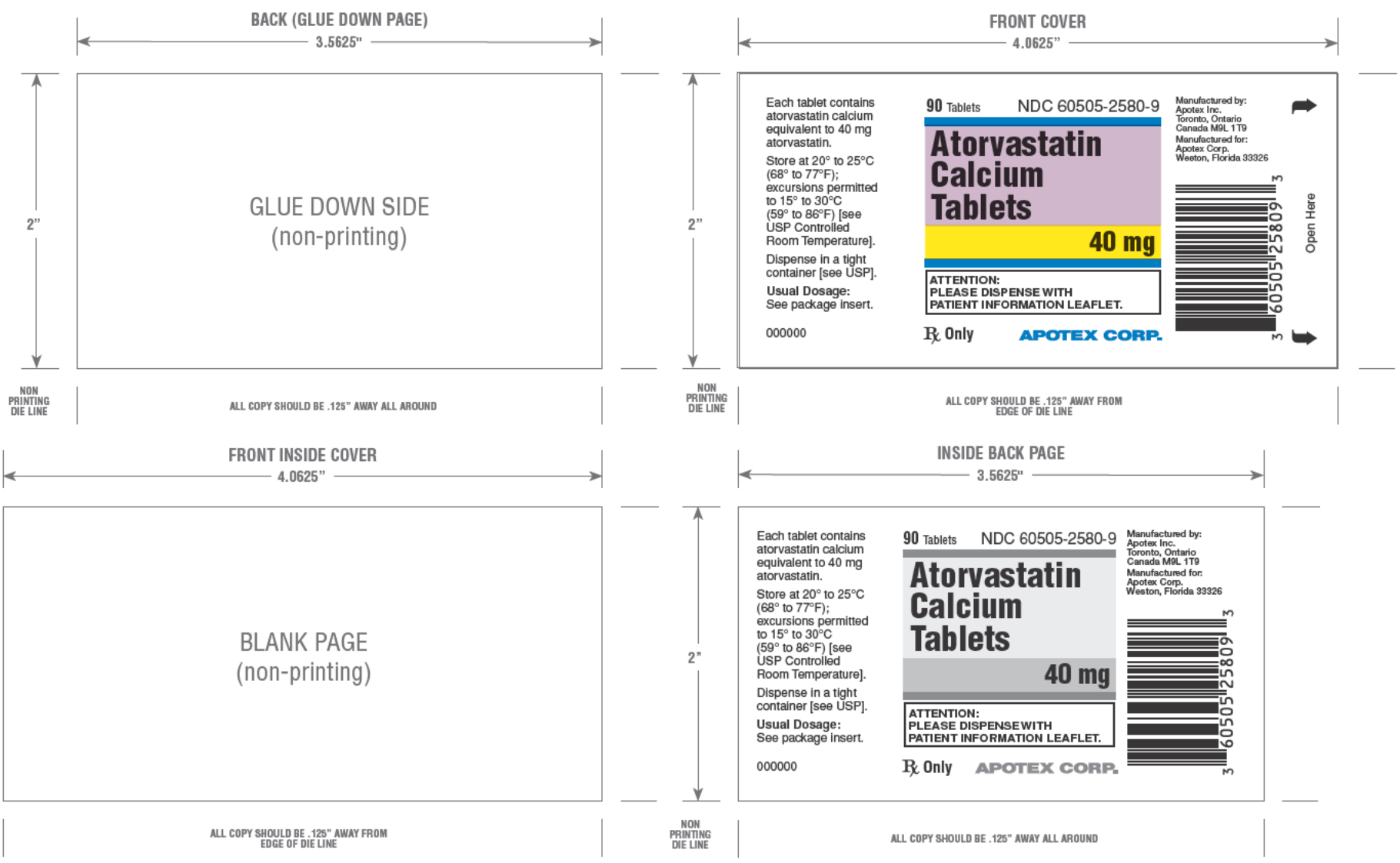
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COMPOSITE



COVER



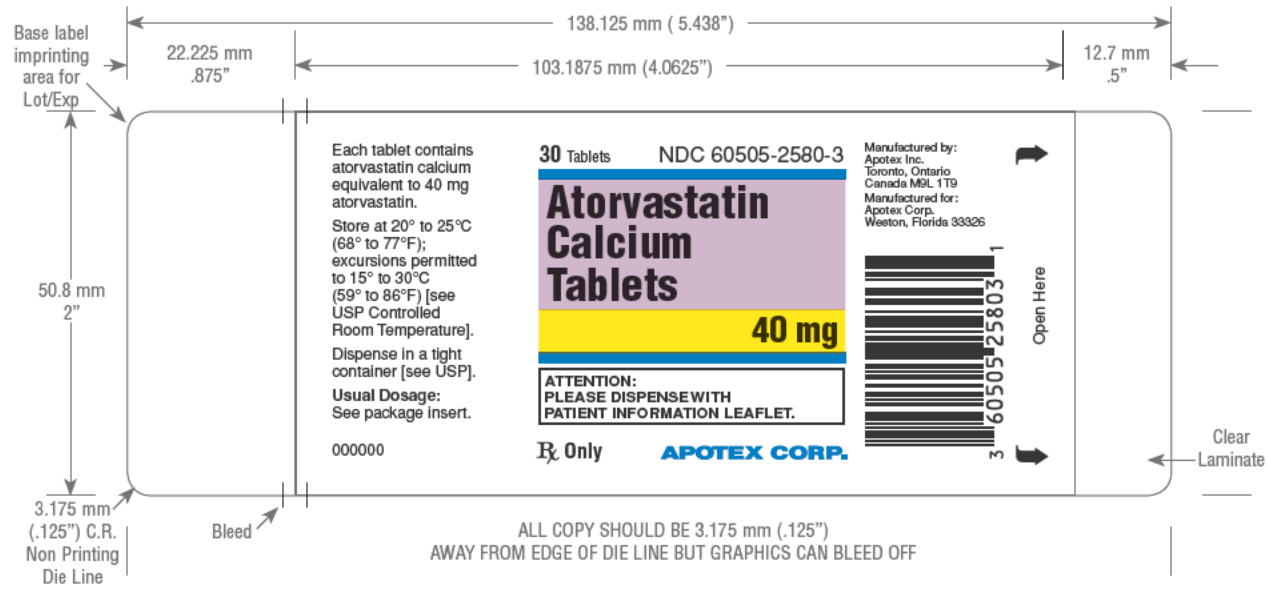
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ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

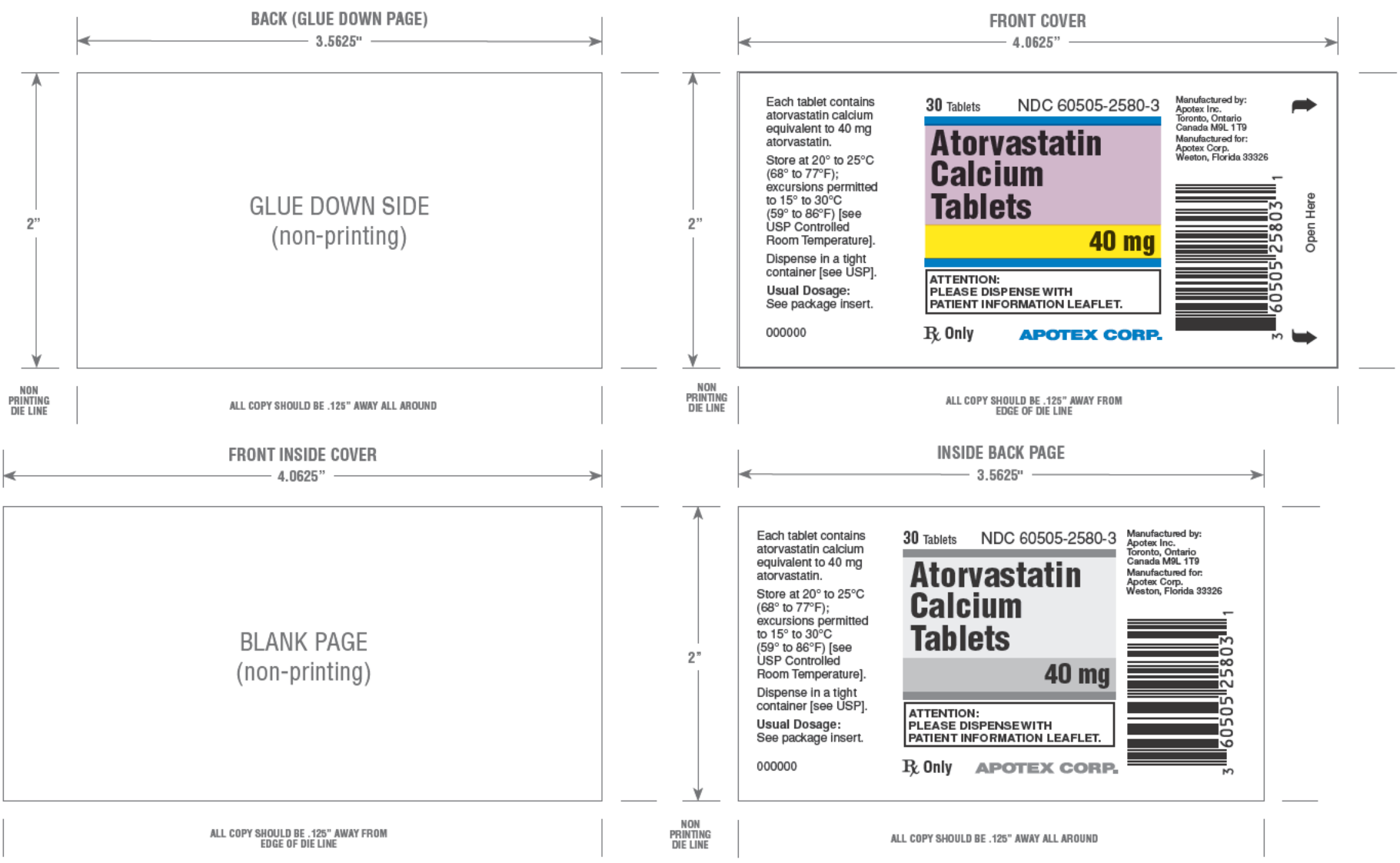
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COMPOSITE



COVER



APOTEX
ADVANCING GENERICS

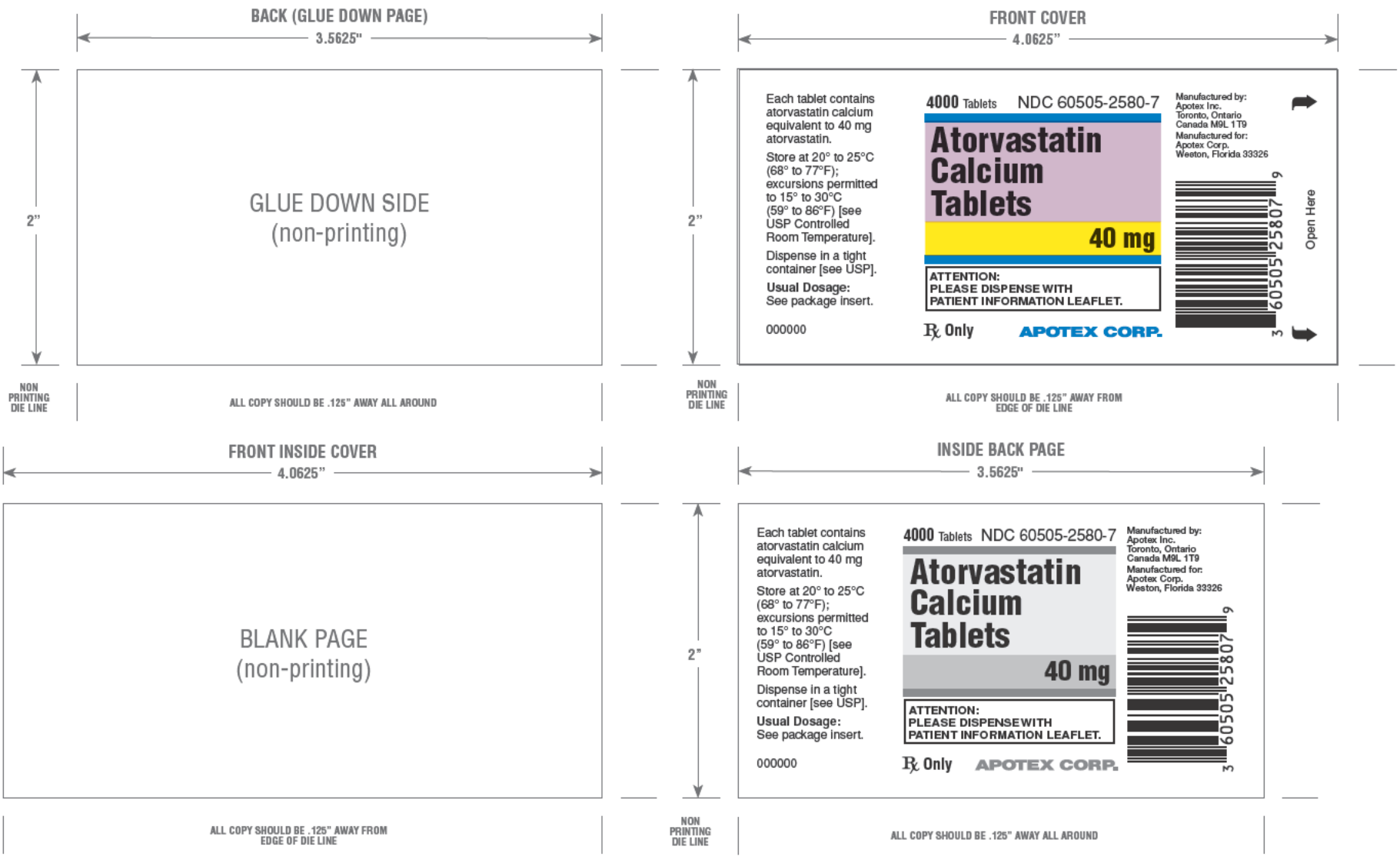
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(b) (4)

COMPOSITE



COVER

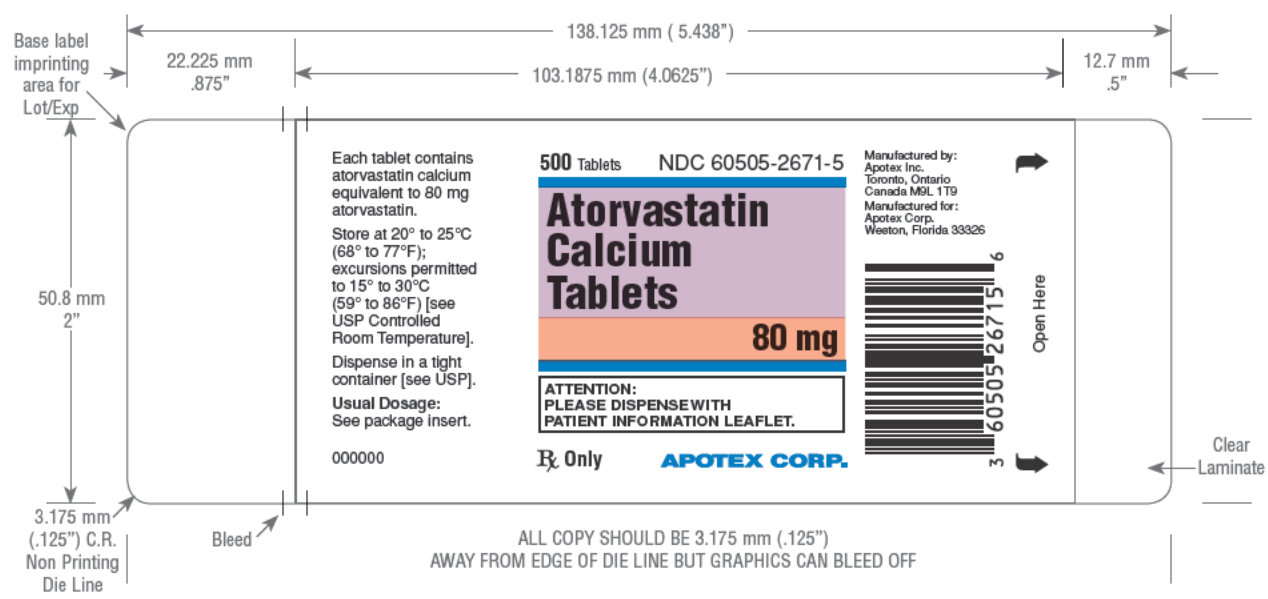


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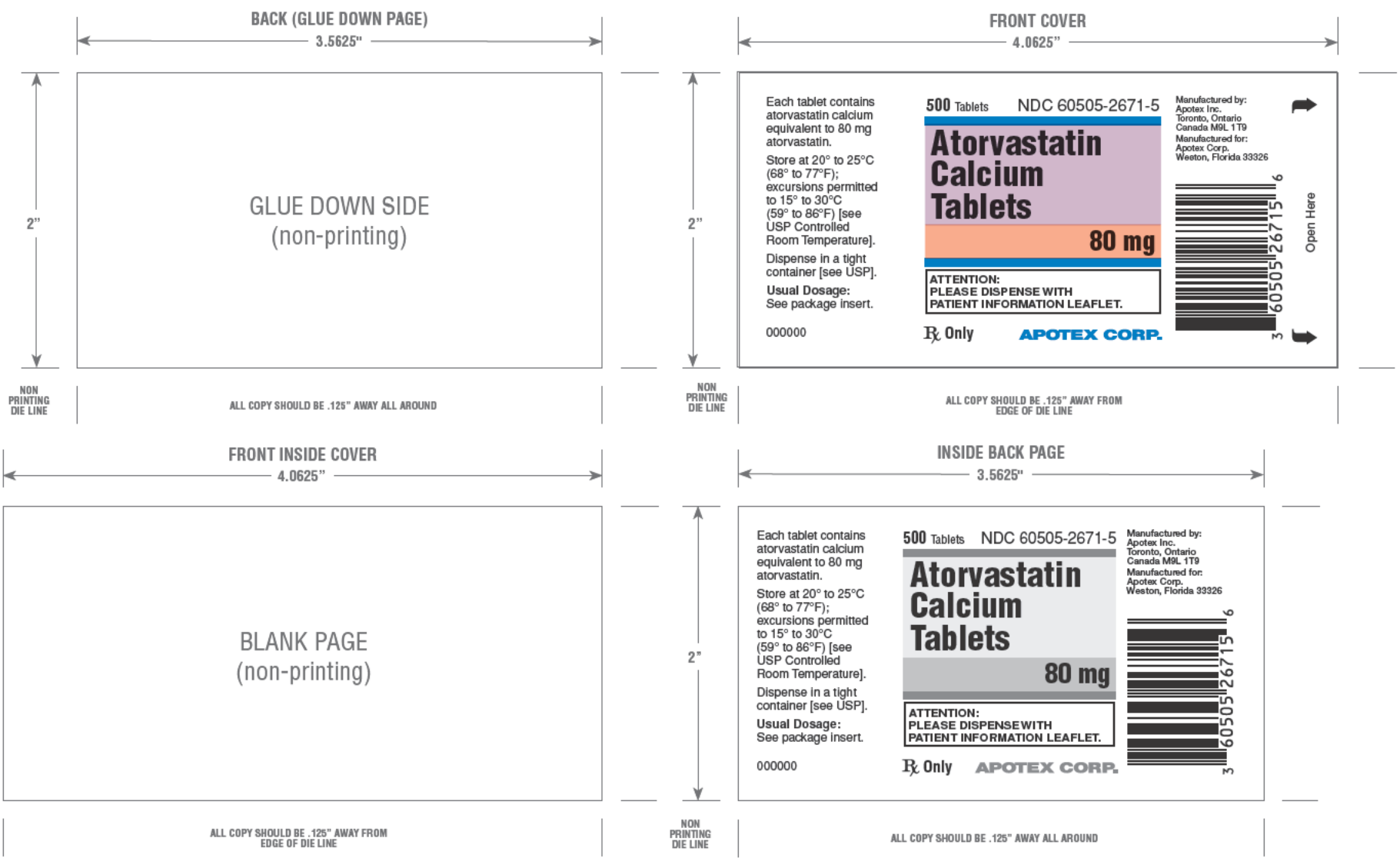
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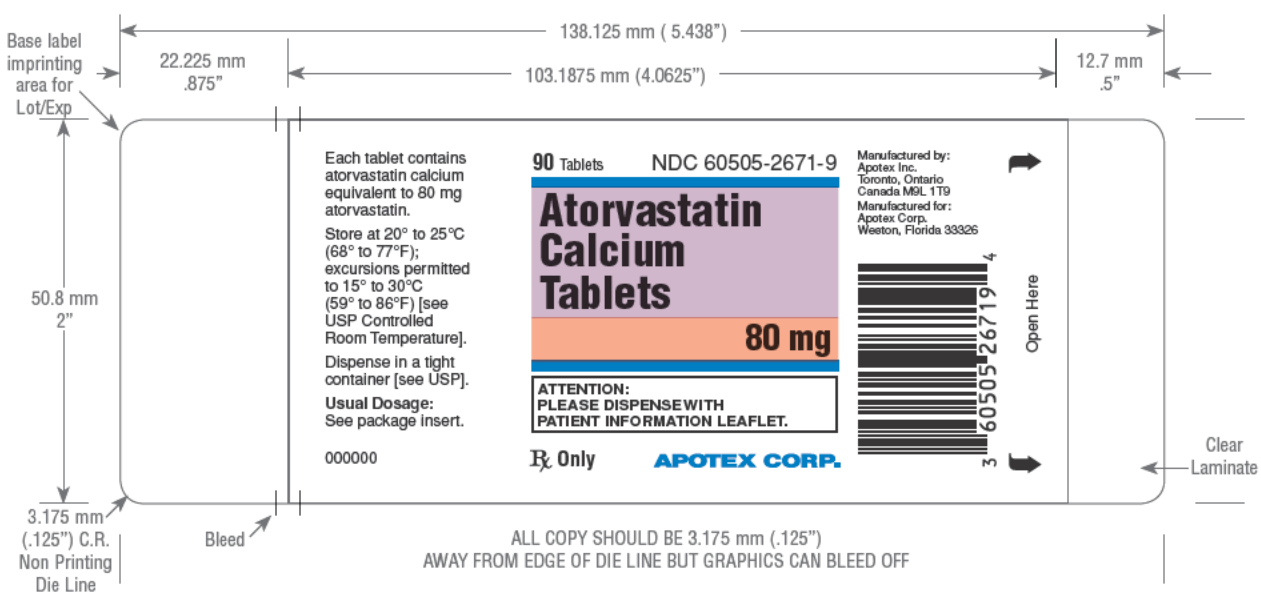


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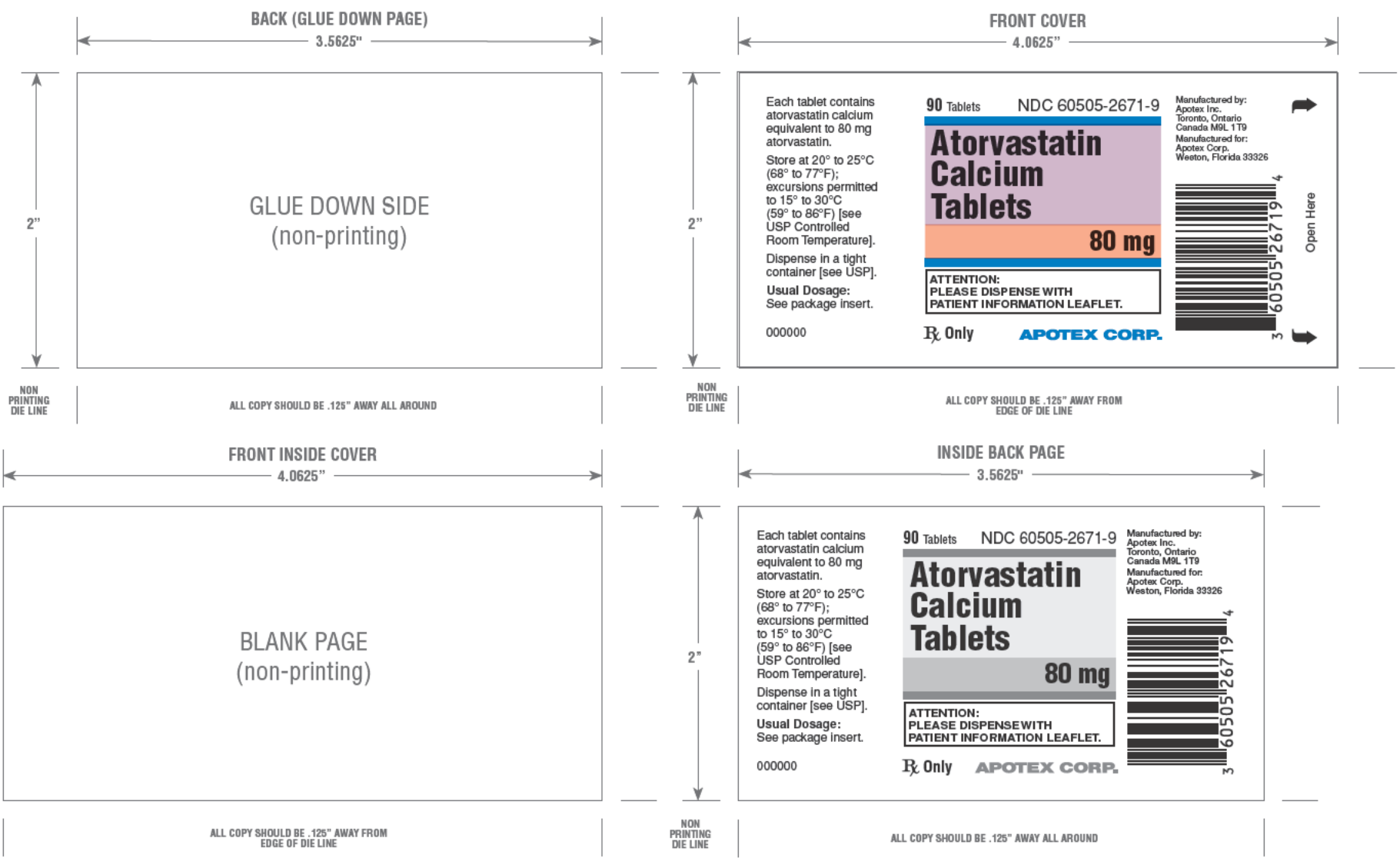
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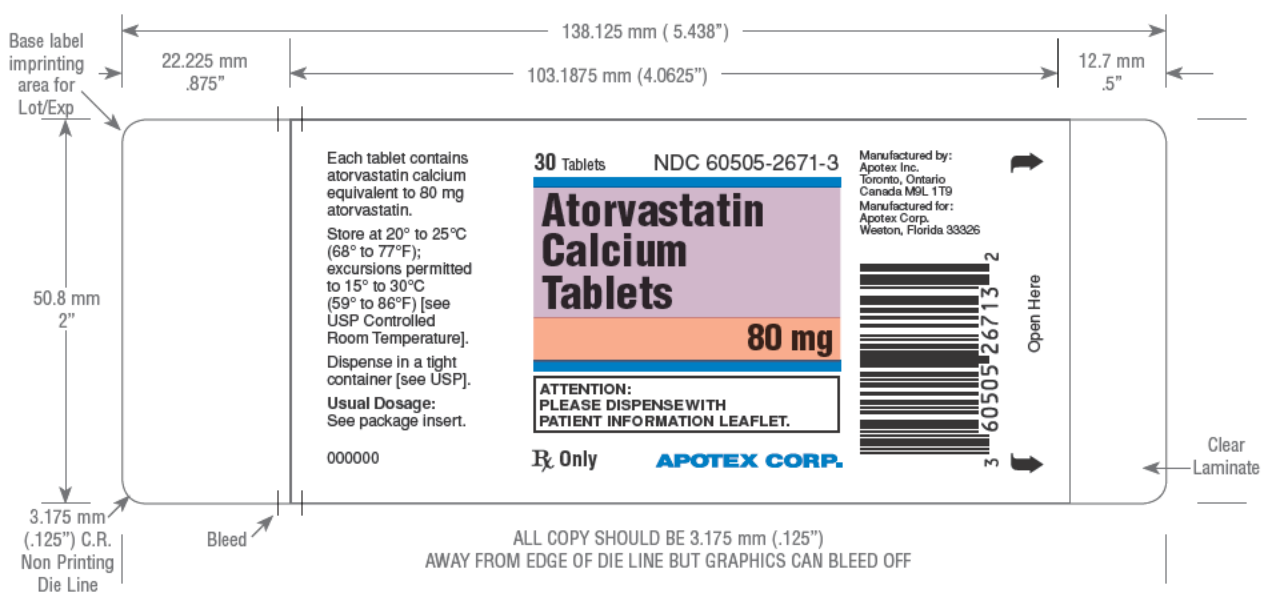


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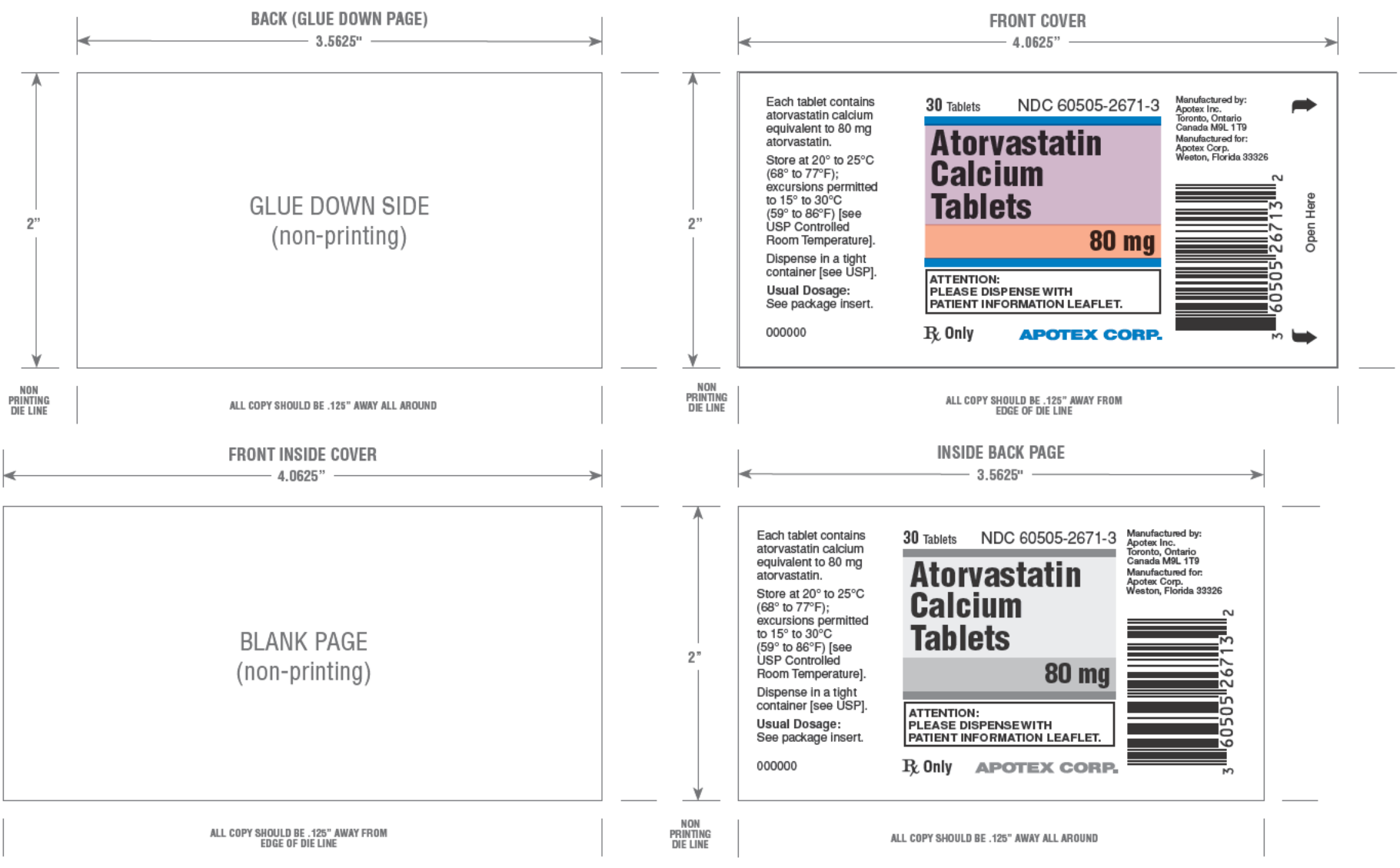
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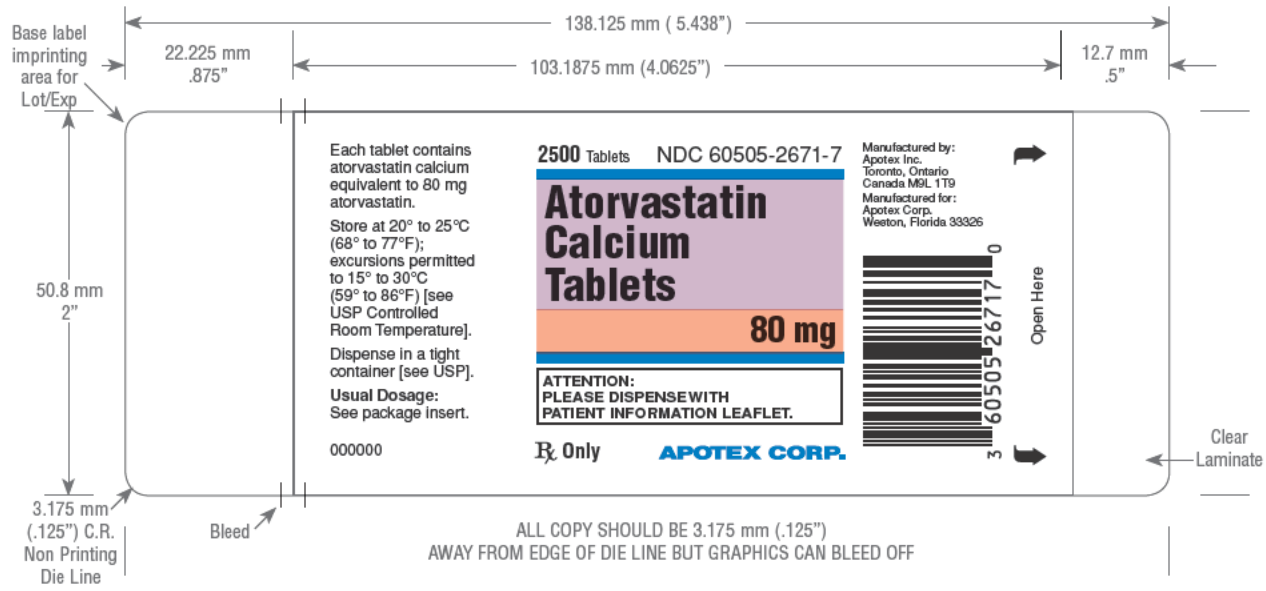
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ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

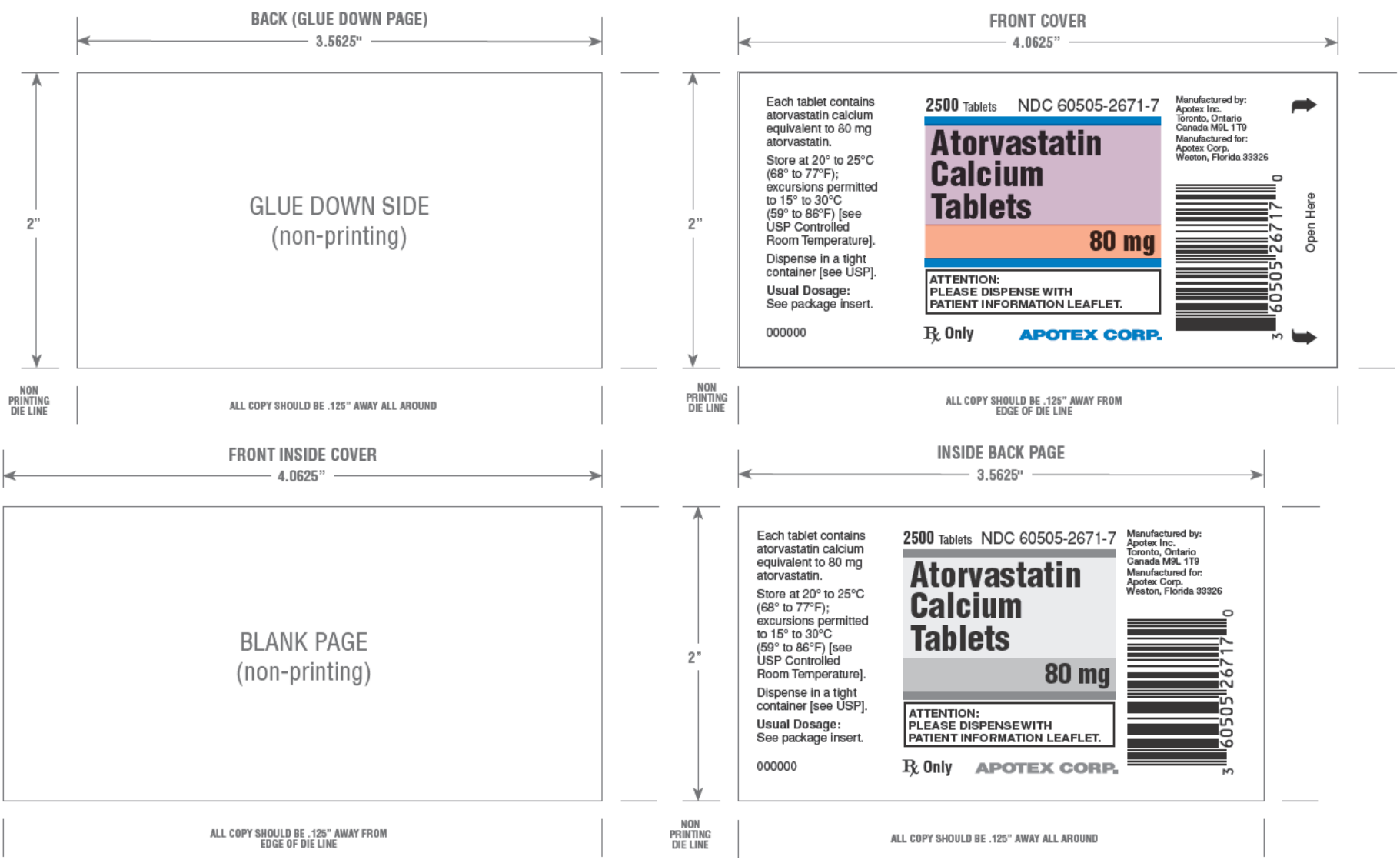
(b) (4)

[redacted]

COMPOSITE



COVER



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90548	ORIG-1		ATORVASTATIN CALCIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
04/27/2010

JOHN F GRACE
04/29/2010

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-548 Date of Submission: May 20, 2009

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

---

Labeling Deficiencies:

1. CONTAINER (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
   40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
   80 mg= bottles of 30s, 90s, 500s, and 2500s):

   Acceptable in final print.

2. CARTON (10 x 10)

   Acceptable in final print.

3. BLISTER (Blister card of 10s)

   Acceptable in final print.

4. INSERT

   Due to changes in the insert labeling for the reference listed drug, Lipitor (20702/S-056, approved 6/17/2009), please revise your labeling to be in accord with RLD. The RLD labeling may be accessed at the Drugs@FDA website.

Submit label and labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No

Container Labels (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
80 mg= bottles of 30s, 90s, 500s, and 2500s): Final print labels acceptable in 5/20/09 e-submission.

Carton (10 x 10): Final print labels acceptable in 5/20/09 e-submission.

Blister (Blister card of 10s): Final print labels acceptable in 5/20/09 e-submission.

Professional Package Insert Labeling: No

Patient Information Sheet: No

Revisions needed before full approval: Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-056; approved 6/17/09.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

E

mail received on 3/4/09

As you might have known "atorvastatin" is (b) (4)
Thus, one can say "atorvastatin calcium equivalent to 10 mg atorvastatin" or (b) (4) of atorvastatin calcium equivalent to (b) (4)" and technically both are correct.
Thus, from technical perspective, the Apotex labeling is accurate.
However, it is your call if you want the Apotex to change the words similar to RLD.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Wednesday, March 04, 2009 8:56 AM
To: Vaithiyalingam, Sivakumar
Cc: Grace, John F
Subject: Atorvastatin 90-548 (Apotex's atorvastatin)

Siva,

I have a problem with the label of 90-548. Please take a look at the attached pdf file. Apotex's label states:

* Each tablet contains (b) (4) of atorvastatin calcium equivalent to (b) (4).

Lipitor's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

TEVA's label states:

* Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Is Apotex's label accurate? Could Apotex state this because their drug substance is atorvastatin calcium in the form of propylene glycol solvate instead of atorvastatin calcium in the hydrate form. I'm concerned because the label should be consistent between the generic and brand.

Thanks
Ann

Email received on 3/3/09:

Ann,

The RLD is a hydrate whereas the ANDA is a solvate with propylene glycol. Under our current guidance, these drug substances are considered equivalent.

Thanks. Siva

From: Vu, Thuyanh (Ann)
Sent: Tuesday, March 03, 2009 1:56 PM
To: Vaithiyalingam, Sivakumar
Cc: Vu, Thuyanh (Ann)
Subject: 90-548 (Apotex's atorvastatin calcium)

The DS in Apotex's atorvastatin is different than the RLD's Lipitor and is this equivalent/acceptable? Thanks Ann

This is Apotex's atorvastatin:

The drug substance used in Atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium

bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{68}CaF_2N_4O_{10} * C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:

Lipitor's insert:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, s-056; approved 6/17/09. Supplement provided for the PLR labeling format.

   Please see the email string with the chemist above. I asked the firm to revise the label to state ""Each tablet contains atorvastatin calcium equivalent to YY mg atovastatin" to be consistent with the RLD and other generic manufacturers even though Apotex is technically/chemically correct.

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	PIII	Same As
5273995	Dec 28, 2010 ped jun 28, 20011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As

RE40667	Jun 28, 2011* PED	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As, certified in 3/19/09 labeling amendment

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None
I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:calcium acetate, croscramellose sodium, sodium carbonate [(b) (4)], microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose [(b) (4)] polyethylene glycol [(b) (4)], titanium dioxide,

[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.1-original submission]

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T 9 Canada

5. CONTAINER/CLOSURE

- HDPE bottles containing 30 or 90 tablets closed with [(b) (4)] screw caps with a [(b) (4)] desiccant. When originally packed, the bottles are also sealed with a [(b) (4)].
- HDPE bottles containing 500 tablets or greater closed with [(b) (4)] screw caps with a [(b) (4)] desiccant. When originally packed, the bottles are also sealed with a [(b) (4)].

- Blister packs comprised of (b) (4) and a (b) (4)
  Packed in cartons containing 10 strips of 10 tablets (100 tablets total).

6. FINISHED DOSAGE FORM

RLD:

10 mg: coded “PD 155” on one side and “10” on the other

20 mg: coded “PD 156” on one side and “20” on the other

40 mg: coded “PD 157” on one side and “40” on the other

80 mg: coded “PD 158” on one side and “80” on the other

ANDA:

10 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “A10” on the other side.

20 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV20” on the other side.

40 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV40” on the other side.

80 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV80” on the other side.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not USP
RLD: store at CRT 20-25°C (68-77°F) [see USP].
ANDA label: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [See USP Controlled Room Temperature]

8. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight container (see USP).

The carton states: “This unit-dose package is not child-resistant”

9. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the propolyne glycol solvate form rather than the trihydrate

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

RLD: 10 mg, 20 mg = bottles of 90s, 5000s and blisters of 100 (10 x 10) unit dose blisters
40 mg: bottles of 90s, 500s, 2500s and blisters of 100 (10 x 10) unit dose blisters
80 mg: bottles of 90s, 500s, 2500s and blisters of 64 (8 x 8) unit dose blisters

ANDA:10 mg, 20 mg = bottles of 30s, 90s, 1000s, 5000s and blisters of 100 (20 mg= violet color, 10 mg= green color)
40 mg= bottles of 30s, 90s, 500s, 1000s, 4000s and blisters of 100 (container color= yellow)
80 mg= bottles of 30s, 90s, , 500s, 2500 and blisters of 100 (container color= red)

Date of Review: January 14, 2010 Date of Submission: May 20, 2009

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90548	ORIG-1		ATORVASTATIN CALCIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
01/14/2010

JOHN F GRACE
01/20/2010

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-548 Date of Submission: May 1 and August 6, 2008

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

---

Labeling Deficiencies:

1. CONTAINER (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
   40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
   80 mg= bottles of 30s, 90s, 500s, and 2500s):

   Please revise to read "Each tablet contains atorvastatin calcium equivalent to YY mg atorvastatin".

2. CARTON (10 x 10)
   a. Please see container comment.

   b. Please add "This unit-dose package is not-child-resistant. If dispensed for outpatient use, a child-resistant container should be used. [Note: the second sentence is optional]"

3. BLISTER (Blister card of 10s)

   a. Please see CONTAINER comment.

   b. We encourage you to differentiate the strengths by shading, boxing or other means.

4. INSERT

   a. GENERAL COMMENTS

      i. Please revise "-" to "to" when denoting a range (e.g. 40 to 80 years of age vs. 40-80 years of age).

      ii. Please do not cite the RLD "Lipitor" in your insert.

      iii. Please capitalize the "c" in "Cytochrome"

      iv. Revise "atorvastatin calcium tablet" to "atorvastatin calcium" throughout the text with the exception of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections.

   b. CLINICAL PHARMACOLOGY, Clinical Studies, Prevention of Cardiovascular Disease

      Add "Trials" to the title of the Table 3.

   c. INDICATIONS AND USAGE

      Table 7, footnote b, revise to read "...category if an LDL-C [an vs. and]".

d. PRECAUTIONS

Revise the subsection to read:

Pregnancy

Teratogenic Effects

Pregnancy Category X

5. PATIENT INFORMATION SHEET:

a. Please state the number of sheets you intend on providing in order for each patient to receive one.

b. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name is part of a question in the patient package insert.

6. SPL

Please submit your labeling in SPL format.

Submit label and labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA. In addition, please review the guidance for industry titled Providing Regulatory Submissions in Electronic Format-Content of Labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

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BASIS OF TENTATIVE APPROVAL:

TENTATIVE APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No

Container Labels (10 mg, 20 mg and 40 mg: 30s, 90s, 100s and 1000s; 80 mg: 90s, 100s and (b) (4)) No, see comments above.

Professional Package Insert Labeling: No

Patient Information Sheet: No

Revisions needed before full approval: Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-050; approved 9/26/07.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

E mail received on 3/4/09

As you might have known "atorvastatin" is (b) (4)
Thus, one can say "atorvastatin calcium equivalent to 10 mg atorvastatin" or (b) (4) of atorvastatin calcium equivalent to (b) (4)" and technically both are correct.
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The drug substance used in Atorvastatin calcium tablets is atorvastatin calcium in the form of propylene glycol solvate. The chemical name for atorvastatin calcium propylene glycol solvate is calcium bis((3R,5R)-7-[3-(anilinocarbonyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate) propylene glycol solvate. The empirical formula of atorvastatin calcium propylene glycol solvate is $C_{66}H_{68}CaF_2N_4O_{10} * C_3H_8O_2$ and its molecular weight is 1231.46. Its structural formula is:

Lipitor's insert:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, s-050; approved 9/26/07. Supplement provided changes to the WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the PI.

   Please see the email string with the chemist above. I asked the firm to revise the label to state ""Each tablet contains atorvastatin calcium equivalent to YY mg atovastatin" to be consistent with the RLD and other generic manufacturers even though Apotex is technically/chemically correct.

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	PIII	Same As
5273995	Dec 28, 2010 ped jun 28, 20011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	IV	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***

I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None
I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:calcium acetate, croscramellose sodium, sodium carbonate (b) (4), microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose (b) (4), polyethylene glycol (b) (4) titanium dioxide,

[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.1-original submission]

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T 9 Canada

4. CONTAINER/CLOSURE

- HDPE bottles containing 30 or 90 tablets closed with (b) (4) screw caps with a (b) (4) desiccant. When originally packed, the bottles are also sealed with a (b) (4)
- HDPE bottles containing 500 tablets or greater closed with (b) (4) screw caps with a (b) (4) desiccant. When originally packed, the bottles are also sealed with a (b) (4)
- Blister packs comprised of (b) (4) and a (b) (4). Packed in cartons containing 10 strips of 10 tablets (100 tablets total).

5. FINISHED DOSAGE FORM

RLD:

10 mg: coded “PD 155” on one side and “10” on the other

20 mg: coded “PD 156” on one side and “20” on the other

40 mg: coded “PD 157” on one side and “40” on the other

80 mg: coded “PD 158” on one side and “80” on the other

ANDA:

10 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “A10” on the other side.

20 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV20” on the other side.

40 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV40” on the other side.

80 mg: white, oval, biconvex film-coated tablets. Engraved “APO” on one side, “ATV80” on the other side.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not USP
RLD: store at CRT 20-25°C (68-77°F) [see USP].
ANDA label: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [See USP Controlled Room Temperature]

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight container (see USP).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the propolyne glycol solvate form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 10 mg, 20 mg = bottles of 90s, 5000s and blisters of 100 (10 x 10) unit dose blisters
40 mg: bottles of 90s, 500s, 2500s and blisters of 100 (10 x 10) unit dose blisters
80 mg: bottles of 90s, 500s, 2500s and blisters of 64 (8 x 8) unit dose blisters

ANDA: 10 mg, 20 mg = bottles of 30s, 90s, 1000s, 5000s and blisters of 100
40 mg= bottles of 30s, 90s, 500s, 1000s, 4000s and blisters of 100
80 mg= bottles of 30s, 90s, , 500s, 2500 and blisters of 100

Date of Review: March 4, 2009 Dates of Submission: May 1 and August 6, 2008

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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/s/

Thuyanh Vu
3/6/2009 11:01:12 AM
LABELING REVIEWER

John Grace
3/12/2009 06:44:14 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

CHEMISTRY REVIEWS

ANDA 090548

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Apotex Inc

Raghu Samy, PhD

Office of Generic Drugs

Division of Chemistry III, Team 33

(b) (4)



CMC REVIEW DATA SHEET

1. ANDA #: 090548 2. REVIEW #: 05-Addendum-1
3. REVIEW DATE: May 1, 2012; May 10, 2012 4. REVIEWER: Raghu Samy
5. PREVIOUS DOCUMENTS:

Submission(s)	Document Date
Original	05-01-2008
Amendment	08-06-2008
Amendment	02-11-2009
Amendment	03-01-2010
Amendment	06-23-2009
Amendment	11-09-2010
Amendment	02/22/2011
Amendment	03/17/2011
Amendment	May 18, 2011
Amendment	July 12, 2011
Amendment	August 10, 2011
Amendment	August 12, 2011
Amendment	August 29, 2011
Amendment	September 19, 2011
Amendment	September 28, 2011
Amendment	October 20, 2011
Amendment	November 08, 2011
Amendment	November 17, 2011
Amendment	November 21, 2011
Amendment	November 22, 2011

6. SUBMISSION(S) BEING REVIEWED:

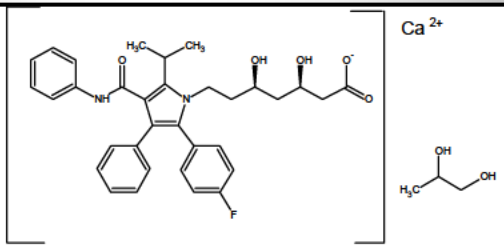
Submission(s) Reviewed	Document Date
Amendment	April 25, 2012
Telephone Amendment	May 9, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada Apotex Corp., 2400 N. Commerce Parkway, Suite 400, Weston, FL 33326
Representative:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	866-392-1774

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
Patent Information: **P IV**
10. PHARMACOL. CATEGORY: Lipid Lowering Agent
11. DOSAGE FORM: Tablets, **MDD 80 mg**
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:
Molecular Structure:

Reference ID: 3131072



Molecular Formula: $C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$, *Molecular Weight:* 1231.46 (b) (4) Atorvastatin Ca)

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21574	II	Apotex Pharmachem Inc	Atorvastatin Ca Propylene Glycol Solvate	1	Adequate	**11/22/2011**	Adequate
(b) (4)	III	(b) (4)		4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
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	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (Enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	04/23/2012	M. Stock
Methods Validation	Not Applicable		
Labeling	Acceptable	04/18/2012	Betty Turner
Bioequivalence	Adequate	06/08/2010	Li Gong
EA	Adequate		
Radiopharmaceutical	Not Applicable		
Pharm/Tox, # 2009-0305	**Yes**	**04-28-2009**	**Indra Antonipillai**

19. ORDER OF REVIEW: The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: (Review # 5): Approvable

A. Description of the Drug Product(s) and Drug Substance(s)

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, biconvex film-coated tablets: Engraved "APO" on one side, "A10" on the other side. 20 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV20" on the other side. 40 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV40" on the other side. 80 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV80" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4) . The DS is about (b) (4)% w/w of the dosage form. The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4) croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is a propylene glycol solvate of atorvastatin calcium. Drug substance meets the IR identification test under the modified <197K> conditions to the current USP monograph*. The DS is (b) (4) form and is stored at room temperature. RLD is crystalline atorvastatin calcium trihydrate. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers.

B. Description of How the Drug Product is Intended to be Used

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 30 and 90 counts and in bulk packages for pharmacy. The DP is manufactured by (b) (4) using (b) (4). The unit operations are (b) (4) . Long term data indicates a tentative expiration period of 24 months at room conditions. Based on the MDD of 80 mg, DS IT is 0.10% and QT is 0.15% and the DP RT is 0.1%, IT is 0.2% and QT is (b) (4)%.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review, other disciplines and/or EES. This CMC review may require an addendum based on recommendations made by other review disciplines.

*Apotex Drug substance meets current USP monograph identity test under the modified <197K> conditions. FDA Drug Product Analysis Laboratories at St. Louis, MO has confirmed the results. Please refer to the API sameness memo from P. Schwartz, Ph.D. dated November 30, 2011 in DARRTS.

Reference ID: 3131072

Chemistry Assessment

This review document has two parts:

- **Part 1:** Review of amendment dated April 25, 2012 (current review)
- **Part 1a:** Review of telephone amendment dated May 9, 2012 (current review)

Part 1: Review of amendment dated April 25, 2012 (current review)

The CMC portion of this application was acceptable as of December 1, 2011 review. The labeling portion of this application was acceptable as of April 18, 2012 review (amendment dated March 21, 2012). There is no new CMC information submitted in the labeling amendment dated March 21, 2012. The application was tentatively approved on April 24, 2012.

However, the firm in the [redacted] (b) (4) had proposed a reporting category for alternate drug product manufacturing facility as a CBE-0, which is not approvable in its current form. The firm will be asked to provide a commitment via an appropriate supplement indicating when the changes are going to be implemented.

DMF 21574 was reviewed on November 22, 2011 and found to be adequate.

EES was acceptable as of April 23, 2012.

Part 1a: Review of telephone amendment dated May 9, 2012 (current review)

The following deficiency was communicated by the agency to the firm via a telephone conversation on May 8, 2012:

Please provide a commitment with respect to the alternate drug product manufacturing facility in the [redacted] (b) (4) via an appropriate supplement indicating when the changes are going to be implemented.

Reviewer's comment: The firm responded on May 9, 2012 via an amendment stating that they would like to withdraw the submitted [redacted] (b) (4) with respect to the alternate drug product manufacturing facility. In addition, the firm also provided a commitment to adhere to the Guidance for Industry-Changes to an Approved NDA or ANDA and the appropriate reporting category for any post approval changes.

Conclusion: The firm's response is satisfactory.

Endorsements:

Reviewer: HFD-630/R. Samy, Ph.D./5/2/12; 5/10/12
Team Leader: HFD-630/S. Patankar, Ph.D./ 5/4/12; 5/14/12
Project manager: HFD-617L. Sears/5/15/2012

TYPE OF LETTER: APPROVABLE

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/s/

RAGHU SAMY
05/15/2012

SUHAS J PATANKAR
05/15/2012

LEIGH A SEARS
05/15/2012

ANDA 090548

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Apotex Inc

Sivakumar R. Vaithiyalingam, PhD

Office of Generic Drugs

Division of Chemistry III, Team 33

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Section IV:	Review of Amendment Dated November 9, 2010 (Adopted)	20
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Section VI:	Review of Amendment Dated March 17, 2011 (Adopted)	30
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	Drug Product Description and Composition	53
	Drug Product In-Process Control	56
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	Drug Product Specification (Stability)	64

(b) (4)

[redacted]

Reference ID: 3052220

CMC REVIEW DATA SHEET

1. ANDA #: 090548
2. REVIEW #: 05
3. REVIEW DATE: 09/30/2011 - 11/23/11
4. REVIEWER: SR Vaithiyalingam, PhD
5. PREVIOUS DOCUMENTS:

Submission(s)	Document Date
Original	05-01-2008
Amendment	08-06-2008
Amendment	02-11-2009
Amendment	03-01-2010
Amendment	06-23-2009
Amendment	11-09-2010
Amendment	02/22/2011
Amendment	03/17/2011

6. SUBMISSION(S) BEING REVIEWED:

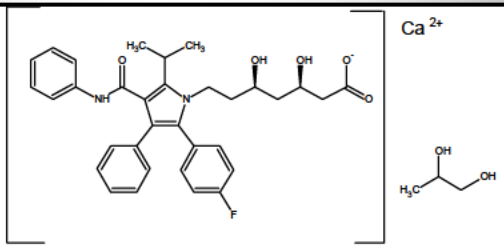
Submission(s) Reviewed	Document Date
Amendment	May 18, 2011
Amendment	July 12, 2011
Amendment	August 10, 2011
Amendment	August 12, 2011
Amendment	August 29, 2011
Amendment	September 19, 2011
Amendment	September 28, 2011
Amendment	October 20, 2011
Amendment	November 08, 2011
Amendment	November 17, 2011
Amendment	November 21, 2011
Amendment	November 22, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada Apotex Corp., 2400 N. Commerce Parkway, Suite 400, Weston, FL 33326
Representative:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	866-392-1774

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
Patent Information: **P IV**
10. PHARMACOL. CATEGORY: Lipid Lowering Agent
11. DOSAGE FORM: Tablets, **MDD 80 mg**
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:
Molecular Structure:

Reference ID: 3052220



Molecular Formula: $C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$, *Molecular Weight:* 1231.46 (b) (4), Atorvastatin Ca)

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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	III			4			
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	III			4			
	III			4			

codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

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3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (Enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending		
Methods Validation	Not Applicable		
Labeling	Acceptable	11/18/2011	Ann Vu
Bioequivalence	Adequate	06/08/2010	Li Gong
EA	Adequate		
Radiopharmaceutical	Not Applicable		
Pharm/Tox, # 2009-0305	**Yes**	**04-28-2009**	**Indra Antonipillai**

19. ORDER OF REVIEW: The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

Reference ID: 3052220

The Executive Summary

Recommendation and Conclusion on Approvability: (Review # 5): Approvable

A. Description of the Drug Product(s) and Drug Substance(s)

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, biconvex film-coated tablets: Engraved "APO" on one side, "A10" on the other side. 20 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV20" on the other side. 40 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV40" on the other side. 80 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV80" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4) The DS is about (b) (4)% w/w of the dosage form. The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4) croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is a propylene glycol solvate of atorvastatin calcium. Drug substance meets the IR identification test under the modified <197K> conditions to the current USP monograph*. The DS is (b) (4) form and is stored at room temperature. RLD is crystalline atorvastatin calcium trihydrate. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers.

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The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 30 and 90 counts and in bulk packages for pharmacy. The DP is manufactured by (b) (4) using (b) (4). The unit operations are (b) (4). Long term data indicates a tentative expiration period of 24 months at room conditions. Based on the MDD of 80 mg, DS IT is 0.10% and QT is 0.15% and the DP RT is 0.1%, IT is 0.2% and QT is (b) (4)%.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review, other disciplines and/or EES. This CMC review may require an addendum based on recommendations made by other review disciplines.

*Apotex Drug substance meets current USP monograph identity test under the modified <197K> conditions. FDA Drug Product Analysis Laboratories at St. Louis, MO has confirmed the results. Please refer to the API sameness memo from P. Schwartz, Ph.D. dated November 30, 2011 in DARRTS.

Reference ID: 3052220
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/s/

SIVAKUMAR R VAITHIYALINGAM
12/01/2011

SUHAS J PATANKAR
12/01/2011

ROBERT T GAINES
12/01/2011

Addendum
ANDA 090548 Atorvastatin Calcium Tablets, 10, 20, 40, 80 mg by Apotex

There are references to the authorized pending USP drug substance monograph in the CMC reviews. This addendum is included to confirm that the atorvastatin calcium active ingredient in this application meets the standards of identity set forth in the current USP drug substance monograph for atorvastatin calcium.

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III

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/s/

VILAYAT A SAYEED
12/01/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-3858
FAX (314) 539-2113

Date: November 16, 2011

To: Suhas Patankar, Ph.D., CDER/OGD

From: Jason D. Rodriguez, Ph.D., Chemist, OPS/OTR/ DPA
Anjanette P. Smith, Chemist, OPS/OTR/DPA

Through: B.J. Westenberger, Deputy Director, OPS/OTR/ DPA

Subject: Sample Preparation Study for Apotex Atorvastatin Calcium API

Background

In a previous report (DPATR-FY12-013), atorvastatin calcium active pharmaceutical ingredient (API) from four different applicants was evaluated using infrared (IR) spectroscopy. The solvent <197K> procedure proved to be more appropriate for accurate identification of the samples compared to the dry <197K> procedure. Using the solvent method, test samples for three of the four applicants passed both the United States Pharmacopeia (USP) criteria and the computer-based correlation coefficient test. Although the sample submitted by Apotex successfully met the computer-based criteria, it failed to meet the USP criteria due to an additional maximum at ~ (b) (4) in the IR spectrum of this sample when compared to the USP reference standard (USPRS) obtained under similar conditions. Since the sample belonging to Apotex is actually a propylene glycol (PG) solvate, this maximum was attributed to residual (b) (4)

Reference ID: 3047003

Appendices

Appendix A: Methods
Appendix B: IR spectra of Atorvastatin Calcium API Samples Acquired Using Different Methods in Appe
Appendix C: IR spectra in the (b) (4) Region of Atorvastatin Calcium API
Appendix D: Decrease of Propylene Glycol Spectral Features Upon Preparation In (b) (4)
Appendix E: Results of Identification Tests

5 pages have been withheld as b4 (CCI/TS) immediately following this page

Reference ID: 3047003

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES F ALLGIRE
11/18/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-3858
FAX (314) 539-2113

Date: November 10, 2011

To: Suhas Patankar, Ph.D., CDER/OGD

From: Jason D. Rodriguez, Ph.D., Chemist, OPS/OTR/ DPA
Anjanette P. Smith, Chemist, OPS/OTR/DPA

Through: B.J. Westenberger, Deputy Director, OPS/OTR/ DPA

Subject: IR Spectroscopic Study of Atorvastatin Calcium API

Background

The Office of Generic Drugs (OGD) requested the infrared (IR) spectroscopic analysis of test and USP Reference Standard samples for atorvastatin calcium active pharmaceutical ingredient (API) provided by four different applicants. Each test and reference sample was prepared for IR analysis using the dry United States Pharmacopeia (USP) <197K> method and the additional <197K> method with use of solvent. A summary of the methods is given in Appendix A. This report contains the IR spectroscopic identification results using these two preparatory routes.

Conclusion

The preparation method used for IR identification tests was shown to be critical in determining whether a particular test sample matched the USP reference standard. Test samples from all four applicants fail to meet the USP specification using the dry <197K> procedure. Test samples from three of the four applicants meet the USP specification using the solvent <197K> procedure. The Apotex test sample fails the USP specification due to an additional maximum at (b) (4) cm^{-1}. This peak is likely due to residual (b) (4) present in the sample preparation. Similarity for all samples was evaluated using both the USP criteria (visual peak maxima comparison) and a computer-based correlation coefficient. The computer-based correlation coefficient indicated a strong match (>95%) for all samples using the solvent procedure.

Appendices

Appendix A: Preparation Details for Samples Analyzed by IR Spectroscopy
Appendix B: Brief Description of Spectroscopic Techniques and Methods used for Identification Tests
Appendix C: Results of Identification Tests

Reference ID: 3046737

Appendix A: Preparation Details for Samples Analyzed by IR Spectroscopy

Sample Number	Manufacturer (Applicant)	USP <197K> Method	USP<197K> with use of solvent
12-12A-000	Teva Pharmaceutical	Mixed 2 mg of USPRS with 300 mg KBr and pressed mixture into a pellet for analysis. Repeated procedure for test sample.	Dissolved equal portions of test sample and USPRS in equal volumes methanol, evaporated to dryness in similar containers under identical conditions. Mixed 2 mg of resulting residue with 300 mg KBr and pressed mixture into pellet for analysis.
12-12A-001	LEK D.D. (Sandoz)	Mixed 2 mg of USPRS with 300 mg KBr and pressed mixture into a pellet for analysis. Repeated procedure for test sample.	Dissolved equal portions of test sample and USPRS in equal volumes methanol, evaporated to dryness in similar containers under identical conditions. Mixed 2 mg of resulting residue with 300 mg KBr and pressed mixture into pellet for analysis.
12-12A-002	Matrix Pharmaceuticals Ltd. (Mylan)	Mixed 2 mg of USPRS with 300 mg KBr and pressed mixture into a pellet for analysis. Repeated procedure for test sample.	Applicant's method: Dissolved 5 mg test sample and USPRS in 1 mL methanol. Dried in petri dish in oven at 45°C for 15 min under vacuum (10-15 mm Hg). Mixed 2 mg of resulting residue with 300 mg KBr and pressed mixture into pellet for analysis.
11-90-548	Apotex	Mixed 2 mg of USPRS with 300 mg KBr and pressed mixture into a pellet for analysis. Repeated procedure for test sample.	Applicant's method: Dissolved 2 mg test sample and USPRS in 0.5mL of methanol then added 300 mg KBr. Dried entire mixture with nitrogen flow.and pressed mixture into pellet for analysis.

Important Abbreviations: USPRS (United States Pharmacopeia Reference Standard)
KBr (Potassium Bromide, a transparent material used for IR analysis)

Reference ID: 3046737

Appendix B: Brief Description of Spectroscopic Techniques and Methods used for Identification Tests

Sample Acquisition

Following the sample preparation techniques described in Appendix A, the samples were analyzed using the transmission sampling module on the Bruker Alpha-T FTIR spectrometer at DPA. Spectra were acquired under identical acquisition parameters: 4 cm^{-1} resolution, 16 scans (sample and background), and (b) (4) spectral range. Spectra were reported using transmittance (%) vs. wavenumber (cm).

Identification Tests

Two types of identification tests were used to evaluate the spectra: 1) USP method and 2) Computer-based evaluation. Under the criteria used by the USP method, a test spectrum is assigned a "Pass" (i.e., is the same as the USP reference spectrum) if the spectrum contains maxima at the same wavelengths as that of a similar preparation of the corresponding USP reference standard. For the computer-based evaluation, the OPUS software from the Bruker instrument is programmed to compare the spectrum (using the "Quick Compare" functionality) of the USP reference sample to the test sample by calculating the correlation coefficient. This value ranges between -1 to +1, but the program utilizes only the positive range and the negative values are reported as 0. Under this convention, the working range of the correlation coefficient is between 0 (poorest match) and 1 (perfect match). The OPUS program reports these values as percentages, so the range is essentially 0% to 100% and the value may be thought of as a hit quality index (HQI)[1]. Since broad baselines in the spectra may artificially result in high correlations,[2] even for obviously different spectra, we added first derivative preprocessing to reduce baseline effects. The threshold that must be met for a "Pass" is 95%.

[1.] Rodriguez, J. D.; Westenberger, B. J.; Buhse, L. F.; Kauffman, J. F. Quantitative Evaluation of the Sensitivity of Library-Based Raman Spectral Correlation Methods. *Anal. Chem.***2011**, *83*, 4061.

[2.] Kauffman, J. F.; Rodriguez, J. D.; Buhse, L. F. Spectral Preprocessing for Raman Searches. *Am. Pharm. Review*.**2011**, *14*, 34.

Reference ID: 3046737

Appendix C: Results of Identification Tests

Sample Number	Manufacturer (Applicant)	USP RS Lot #	Test Sample Lot #	<197K> Preparation USP Criteria ID Test	<197K> Preparation Quick Compare Test (HQI)	USP<197K> with use of solvent USP Criteria ID Test	USP<197K> with use of solvent Quick Compare Test (HQI)
12-12A-000	Teva Pharmaceutical	G0J276	7854ST01-786608810	FAIL	FAIL 65.37 %	PASS	PASS 99.46%
		G0J276	7866-24111	FAIL	FAIL 65.14%	PASS	PASS 98.12%
		G0J276	7866-24211	FAIL	FAIL 63.37%	PASS	PASS 99.15%
		G0J276	7866-24311	FAIL	FAIL 64.82%	PASS	PASS 99.90%
12-12A-001	LEK D.D. (Sandoz)	G0J276	B077055	FAIL	FAIL 62.95%	PASS	PASS 99.59%
12-12A-002	Matrix Pharmaceuticals Ltd. (Mylan)	F0I169	QCD-3/ASC/WS001/10	FAIL	FAIL 61.69%	PASS	PASS 99.74%
11-90-548	Apotex	G0J276	JX9789[a]	FAIL	FAIL 72.15%	Fail[b]	PASS 98.84% 97.83%

Note: USP Test Pass/Fail Criteria: Based on visual inspection of overlay of USP RS and test spectrum to meet criteria outlined in Appendix B. Quick Compare Test Criteria: Must be above the 95% similarity threshold. [a] Apotex lot JX9789 was run twice on different days. [b] Due to an extra peak in the test spectrum (for both trials) at (b) (4) cm^{-1} that is likely due to residual (b) (4) present in the sample.

Reference ID: 3046737

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/s/

JAMES F ALLGIRE
11/18/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Suhas Patankar, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Suhas.patankar@fda.hhs.gov
Phone: (240)-276-8464
Fax: (240)-276-8474

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: ANDA-090548

Name of Product: Atorvastatin Calcium Tablets, 10mg, 20 mg,40 mg and 80 mg

Applicant: Apotex Corp

Applicant's Contact Person: Kiran Krishnan

Telephone: 954-384-3986 Fax: 866-392-1774

Date Methods Validation Consult Request Form Received by DPA: N/A

Date Methods Validation Package Received by DPA: N/A

Date Samples Received by DPA: 9/27/11

Date Analytical Completed by DPA: 10/7/11

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

Report and summary of results are attached.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-2135
FAX (314) 539-2113

Date: October 7, 2011

To: Suhas Patankar, Ph.D., Lead Chemist (HFD-630)

Through: B.J.Westenberger, Deputy Director, Division of Pharmaceutical Analysis (HFD-920)

From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis (HFD-920)

Subject: Evaluation of ANDA 90-548
Atorvastatin Calcium Propylene Glycol Solvate
APOTEX Corp.

Background: The Division of Chemistry III requested the Division of Pharmaceutical Analysis (DPA) to evaluate the IR identification test for Atorvastin Calcium Propylene Glycol Solvate.

Conclusion: The ANDA method is acceptable for control and regulatory purposes; however, the applicant's product does not precisely match the USP reference standard by this method because of two small additional peaks in the applicant's product.

Results: The test was performed without methanol as per USP and the IR spectra for Atorvastatin Calcium Propylene Glycol Solvate and Atorvastatin Calcium USP Reference Standard were different. This difference may be due to polymorphism.

The ANDA method is (b) (4) The spectrum for the applicant's Atorvastatin Calcium Propylene Glycol Solvate had peaks a (b) (4) and (b) (4) which were not seen in the Atorvastatin Calcium USP Reference Standard. The standard and solvate spectra agreed over the rest of the spectra range. (See the attached overlaid spectra.) This is similar to what the innovator reported in the method validation report for the method.


(b) (4)

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/s/

JAMES F ALLGIRE
10/11/2011

BENJAMIN J WESTENBERGER
10/11/2011

ANDA 090548

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Apotex Inc

Sivakumar R. Vaithiyalingam, PhD

Office of Generic Drugs

Division of Chemistry III, Team 33

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Section V:	Review of Amendment Dated February 22, 2011 (Current Review)	
Section VI:	Review of Amendment Dated March 17, 2011 (Current Review)	
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	Drug Product Specification (Stability)	52
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(b) (4)

Reference ID: 2937666

CMC REVIEW DATA SHEET

1. ANDA #: 090548
2. REVIEW #: 04
3. REVIEW DATE: 03/11/2011
4. REVIEWER: SR Vaithiyalingam, PhD
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	05-01-2008
Amendment	08-06-2008
Amendment	02-11-2009
Amendment	03-01-2010
Amendment	06-23-2009
Amendment	11-09-2010

6. SUBMISSION(S) BEING REVIEWED:

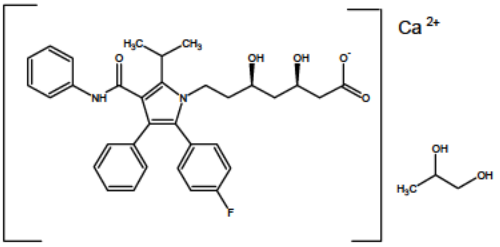
Submission(s) Reviewed	Document Date
Amendment	02/22/2011
Amendment	03/17/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Apotex Inc.
Address: 150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada
Apotex Corp., 2400 N. Commerce Parkway, Suite 400, Weston, FL 33326
Representative: Kiran Krishnan
Telephone: 954-384-3986
Fax: 866-392-1774

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
Patent Information: **P IV**
10. PHARMACOL. CATEGORY: Lipid Lowering Agent
11. DOSAGE FORM: Tablets, **MDD 80 mg**
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:

Molecular Structure:



(b)

Molecular Formula: $C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$, *Molecular Weight:* 1231.46 (b) (4) Atorvastatin Ca)

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21574	II	Apotex	Atorvastatin Ca Propylene Glycol	1	Not	03/21/2011	Not

Reference ID: 2937666

(b) (4)		(b) (4)				
	III		4	Adequate		Adequate
	III		4			
	III		4			
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[1] Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (Enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Withhold	03/10/2011	Several sites of APOTEX related to this ANDA is withheld
Methods Validation	Not Applicable		
Labeling	Acceptable	04/29/2010	Ann Vu
Bioequivalence	Adequate	06/08/2010	Li Gong
EA	Adequate	01-20-09	
Radiopharmaceutical	Not Applicable		
Pharm/Tox, # 2009-0305	**Yes**		**Indra Antonipillai, 04/28/2009**

19. ORDER OF REVIEW: The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #4)

A. Description of the Drug Product(s) and Drug Substance(s)

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, biconvex film-coated tablets: Engraved "APO" on one side, "A10" on the other side. 20 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV20" on the other side. 40 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV40" on the other side. 80 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV80" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4). The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4) croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug

Reference ID: 2937666

Substance: The DS is a propylene glycol solvate of atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The MDD for adults is 80 mg.

B. Description of How the Drug Product is Intended to be Used

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 30 and 90 counts and in bulk packages for pharmacy. The DP is manufactured by (b) (4) using (b) (4). The unit operations ar (b) (4) Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions. Based on the MDD of 80 mg, DS IT is 0.10% and QT is 0.15% and the DP RT is 0.1%, IT is 0.2% and QT is (b) (4)%.

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to few CMC related minor deficiencies.

Section II: Review of Amendment Dated June 23, 2009 (Adopted from previous review)

Deficiency 1 (b) (4)

(b) (4)

Reference ID: 2937666
53 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

SIVAKUMAR R VAITHIYALINGAM
04/25/2011

ROBERT T GAINES
04/25/2011

SUHAS J PATANKAR
04/25/2011

ANDA 090548

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Apotex Inc

Sivakumar R. Vaithiyalingam, PhD

Office of Generic Drugs

Division of Chemistry III, Team 33

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	Drug Product Description and Composition	41
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List of Deficiencies To Be Communicated		55

(b) (4)



CMC REVIEW DATA SHEET

1. ANDA #: 090548
2. REVIEW #: 03
3. REVIEW DATE: 11/30/2010
4. REVIEWER: SR Vaithiyalingam, PhD
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	05-01-2008
Amendment	08-06-2008
Amendment	02-11-2009
Amendment	03-01-2010
Amendment	06-23-2009

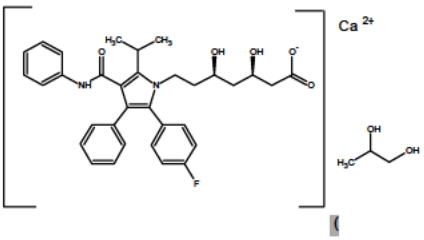
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	11/09/2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada Apotex Corp., 2400 N. Commerce Parkway, Suite 400, Weston, FL 33326
Representative:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	954-349-4233

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
10. PHARMACOL. CATEGORY: Lipid Lowering Agent
11. DOSAGE FORM: Tablets, **MDD 80 mg**
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:
Molecular Structure:



Molecular Formula: $C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$, *Molecular Weight:* 1231.46 ([(b) (4)], Atorvastatin Ca)

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21574	II	Apotex Pharmachem Inc	Atorvastatin Ca Propylene Glycol Solvate	1	Not Adequate	07-20-10	Not Adequate
[(b) (4)]	III	[(b) (4)]		4			

(b) (4)	III	(b) (4)	4			
	III		4			
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	III		4			

Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (Enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Withhold	07/29/2010	Several sites of APOTEX related to this ANDA is withheld
Methods Validation	Not Applicable		
Labeling	Acceptable	04/29/2010	Ann Vu
Bioequivalence	Adequate	06/08/2010	Li Gong
EA	Adequate	01-20-09	
Radiopharmaceutical	Not Applicable		
Pharm/Tox, # 2009-0305	**Yes**		**Indra Antonipillai, 04/28/2009**

19. ORDER OF REVIEW: The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #3)

A. Description of the Drug Product(s) and Drug Substance(s)

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, biconvex film-coated tablets: Engraved "APO" on one side, "A10" on the other side. 20 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV20" on the other side. 40 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV40" on the other side. 80 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV80" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4). The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4) croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is a propylene glycol solvate of atorvastatin calcium. The DS is "low soluble" in

water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The MDD for adults is 80 mg.

B. Description of How the Drug Product is Intended to be Used

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 30 and 90 counts and in bulk packages for pharmacy. The DP is manufactured by (b) (4) using (b) (4). The unit operations are (b) (4). Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions. Based on the MDD of 80 mg, DS IT is 0.10% and QT is 0.15% and the DP IT is 0.2% and QT is (b) (4)%.

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to few CMC related minor deficiencies.

53 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

SIVAKUMAR R VAITHIYALINGAM
01/11/2011

ROBERT T GAINES
01/11/2011

GUOPING SUN
01/12/2011

ANDA 090548

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Apotex Inc

Sivakumar R. Vaithiyalingam, PhD

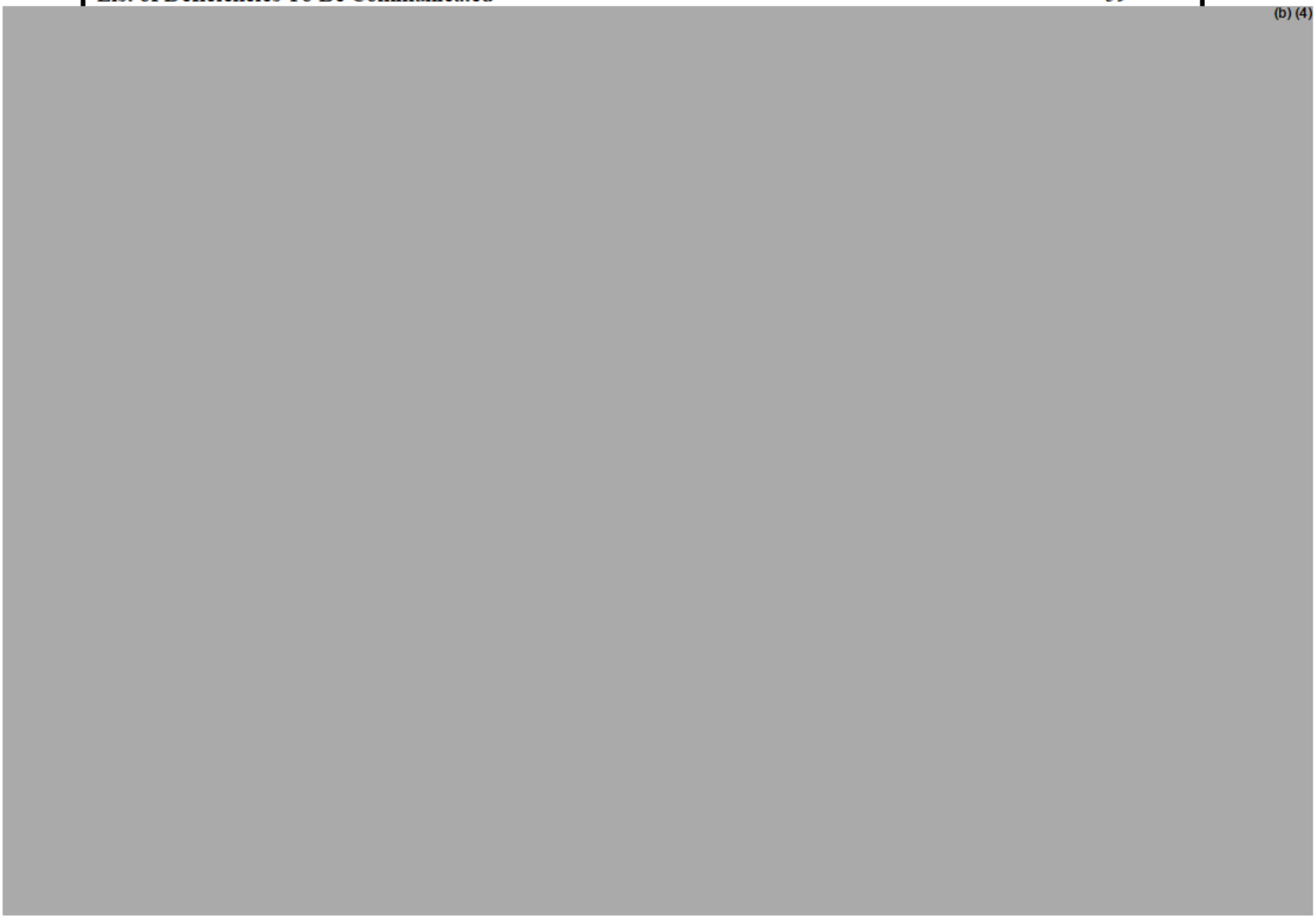
Office of Generic Drugs

Division of Chemistry III, Team 12

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	Drug Product Specification (Stability)	55
List of Deficiencies To Be Communicated		59

(b) (4)



CMC REVIEW DATA SHEET

1. ANDA #: 090548
2. REVIEW #: 02
3. REVIEW DATE: 07/19/2010
4. REVIEWER: SR Vaithiyalingam, PhD
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	05-01-2008
Amendment	08-06-2008
Amendment	02-11-2009

6. SUBMISSION(S) BEING REVIEWED:

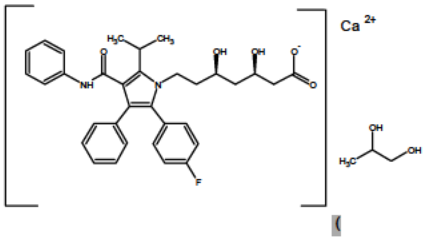
Submission(s) Reviewed	Document Date
Amendment	03-01-2010
Amendment	06-23-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada Apotex Corp., 2400 N. Commerce Parkway, Suite 400, Weston, FL 33326
Representative:	Kiran Krishnan
Telephone:	954-384-3986
Fax:	954-349-4233

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
10. PHARMACOL. CATEGORY: Lipid Lowering Agent
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:

Molecular Structure:



Molecular Formula: $C_{66}H_{68}CaF_2N_4O_{10} \cdot C_3H_8O_2$
Molecular Weight: 1231.46 (b) (4) Atorvastatin Calcium)

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21574	II	Apotex Pharmachem Inc	Atorvastatin Ca Propylene Glycol Solvate	1	Not Adequate	01-30-2008	Not Adequate
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (Enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending	07/29/2010	Several sites of APOTEX related to this ANDA is withheld
Methods Validation	Not Applicable		
Labeling	Acceptable	04/29/2010	Ann Vu
Bioequivalence	Adequate	06/08/2010	Li Gong
EA	Adequate	01-20-09	
Radiopharmaceutical	Not Applicable		
Pharm/Tox	None		

19. ORDER OF REVIEW: The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #1)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval,

biconvex film-coated tablets: Engraved "APO" on one side, "A10" on the other side. 20 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV20" on the other side. 40 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV40" on the other side. 80 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV80" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4). The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4) croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is a propylene glycol solvate of atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The MDD for adults is 80 mg.

B. Description of How the Drug Product is Intended to be Used

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 30 and 90 counts and in bulk packages for pharmacy. The DP is manufactured by (b) (4). The unit operations are (b) (4). Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions. Based on the MDD of 80 mg, DP IT is 0.10% and QT is 0.15% and the DS IT is 0.2% and QT is (b) (4)%.

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to few CMC related minor deficiencies.

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/s/

SIVAKUMAR R VAITHIYALINGAM
09/17/2010

ROBERT T GAINES
09/20/2010

ALOKA SRINIVASAN
09/20/2010

ANDA 90-548

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Apotex Inc

Sivakumar R. Vaithiyalingam, PhD

Office of Generic Drugs

Division of Chemistry III, Team 12

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(b) (4)

[redacted]

CMC REVIEW DATA SHEET

1. ANDA #: 90-548
2. REVIEW #: 01
3. REVIEW DATE: 01-26-09
4. REVIEWER: SR Vaithiyalingam, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents: None	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	05-01-2008
Amendment	08-06-2008
Amendment	02-11-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Apotex Inc.
150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada

Address: Apotex Corp.
2400 N. Commerce Parkway, Suite 400
Weston, FL 33326

U.S. Representative: Kiran Krishnan
Telephone: 954-384-3986
Fax: 954-349-4233

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
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11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:
Please see 2.3.S
17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

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(b) (4)	III		(b) (4)	4			
	III			4			

(b) (4)		(b) (4)				
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			

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[2] Adequate, Inadequate, or N/A (Enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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EES	Pending	01-20-09	
Methods Validation	Not Applicable		
Labeling	Pending	01-20-09	Ann Vu
Bioequivalence	Pending	01-20-09	
EA	Adequate	01-20-09	
Radiopharmaceutical	Not Applicable		
Pharm/Tox	None		

19. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No
If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #1)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, biconvex film-coated tablets: Engraved "APO" on one side, "A10" on the other side. 20 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV20" on the other side. 40 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV40" on the other side. 80 mg strength is a White, oval, biconvex film-coated tablets: Engraved "APO" on one side, "ATV80" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4). The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS

may be critical since this DS is "low soluble" (BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4) croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is a propylene glycol solvate of atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The MDD for adults is 80 mg.

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The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 30 and 90 counts and in bulk packages for pharmacy. The DP is manufactured by (b) (4). The unit operations are (b) (4) Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions DS IT is 0.10% and QT is 0.15% and the DS IT is (b) (4)% and QT is (b) (4)%.

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to few CMC related minor deficiencies.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

1.1.2. Form 356h – Provided and Complete

1.3. Administrative Documents

1.3.2. Field Certification:	Not Available (Not applicable for electronic application)
1.3.3. Debarment Certification:	Provided
1.3.4. Financial Certifications:	Provided
1.3.5.1. Patent Information:	Provided
1.3.5.2.Patent Certification	Provided

1.4. References

1.4.1. Letters of Authorization:	Provided

1.12. Other Correspondence

1.12.11. Basis of Submission:	Provided
1.12.12. Comparison between Generic and RLD:	Provided

1.12.14. Request for Exclusion from Requirement for Environmental Impact Analysis Statement: Exclusion from requirement for environmental assessment statement is provided and is satisfactory.

1.12.15 Request for Bio-waiver: Provided

1.14 Labeling: Provided

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/s/

Sivakumar R Vaithiyalingam
3/17/2009 08:47:33 AM
CHEMIST

Jeanne Skanchy
3/17/2009 02:51:54 PM
CSO

Robert Iser
3/18/2009 01:18:40 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	090548		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	10 mg, 20 mg, 40 mg and 80 mg		
Applicant Name	Apotex Inc.		
Address	150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	U.S. Agent: Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	
Applicant's Point of Contact	Kiran Krishnan		
Contact's Telephone Number	954-384-3986		
Contact's Fax Number	866-392-1774		
Original Submission Date(s)	August 7, 2008		
Submission Date(s) of Amendment(s) Under Review	February 22, 2010 (current amendment)		
Reviewer	Li Gong, Ph.D.		
Study Number (s)	Fasting	Fed	
Study Type (s)	ATOR-IMTB-05EB05-2FA-(2) (AQ4221)	ATOR-IMTB-05EB03-2FE (AQ3681)	
Strength (s)	80 mg	80 mg	
Clinical Site	Apotex Inc.		
Clinical Site Address	BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario CANADA		
Analytical Site	(b) (4)		
Analytical Site Address	(D) (4)		
OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
Bioequivalence Study Tracking/supporting Document #	**Study / Test Type**	**Strength**	**Review Result**
44	**Dissolution**	**10, 20, 40 and 80 mg**	**Adequate**
44	**Fasting**	**80 mg**	**Adequate**
1, 2 & 5	**Fed**	**80 mg**	**Adequate**

Review of an Amendment

I. Executive Summary

The DBE conducted a "dissolution only" review on this ANDA [**1st review - DARRTS for ANDA 090548 of JIANG, XIAOJIAN 11/25/2008 N/A 11/25/2008 REV-BIOEQ-02(Dissolution Review) Original-1 Archive**]. As per this 1st review, there were 2 deficiencies. The DBE also conducted a "full ANDA" review along with the dissolution amendment (a response to 2 deficiencies) [**2nd review - DARRTS for ANDA 090548 of GONG, LI 01/28/2010 N/A 01/28/2010 REV-BIOEQ-01(General Review) Original-1 Archive**]. As per the 2nd review, the firm submitted the results of a fasting and a fed BE studies, comparing its test product, Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Lipitor® (Atorvastatin Calcium), 80 mg, from Pfizer (NDA 021595). The firm's fed study was adequate. However, its fasting BE study was incomplete because of the 2 deficiencies. As a 1st deficiency, the firm was asked to provide explanation(s) for a discrepancy between the reanalysis tables in the bioanalytical part of the study. As a 2nd deficiency, the firm was asked to acknowledge the FDA-recommended dissolution method and specification.

In the current amendment the firm has submitted its response to the 2 deficiencies. The firm's response is acceptable. Therefore, the firm's fasting and fed BE studies are now both **adequate**. Also, the dissolution testing is complete (**adequate**) because the firm acknowledged our recommendation of the dissolution method and specification.

The DBE grants the waiver requests for *in vivo* BE study requirements for the following strengths: (i) 10 mg, (ii) 20 mg, and (iii) 40 mg of the test product, based on criteria set forth in 21 CFR § 320.22 (d) (2).

No Division of Scientific Investigations (DSI) inspection is pending or necessary. Both clinical and analytical sites were last inspected on 2/21/2008 and the inspection results for the ANDA (b) (4) of both sites were "VAI".

The amendment is **adequate.**

II. II. Table of Contents

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D. Deficiency Comments....6
E. Recommendations....6
F Appendix....7
G. Outcome Page....13

III. III. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See DARRTS for ANDA 090548 of GONG, LI 01/28/2010 N/A 01/28/2010 REV-BIOEQ-01(General Review) Original-1 Archive, and JIANG, XIAOJIAN 11/25/2008 N/A 11/25/2008 REV-BIOEQ-02(Dissolution Review) Original-1 Archive

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Review of Amendment Submissions

Deficiency #1: *For your fasting study (Study No. AQ4221), there was discrepancy between the numbers of sample reassays for code B (29 for the test product and 23 from the reference product per your CTD summary for "Reanalysis of Study Samples") and those for the same code in the reassay individual data submitted (50 for the test product*

and 40 for the reference product; Appendix 16.5.1.8.6.1 & 2 Summary of Repeat Assays Study AQ4221). You should provide explanation(s) for the discrepancy. Also, you are advised to provide a table listing all the original (if any) and repeat values for samples that were reassayed for the reason of "Analysis incomplete".

Firm's Response to Deficiency #1:

"Please see the updated tables 9.1, 9.2, and 9.3 which summarize the reanalysis of study samples in Attachment 1. This updated summary for reanalysis of study samples shows 28 for the test product and 24 for the reference product for sample reassays (Total = 52) coded B for each of the analytes (updated from 29 and 23 as previously reported.)

Table 16.5.1.8.6.2 in the report samples coded B but lists each sample only once and is not specified by analyte as in Table 16.5.1.8.6.1. Each of these samples were repeated for each of the three analytes AQ, OAQ and PAQ therefore, the total reassay of individual data in table 16.5.1.8.6.2 is 33 samples x 3 analytes = 99.
Table 16.5.1.8.6.1 shows 57 B coded samples for a total of 156 B coded samples in both tables. This is consistent with the total number of B coded samples in the CTD summary for "Reanalysis of Study Samples" for 3 analytes (52 B coded samples x 3 analytes = 156).

A table listing original and repeat values for samples that were reassayed for the reason of 'Analysis incomplete' is included. Please refer to Attachment 2, entitled 'Tables Coded B in Study AQ4221'. Note that in all cases there were no original values for any of these repeat samples."
AQ3681.

Reviewer's Comments on Firm's Response to Deficiency #1:

- There was a counting error in our 1st deficiency. Thus the firm's answer to a wrong question is not expected to be appropriate.
- This reviewer therefore revisited the original raw data and found out that there was **no discrepancy**. The entire situation is explained below.
- From each sample an assay measures 3 analytes (atorvastatin, 2-OH-A and 4-OH-A).
- The CTD Summary Tables showed that 29 test samples and 23 reference samples (Total of 52 samples) were reanalyzed under the code B (Incomplete analysis) for all 3 analytes. The firm has revised that by stating 28 test samples and 24 reference samples (Total of 52 samples) were reanalyzed under the code B (incomplete analysis). This is acceptable (see below).
- In the original raw data the firm provided two other tables detailing all reassayed samples. Of these 2, the Table 16.5.1.8.6.1 showed 19 samples (11 tests + 8 references) were reassayed under the code B. In this table the firm instead of

reporting 19 reassays reported them as 57 reassays (19 x 3 analytes) and that caused our counting error in the 1st deficiency.

- The 2nd reassay table 16.5.1.8.6.2 showed 33 samples (17 tests and 16 references) samples reassayed under the code B. In this table the firm did not report reanalysis on basis of 3 analytes.
- Thus, these two tables have 19 + 33 = 52 reassays (28 for test + 24 for reference) under the code B. This count matches with the count in the CTD summary table in the bullet 4.
- The reviewer made sure that there were a total of 52 samples for reassay under the code B in original submission and confirmed by the updated raw data submitted in this amendment. The updated raw data are shown on the page 7.

- Thus, there was no deficiency 1 and the firm's response is acceptable.

Deficiency #2: *Your dissolution testing data are acceptable. However, your proposed specification of NLT (b)(4)% (Q) in (b)(4) minutes is not acceptable. Based on the dissolution data submitted, the DBE recommends a more appropriate specification. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:*

The dissolution should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37 ± 0.5°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> *NLT (b)(4)% (Q) amount of the labeled Atorvastatin Calcium is dissolved in 15 minutes.*

Firm's Response to Deficiency #2:

"We acknowledge and accept the following DBE recommended dissolution method and specification:

The dissolution should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37 ± 0.5°C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

NLT (b)(4)% (Q) amount of the labeled Atorvastatin Calcium is dissolved in 15 minutes.

Apotex commits to revising the drug product method and specifications for all strengths according to the above DBE recommendations."

Reviewer's Comments on Firm's Response to Deficiency #2:

- The firm's response is acceptable.

- Therefore, the firm's dissolution testing is now adequate.

D. Deficiency Comments

None.

E. Recommendations

1. The Division of Bioequivalence (DBE) accepts the fasting bioequivalence (BE) study (Study No. AQ4221) conducted by Apotex Inc on its Atorvastatin Calcium Tablets, 80 mg, Lot # FD051-317, comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot # 24856V**.**

2. The DBE accepts the fed BE study (Study No. AQ3681) conducted by Apotex Inc on its Atorvastatin Calcium Tablets, 80 mg, Batch# Lot # FD051-317, comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot # 24856V**.**

3. The firm's *in vitro* dissolution testing is adequate. The dissolution testing should be conducted in 900 mL of 0.05 M Phosphate buffer, pH 6.8, at 37ºC $\pm$ 0.5º C using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) of Atorvastatin Calcium is dissolved in 15 minutes.

4. The DBE grants the waiver requests for *in vivo* BE study requirements for the following strengths: (i) 10 mg, (ii) 20 mg, and (iii) 40 mg of the test product, based on criteria set forth in 21 CFR § 320.22 (d) (2).

5. The DBE deems the test product, Atorvastatin Calcium Tablets,, 10 mg, 20 mg, 40 mg and 80 mg, manufactured by Apotex Inc, to be bioequivalent to the reference product, Lipitor® (Atorvastatin Calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg, manufactured by Pfizer.

The amendment is **adequate**.

F. Appendix

1. Updated Tables:

Table 9.1 Reanalysis of Study Samples

Fasting Study, Study No. ATOR-IMTB-05EB05-2FA (AQ4221) Analyte: Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	28	24	0.72	0.61	0.0	0.0	0.0	0.0
G: Highest and/or Lowest Std Missing	4	4	0.10	0.10	0.0	0.0	0.0	0.0
F: Outside Range	0	1	0.00	0.03	0.0	0.0	0.0	0.0
Total	33	28	0.82	0.74	0.0	0.0	0.0	0.0

Table 9.2 Reanalysis of Study Samples

Fasting Study, Study No. ATOR-IMTB-05EB05-2FA (AQ4221) Analyte: 2-Hydroxy-Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	28	24	0.72	0.61	0.0	0.0	0.0	0.0
C: Poor Chromatography	0	1	0.00	0.03	0.0	0.0	0.0	0.0
G: Highest and/or Lowest Std Missing	4	2	0.10	0.05	0.0	0.0	0.0	0.0
Total	32	27	0.82	0.69	0.0	0.0	0.0	0.0

Table 9.3 Reanalysis of Study Samples

Fasting Study, Study No. ATOR-IMTB-05EB05-2FA (AQ4221) Analyte: 4-Hydroxy-Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	28	24	0.72	0.61	0.0	0.0	0.0	0.0
C: Poor Chromatography	0	2	0.00	0.05	0.0	0.0	0.0	0.0
G: Highest and/or Lowest Std Missing	14	19	0.36	0.49	0.0	0.0	0.0	0.0
Total	42	45	1.08	1.15	0.0	0.0	0.0	0.0

2. Tables Coded B in Fasting Study No. AQ4221

Sample Name	Analyte	Reason	Original values (ng/mL)	Repeat values (ng/mL)
(b) (4)				

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(b) (4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090548

APPLICANT: Apotex Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

The DBE acknowledges that the dissolution testing for the test product will be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37°C ± 5°C, using USP apparatus 2 (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than (b)(4)% (Q) of the labeled amount of Atorvastatin Calcium in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

G. Outcome Page

ANDA: 090548

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11342	02/22/2010	Other	Study Amendment	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90548	ORIG-1		ATORVASTATIN CALCIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI GONG
06/04/2010

SHRINIWAS G NERURKAR
06/04/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/08/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090548	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength(s)	10 mg, 20 mg, 40 mg and 80 mg	
Applicant Name	Apotex Inc.	
Address	150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	U.S. Agent: Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
Applicant's Point of Contact	Kiran Krishnan	
Contact's Telephone Number	954-384-3986	
Contact's Fax Number	416-401-3809	
Original Submission Date(s)	DATE OF APPLICATION: August 6, 2008 DATE (RECEIVED) ACCEPTABLE FOR FILING: August 7, 2008	
Submission Date(s) of Amendment(s) Under Review	December 24, 2008 (Dissolution amendment)	
Reviewer	Li Gong, Ph.D.	
Study Number (s)	Fasting	Fed
Study Type (s)	ATOR-IMTB-05EB05-2FA-(2) (AQ4221)	ATOR-IMTB-05EB03-2FE (AQ3681)
Strength (s)	80 mg	80 mg
Clinical Site	Apotex Inc.	
Clinical Site Address	BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario CANADA	
Analytical Site	(b) (4)	
Analytical Site Address		
OVERALL REVIEW RESULT	**INADEQUATE**	
WAIVER REQUEST RESULT	**INADEQUATE**	
DSI REPORT RESULT	**ADEQUATE**	

Bioequivalence Study Tracking/supporting Document #	**Study / Test Type**	**Strength**	**Review Result**
5	**Dissolution**	**10, 20, 40 and 80 mg**	**Inadequate**
1, 2 & 5	**Fasting**	**80 mg**	**Inadequate**
1, 2 & 5	**Fed**	**80 mg**	**Adequate**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfzier's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The results are summarized in the tables below.

Fasting: For Atorvastatin:

Atorvastatin Calcium Tablets, 1 x 80 mg Fasting Bioequivalence Study No. AQ4221, N=85 (Male=85 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	166.74	158.53	1.05	100.84	109.70
AUC∞ (ng·hr/mL)	169.04	160.64	1.05	101.20	109.41
Cmax (ng/mL)	36.05	35.81	1.01	92.43	109.64

Fasting: For 2-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets, 1 x 80 mg Fasting Bioequivalence Study No. AQ4221, N=85 (Male=85 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	178.27	173.30	1.03	97.00	109.09
AUC∞ (ng·hr/mL)	182.78	177.43	1.03	97.65	108.68
Cmax (ng/mL)	29.10	28.50	1.02	92.62	112.60

Fasting: For 4-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets, 1 x 80 mg Fasting Bioequivalence Study No. AQ4221, N=85 (Male=85 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	17.95	16.66	1.08	100.08	116.00
AUC∞ (ng·hr/mL)	22.04	20.39	1.08	103.23	113.18
Cmax (ng/mL)	1.05	0.98	1.07	97.05	118.29

Fed: For Atorvastatin:

Atorvastatin Calcium Tablets, 1 x 80 mg Fed Bioequivalence Study No. AQ3681, N=49 (Male=49 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	146.48	146.57	1.00	95.65	104.41
AUC∞ (ng·hr/mL)	148.30	148.53	1.00	95.61	104.28
Cmax (ng/mL)	30.71	29.24	1.05	93.74	117.65

Fed: For 2-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets, 1 x 80 mg Fed Bioequivalence Study No. AQ3681, N=49 (Male=49 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	140.37	134.07	1.05	101.01	108.52
AUC∞ (ng·hr/mL)	144.61	138.64	1.04	100.76	107.99
Cmax (ng/mL)	18.96	17.10	1.11	101.38	121.21

Fed: For 4-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets, 1 x 80 mg Fed Bioequivalence Study No. AQ3681, N=49 (Male=49 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	16.58	15.76	1.05	100.60	110.01
AUC∞ (ng·hr/mL)	20.42	19.25	1.06	100.75	111.62
Cmax (ng/mL)	1.15	1.04	1.10	101.70	119.54

The firm's fed BE study is adequate. However, the firm's fasting BE study is **inadequate** due to the deficiency related to the analytical parts of the study. There were some discrepancies of numbers of sample reassays between the firm's CTD Summary Table for "Reanalysis of Study Samples" and the individual reassay data submitted. The firm should provide its explanation(s) for such discrepancies.

The firm has conducted acceptable comparative dissolution testing on strengths of 20 mg, 40 mg and 80 mg of Atorvastatin Calcium Tablets, using the FDA-recommended method [DARRTS: 11/25/2008 REV-BIOEQ-02 (Dissolution Review)]. On 12/24/2008, the firm submitted the repeated dissolution testing data for the strength of 10 mg of the test and reference product). The firm's data for the additional dissolution testing on the 10 mg strength tablets is acceptable. However, the firm's specification [(b)(4)% (Q) in (b)(4) minutes] differs from the one recommended by the FDA [(b)(4)% (Q) in 15 minutes]. The firm should acknowledge its acceptance of the FDA-recommended method and specification. The dissolution testing is **inadequate**.

The waiver requests for *in vivo* BE study requirements for the firm's lower strengths of the test product, 10 mg, 20 mg and 40 mg, can **NOT** be granted at this time, pending firm's acceptable fasting BE study.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. Both clinical and analytical sites were last inspected on 2/21/2008 and the inspection results for the ANDA (b)(4) of both sites were "VAI".

The application is **inadequate**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Reference Product	Lipitor® (Atorvastatin calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg
RLD Manufacturer	Pfizer, Inc.
NDA No.	20-702
RLD Approval Date	December 17, 1996 (for 10 mg, 20 mg, and 40 mg strengths); April 7, 2000 (for 80 mg strength)

[1] RLD Labeling

Indication	Lipitor®'s indications are as follows: **(1) Prevention of cardiovascular disease** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina **(2) Hypercholesterolemia** LIPITOR is indicated: • as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb); • as an adjunct to diet for the treatment of patients with elevated serum TG levels*(Fredrickson* Type IV); • for the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet; • to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable;

	• as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL or b. LDL-C remains ≥ 160 mg/dL and: - there is a positive family history of premature cardiovascular disease or - two or more other CVD risk factors are present in the pediatric patient

PK/PD Information[1, 2, 3]

Bioavailability & Absorption	Atorvastatin is rapidly absorbed after oral administration. The absolute bioavailability of atorvastatin (parent drug) is approximately 14%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
Food Effect	Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, reduction is similar whether atorvastatin is given with or without food.
Tmax	1 – 2 hours
Metabolism	Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products which account for approximately70% of the circulating HMG-CoA reductase inhibitory activity. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.
Excretion	Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.
Half-life	14 hours (parent, atorvastatin) 20 – 30 hours (active metabolites)
Drug Specific Issues (if any)	**WARNINGS AND PRECAUTIONS:** • HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum

[2] Clinical Pharmacology On-line (2009): http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=672&sec=monphar
[3] MICROMEDEX (2009) On-line: http://csi.micromedex.com/DATA/TM/TM653.HTM?Top=Yes#8

	transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively. • It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. • Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. • Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures). • Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems

3.2 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	80 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	80 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	Atorvastatin, ortho- and parahydroxylated metabolites of atorvastatin. The ortho- and parahydroxylated metabolites of atorvastatin are formed by presystemic metabolism and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.
Bioequivalence based on:	90% CI of Atorvastatin
Waiver request of in-vivo testing:	10 mg, 20 mg and 40 mg
Source of most recent recommendations:	Individual Product Bioequivalence Recommendations: Atorvastatin, May 2008 (Final) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082580.pdf
Summary of OGD or DBE History:	The DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets: • ANDA #76-477 (Ranbaxy Labs) • ANDA #78-773 (Teva) • ANDA #77-575 (Sandoz) • ANDA #91-226 (Matrix Labs) • ANDA #90-548 (Apotex, current ANDA) The following studies are recommended to establish BE studies of atorvastatin tablets: a) single-dose, two-way crossover fasting *in-vivo* BE study comparing Atorvastatin CalciumTablets, 80 mg, to the RLD, Lipitor® Tablets, 80 mg. b) single-dose, two-way crossover fed *in-vivo* BE study comparing Atorvastatin Calcium Tablets, 80 mg, to RLD, Lipitor® Tablets, 80 mg. The firms are requested to measure atorvastatin, and ortho- and parahydroxylated metabolites of atorvastatin. (b) (4) 10 mg, 20 mg, and 40 mg, may be considered for waivers of *in-vivo* BE testing based on (1) acceptable BE studies on the 80 mg strength, (2) acceptable dissolution testing of the 10 mg, 20 mg, 40 mg, and 80 mg strengths, and (3) proportional similarity in the formulations of 10 mg, 20 mg, 40 mg, and 80 mg strengths

3.3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	-
In vitro dissolution	Yes	Reviewed in a separate report
Waiver requests	Yes	3
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	Yes	1 (Dissolution amendment)

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data		
Bioanalytical method validation report location	Section 16.6	Section 16.6	Section 16.6
Analyte	Atorvastatin	2-Hydroxyatorvastatin	4-Hydroxyatorvastatin
Internal standard (IS)	Atorvastatin D5	o-Hydroxyatorvastatin D5	p-Hydroxyatorvastatin D5
Method description	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction
Limit of quantitation	0.100 ng/mL	0.250 ng/mL	0.125 ng/mL
Average recovery of drug (%)	78.60 %	74.52 %	86.68 %
Average recovery of IS (%)	77.94 %	74.39 %	88.00 %
Standard curve concentrations (ng/mL)	0.100 to 100.030	0.250 to 100.000	0.125 to 50.010
QC concentrations (ng/mL)	QC A: 0.300 ng/mL, QC B: 36.014 ng/mL, QC C: 72.029 ng/mL	QC A: 0.750 ng/mL, QC B: 36.007 ng/mL, QC C: 72.014 ng/mL	QC A: 0.375 ng/mL, QC B: 18.005 ng/mL, QC C: 36.011 ng/mL
QC Intraday precision range (%)	QC A: 1.8 to 6.0 % QC B: 0.7 to 2.3 % QC C: 0.8 to 2.1 %	QC A: 2.3 to 4.4 % QC B: 1.1 to 2.5 % QC C: 0.8 to 1.8 %	QC A: 2.8 to 6.0 % QC B: 1.1 to 2.6 % QC C: 1.2 to 2.5 %
QC Intraday accuracy range (%)	QC A: 5.0 to 15.7 % QC B: 4.7 to 8.2 % QC C: 2.6 to 5.6 %	QC A: 3.3 to 12.3 % QC B: 1.1 to 8.3 % QC C: -1.8 to 7.2 %	QC A: -3.2 to 6.1 % QC B: -3.9 to 0.9 % QC C: -4.2 to 0.1 %
QC Interday precision range (%)	1.9 to 5.5 %	3.1 to 4.8 %	2.2 to 5.5 %
QC Interday accuracy range (%)	3.2 to 9.7 %	1.8 to 7.9 %	-2.5 to 1.1 %
Bench-top stability (hrs)	20 @ room temperature	20 @ room temperature	20 @ room temperature
Stock stability (days)	244 days @ 4ºC	244 days @ 4ºC	244 days @ 4ºC
Processed stability (hrs)	24 hours @ room temperature; 101 hours @	24 hours @ room temperature; 101 hours @ 4ºC	24 hours @ room temperature; 101 hours @ 4ºC

	4°C		
Freeze-thaw stability (cycles)	3 cycles	3 cycles	3 cycles
Long-term storage stability (days)	99 days @ -30°C set point freezer	99 days @ -30°C set point freezer	99 days @ -30°C set point freezer
Dilution integrity	Concentration diluted 2-fold and 4-fold	Concentration diluted 2-fold and 4-fold	Concentration diluted 2-fold and 4-fold
Selectivity	No known metabolites, endogenous plasma components or common drug/metabolites interfere with the analytical assay.	No known metabolites, endogenous plasma components or common drug/metabolites interfere with the analytical assay.	No known metabolites, endogenous plasma components or common drug/metabolites interfere with the analytical assay.

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

The long-term storage data of 99 days exceeds the storage period for the samples of the fasting (45 days) and fed (26 days) BE study. The anticoagulant used in the pre-study validation was Sodium Heparin and is the same as used in within study analysis. The pre-study validation data are acceptable.

3.5 In Vivo Studies

Table 1a. Fasting & Fed BE Study (Study Nos. AQ4221 & AQ3681): Atorvastatin

Study Ref. No.	†Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	‡T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
ATOR-IMTB-05EB03-2FE (AQ3681)	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Parke Davis), (USA) under fed conditions	Randomized single-dose 2-way crossover	Atorvastatin Calcium Tablets, (1 x 80 mg Oral Dose) [Lot # FD051-317]	49 (49/0) completing Healthy subjects 35.24 (21 - 54)	37.358 ±25.783	1.67 (0.52 – 5.06)	160.066 ±73.415	162.661 ±73.520	10.65 ±2.60	0.06863 ±0.01569	5.3.1.2
			Lipitor® Tablets, (1 x 80 mg Oral Dose) [Lot# 24856V]		35.693 ±25.866	1.33 (0.50 – 5.00)	160.311 ±70.630	163.533 ±71.381	10.64 ±2.86	0.06908 ±0.01604	
ATOR-IMTB-05EB05-2FA (AQ4221)	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Parke Davis), (USA) under fasting conditions	Randomized single-dose 2-way crossover	Atorvastatin Calcium Tablets, (1 x 80 mg Oral Dose) [Lot # FD051-317]	85 (85/0) completing Healthy subjects 34.78 (18 – 55)	38.827 ±18.241	1.33 (0.50 – 5.02)	179.851 ±80.300	182.804 ±80.976	9.89 ±2.91	0.07521 ±0.01960	5.3.1.2
			Lipitor® Tablets, (1 x 80 mg Oral Dose) [Lot# 24856V]		38.456 ±19.284	0.75 (0.37 – 5.00)	171.470 ±83.345	174.710 ±84.290	10.34 ±3.00	0.07220 ±0.01988	

Table 1b. Fasting & Fed BE Study (Study Nos. AQ4221 & AQ3681): 2-Hydroxy-Atorvastatin

Study Ref. No.	†Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	‡T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
ATOR-IMTB-05EB03-2FE (AQ3681)	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Parke Davis), (USA) under fed conditions	Randomized single-dose 2-way crossover	Atorvastatin Calcium Tablets, (1 x 80 mg Oral Dose) [Lot # FD051-317]	49 (49/0) completing Healthy subjects 35.24 (21 - 54)	21.634 ±12.157	2.00 (0.75 – 6.00)	149.638 ±56.480	155.560 ±57.423	11.17 ±2.60	0.06488 ±0.01279	5.3.1.2
			Lipitor® Tablets, (1 x 80 mg Oral Dose) [Lot# 24856V]		18.942 ±8.769	2.00 (0.75 – 5.02)	142.271 ±51.852	149.892 ±52.085	13.82 ±14.24	0.06115 ±0.01671	
ATOR-IMTB-05EB05-2FA (AQ4221)	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Parke Davis), (USA) under fasting conditions	Randomized single-dose 2-way crossover	Atorvastatin Calcium Tablets, (1 x 80 mg Oral Dose) [Lot # FD051-317]	85 (85/0) completing Healthy subjects 34.78 (18 – 55)	33.031 ±16.804	1.33 (0.75 – 7.00)	191.233 ±70.856	197.998 ±70.309	10.76 ±3.39	0.06974 ±0.01870	5.3.1.2
			Lipitor® Tablets, (1 x 80 mg Oral Dose) [Lot# 24856V]		31.324 ±15.391	1.00 (0.50 – 5.00)	184.224 ±66.862	189.557 ±66.968	11.24 ±3.50	0.06699 ±0.01905	

Table 1c. Fasting & Fed BE Study (Study No. AQ4221 & AQ3681): 4-Hydroxy-Atorvastatin

Study Ref. No.	†Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	‡T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
ATOR-IMTB-05EB03-2FE (AQ3681)	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Parke Davis), (USA) under fed conditions	Randomized single-dose 2-way crossover	Atorvastatin Calcium Tablets, (1 x 80 mg Oral Dose) [Lot # FD051-317]	49 (49/0) completing Healthy subjects 35.24 (21 - 54)	1.410 ±1.020	5.00 (0.75 – 16.00)	19.213 ±11.190	24.874 ±11.839	17.59 ±6.82	0.04407 ±0.01404	5.3.1.2
			Lipitor® Tablets, (1 x 80 mg Oral Dose) [Lot# 24856V]		1.252 ±0.881	5.00 (0.75 – 16.00)	18.160 ±10.482	24.371 ±11.689	17.61 ±6.46	0.04376 ±0.01572	
ATOR-IMTB-05EB05-2FA (AQ4221)	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Parke Davis), (USA) under fasting conditions	Randomized single-dose 2-way crossover	Atorvastatin Calcium Tablets, (1 x 80 mg Oral Dose) [Lot # FD051-317]	85 (85/0) completing Healthy subjects 34.78 (18 – 55)	1.218 ±0.768	7.04 (0.75 – 16.02)	20.790 ±11.636	27.401 ±11.766	17.50 ±10.69	0.04847 ±0.01891	5.3.1.2
			Lipitor® Tablets, (1 x 80 mg Oral Dose) [Lot# 24856V]		1.158 ±0.753	9.00 (0.50 – 16.03)	19.418 ±10.523	26.518 ±10.405	16.87 ±5.47	0.04530 ±0.01421	

† Based on number of subjects dosed in period 1
‡ Tmax is presented as median (range)

Table 1. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Fasting: For Atorvastatin:

Atorvastatin Calcium Tablets 80mg Dose (1 x 80mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. AQ4221)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	166.74	158.53	1.05	100.84	109.70
AUC∞ (ng*hr/mL)	169.04	160.64	1.05	101.20	109.41
Cmax (ng/mL)	36.05	35.81	1.01	92.43	109.64

Fasting: For 2-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets 80mg Dose (1 x 80mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. AQ4221)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	178.27	173.30	1.03	97.00	109.09
AUC∞ (ng*hr/mL)	182.78	177.43	1.03	97.65	108.68
Cmax (ng/mL)	29.10	28.50	1.02	92.62	112.60

Fasting: For 4-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets 80mg Dose (1 x 80mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. AQ4221)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	17.95	16.66	1.08	100.08	116.00
AUC∞ (ng*hr/mL)	22.04	20.39	1.08	103.23	113.18
Cmax (ng/mL)	1.05	0.98	1.07	97.05	118.29

Fed: For Atorvastatin:

Atorvastatin Calcium Tablets 80mg Dose (1 x 80mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. AQ3681)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	146.48	146.57	1.00	95.65	104.41
AUC∞ (ng*hr/mL)	148.30	148.53	1.00	95.61	104.28
Cmax (ng/mL)	30.71	29.24	1.05	93.74	117.65

Fed: For 2-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets 80mg Dose (1 x 80mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. AQ3681)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	140.37	134.07	1.05	101.01	108.52
AUC∞ (ng*hr/mL)	144.61	138.64	1.04	100.76	107.99
Cmax (ng/mL)	18.96	17.10	1.11	101.38	121.21

Fed: For 4-Hydroxy-Atorvastatin:

Atorvastatin Calcium Tablets 80mg Dose (1 x 80mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. AQ3681)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	16.58	15.76	1.05	100.60	110.01
AUC∞ (ng*hr/mL)	20.42	19.25	1.06	100.75	111.62
Cmax (ng/mL)	1.15	1.04	1.10	101.70	119.54

Table 2. Reanalysis of Study Samples

Fasting Study, Study No. ATOR-IMTB-05EB05-2FA (AQ4221) Analyte: Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	29	23	0.74	0.59	0.0	0.0	0.0	0.0
G: Highest and/or Lowest Std Missing	4	4	0.10	0.10	0.0	0.0	0.0	0.0
F: Outside Range	0	1	0.00	0.03	0.0	0.0	0.0	0.0
Total	33	28	0.84	0.72	0.0	0.0	0.0	0.0

Fasting Study, Study No. ATOR-IMTB-05EB05-2FA (AQ4221) Analyte: 2-Hydroxy-Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	29	23	0.74	0.59	0.0	0.0	0.0	0.0
C: Poor Chromatography	0	1	0.00	0.03	0.0	0.0	0.0	0.0
G: Highest and/or Lowest Std Missing	4	2	0.10	0.05	0.0	0.0	0.0	0.0
Total	33	26	0.84	0.66	0.0	0.0	0.0	0.0

Fasting Study, Study No. ATOR-IMTB-05EB05-2FA (AQ4221) Analyte: 4-Hydroxy-Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	29	23	0.74	0.59	0.0	0.0	0.0	0.0
C: Poor Chromatography	0	2	0.00	0.05	0.0	0.0	0.0	0.0
G: Highest and/or Lowest Std Missing	14	19	0.36	0.49	0.0	0.0	0.0	0.0
Total	43	44	1.10	1.13	0.0	0.0	0.0	0.0

Fed Study, Study No. ATOR-IMTB-05EB03-2FE (AQ3681) Analyte: Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	3	1	0.14	0.05	3	1	0.14	0.05
F: Outside Range	1	3	0.05	0.14	1	3	0.05	0.14
Total	4	4	0.19	0.19	4	4	0.19	0.19

Fed Study, Study No. ATOR-IMTB-05EB03-2FE (AQ3681) Analyte: 2-Hydroxy-Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	3	1	0.14	0.05	3	1	0.14	0.05
F: Outside Range	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	3	1	0.14	0.05	3	1	0.14	0.05

Fed Study, Study No. ATOR-IMTB-05EB03-2FE (AQ3681) Analyte: 4-Hydroxy-Atorvastatin Additional information in Table 16.5.1.8.6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of samples reanalyzed used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B: Analysis Incomplete	3	1	0.14	0.05	3	1	0.14	0.05
F: Outside Range	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	3	1	0.14	0.05	3	1	0.14	0.05

Did use of recalculated plasma concentration data change study outcome?

See comments below.

Comments from the Reviewer:

- For the firm's fasting study (Study No. AQ4221), there was discrepancy between the numbers of sample reassays for code B and that for the same code in reassay raw data submitted. The firm is asked to provide explanation(s) for the discrepancy.

- Also, the firm should provide a table of the original and repeat values that were reassayed for the reason of "Analysis incomplete".

3.6 Formulation

Location in appendix	See Section 4.2 (Formulation Data)
If a tablet, is the RLD scored?	No (per RLD picture in Clinical Pharmacology website)
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	

3.7 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: 11/25/2008 REV-BIOEQ-02(Dissolution Review)
Source of Method (USP, FDA or Firm)	FDA
Medium	0.05 M Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (paddle)
Rotation (rpm)	75 rpm
Specification(s)	(b)(4)% (Q) of the amount of Atorvastatin is dissolved in 15 minutes (pending the firm's acknowledgment of the DBE-recommended specification)
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	Pending the firm's acknowledgment of the specification above
If not then why?	

Reviewer's notes:

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution data with the FDA-recommended method were acceptable for the 20 mg, 40 mg and 80 mg strengths. However, for the 10 mg strength test product, one tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. The firm was asked to repeat the dissolution testing using the FDA-recommended method for the 10 mg strength only [Reviewed in a separate report; DARRTS: 11/25/2008 REV-BIOEQ-02 (Dissolution Review)]. On 12/24/2008, the firm submitted the repeated dissolution testing data for the strength of 10 mg of the test and reference product. The firm's data for the additional dissolution testing on the 10 mg strength tablets is acceptable. However, the firm's proposed specification [(b)(4)% (Q) in (b)(4) minutes] differs from the one recommended by the FDA (b)(4)% (Q) in 15 minutes]. The firm should acknowledge for acceptance of the FDA-recommended specification. The dissolution testing is **inadequate**.

3.8 Waiver Request(s)

Strengths for which waivers are requested	10 mg, 20 mg and 40 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Pending the firm's acknowledgment of the DBE-recommended specification
Waivers granted?	**WAIVERS DENIED**
If not then why?	Refer to Deficiency section

3.9 Deficiency Comments

1. For the firm's fasting study (Study No. AQ4221), there was discrepancy between the numbers of sample reassays for code B (Total: 156 samples; 29 for test product and 23 for the reference product for the respective analyses of Atorvastatin, 2-Hydroxy-atorvastatin and 4-Hydroxy-atorvastatin per the firm's CTD summary for "Reanalysis of Study Samples") and that for the same code in reassay individual data submitted (Total: 90 samples; 50 for the test product and 40 for the reference product; Appendix 16.5.1.8.6.1 & 2 Summary of Repeat Assays Study AQ4221). The firm is asked to provide explanation(s) for the discrepancy. Also, the firm should provide a table of the original (if any) and repeat values that were reassayed for the reason of "Analysis incomplete".

2. The firm's dissolution specification [(b) (4)% (Q) in (b) (4) minutes] differs from the one recommended by the DBE (b) (4)% (Q) in 15 minutes]. The firm should acknowledge its acceptance of the FDA-recommended dissolution method and specification.

3.10 Recommendations

1. The fasting BE study No. AQ4221 conducted by Apotex Inc, on its Atorvastatin Calcium Tablets, 80 mg, batch FD051-317, comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, lot # 24856V, is **inadequate** due to the above mentioned Deficiencies #1.

2. The fed BE study No. AQ3681 conducted by Apotex Inc, on its Atorvastatin Calcium Tablets, 80 mg, batch FD051-317, comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, lot # 24856V, is **adequate.**

3. The *in vitro* dissolution testing on the 10 mg, 20 mg, 40 mg and 80 mg strengths conducted by the firm, using the FDA-recommended dissolution method, is **inadequate** due to the above mentioned Deficiency #2.

   The dissolution testing should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37 ± 0.5 ^{0}C, using USP apparatus II (paddle) at 75 rpm, and it should meet the following specification:

Not less than (b) (4)% (Q) of amount of the labeled Atorvastatin Calcium is dissolved in 15 minutes.

4. The waiver requests for in vivo BE study requirements for the firm's lower strength of the test product, 10 mg, 20 mg and 40 mg, can NOT be granted at this time due to the above mentioned deficiencies.

The application is **inadequate**.

3.11 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 3 Study Information

Study Number	ATOR-IMTB-05EB05-2FA (AQ4221)
Study Title	Comparative, randomized, 2-way crossover bioavailability study of Atorvastatin Calcium Tablets (Apotex Inc.) and Lipitor® Tablets (Pfizer), (USA) under fasting conditions
Clinical Site (Name & Address)	Apotex Inc. BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario 416-749-9300
Principal Investigator	G. Rai, M.D.
Dosing Dates	Period 1-Group 1 – 02/01/08, Group 2 – 02/02/08, Group 3 – 02/23/08 Period 2-Group 1 – 02/08/08, Group 2 – 02/09/08, Group 3 – 03/01/08
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	02/15/08 to 03/17/08
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	02/01/08 to 3/17/08 45 Days

Table 4. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium Tablets	Lipitor®
Manufacturer	Apotex Inc.	Parke Davis*
Batch/Lot No.	FD051-317	24856V
Manufacture Date	October 22, 2007	
Expiration Date		December 2009
Strength	80 mg	80 mg

Dosage Form	Film Coated Tablets	Film Coated Tablets
Bio-Batch Size	(b) (4)	
Production Batch Size	(b) (4)	
Potency (Assay)	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	100.6%. 0.9%	
Dose Administered	1 x 80 mg	1 x 80 mg
Route of Administration	Oral	Oral

*A division of Pfizer Inc.

Table 5. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	98 dosed, 85 completed and 85 analyzed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	3
Washout Period	7 days
Randomization Scheme	AB: 1, 2, 6, 8, 11, 12, 13, 15, 17, 18, 21, 24, 25, 26, 30, 32, 33, 36, 37, 39, 42, 43, 47, 48, 49, 50, 54, 55, 57, 59, 61, 64, 65, 67, 69, 72, 73, 74, 78, 80, 90, 91, 95, 96, 97, 100, 101, 103,105 BA: 3, 4, 5, 7, 9, 10, 14, 16, 19, 20, 22, 23, 27, 28, 29, 31, 34, 35, 38, 40, 41, 44, 45, 46, 51, 52, 53, 56, 58, 60, 62, 63, 66, 68, 70, 71, 75, 76, 77, 79, 89, 92, 93, 94, 98, 99, 102, 104, 106
Blood Sampling Times	Predose, 0.1667, 0.3333, 0.5, 0.75, 1.00, 1.3333, 1.6667, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 7.00, 9.00, 12.00, 16.00, 24.00, 32.00, 40.00 and 48.00 hours postdose.
Blood Volume Collected/Sample	6 ml
Blood Sample Processing/Storage	Blood samples were drawn by direct venipuncture using vacuum tubes containing sodium heparin, an anticoagulant, then collected into pre-chilled collection tubes, immediately inverted manually and placed into an ice bath. The plasma samples were separated by centrifugation at ~3500 rpm for 10 minutes under refrigerated conditions and transferred into labeled polypropylene snap cap storage tubes. The plasma obtained from the post-dose samples were divided into two portions, transferred into labeled polypropylene snap cap storage tubes and stored in a -30 ± 5°C set point freezer pending for later bioanalysis.
IRB Approval	Approved on 01/22/2008
Informed Consent	Yes
Length of Fasting	Ten hours prior to dosing and additional 4 hours after dosing
Length of Confinement	At least 10 hours proceeding dosing and 48 hours following each dose

Safety Monitoring	Blood pressure, body temperature, heart rate were measured 10 hours before dosing, and 48 and 72 hours postdose during each study period. Also, physical examination recording was done during check-in and discharge of each study period. A clinical laboratory examination of CK, ALT, AST and creatinine was done at 24 and 72 hours post-dose. Adverse events were collected and reports were tabulated.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 6. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. ATOR-IMTB-05EB05-2FA (AQ4221)			
		Treatment Groups	
		Test Product N =86	Reference Product N =86
Age (years)	Mean ± SD	35.30 ± 9.20	35.30 ± 9.20
	Range	18 – 55	18 – 55
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 39	59 (68.6%)	59 (68.6%)
	40 – 64	27 (31.4%)	27 (31.4%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	86 (100.0%)	86 (100.0%)
	Female	0 (0.0%)	0 (0.0%)
Race	Asian	9 (10.5%)	9 (10.5%)
	Black	9 (10.5%)	9 (10.5%)
	Caucasian	41 (47.7%)	41 (47.7%)
	Hispanic or Latino	21 (24.4%)	21 (24.4%)
	Multi-racial	6 (6.9%)	6 (6.9%)
	Aboriginal	0 (0.0%)	0 (0.0%)
BMI	Mean + SD	25.27 ± 2.58	25.27 ± 2.58
	Range	19.6 – 29.7	19.6 – 29.7

Table 7. Dropout Information, Fasting Bioequivalence Study (Study No. ATOR-IMTB-05EB05-2FA)

Study No. ATOR-IMTB-05EB05-2FA			
Subject No.	**Reason**	**Period**	**Replaced?**
08	Elevated AST (in error, as AST had resolved prior to dosing), on 02/08/08 at 07:38, possibly related to the test drug.	Prior to P2 dosing	No
16	Elevated ALT on 02/08/08 at 07:04, possibly related to the reference drug.	Prior to P2 dosing	No
23	Gastroenteritis on 02/08/08 at 07:46, not related to the reference drug.	Prior to P2 dosing	No
37	Elevated Creatinine on 02/08/08 at 07:05, possibly related to the test drug.	Prior to P2 dosing	No
39	Timing of A/E (Vomiting) on 02/01/08 at 09:13, possibly related to the test drug.	P1	No
55	Elevated ALT on 02/09/08 at 07:53, possibly related to the test drug.	Prior to P2 dosing	No
65	Diarrhea and Epigastric burning on 02/08/08 at 20:22 possibly related to the test drug.	Prior to P2 dosing	No
75	Elevated ALT on 02/09/08 at 07:11, possibly related to the reference drug.	Prior to P2 dosing	No
77	Withdrawn due to a Serious Adverse Event on 02/08/08 at 01:00, not related to the reference drug.	Prior to P2 dosing	No
79	No show for P2 check-in on 02/08/08 at 19:30	Prior to P2 dosing	No
80	Timing of A/E (Vomiting) on 02/04/08 at 10:58, probably related to the test drug.	P1	No
98	Voluntarily withdrew on 03/03/08 at 01:43	P2	No
100	Elevated ALT 03/01/08 at 07:25, possibly related to the test drug.	Prior to P2 dosing	No

Table 8. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Study No. (Study No. ATOR-IMTB-05EB05-2FA)	
	Test	**Reference**
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	0 (0.0%)	1 (1.1%)
Rash	0 (0.0%)	1 (1.1%)
Acne	1 (1.1%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders		

Cough	1 (1.1%)	0 (0.0%)
Dry Throat	0 (0.0%)	1 (1.1%)
Nasal Congestion	3 (3.3%)	0 (0.0%)
Rhinorrhoea	1 (1.1%)	1 (1.1%)
Pharyngolaryngeal	2 (2.2%)	0 (0.0%)
Nervous System Disorders		
Dizziness	1 (1.1%)	0 (0.0%)
Headache	5 (5.4%)	6 (6.6%)
Presyncope	1 (1.1%)	0 (0.0%)
Convulsion	0 (0.0%)	1 (1.1%)
Musculoskeletal and Connective Tissue Disorders		
Flank pain	1 (1.1%)	0 (0.0%)
Back pain	0 (0.0%)	1 (1.1%)
Muscle spasms	0 (0.0%)	1 (1.1%)
Investigations		
Blood pressure decreased	1 (1.1%)	0 (0.0%)
Blood pressure increased	6 (6.5%)	7 (7.7%)
Alanine Aminotransferase Increased	4 (4.3%)	3 (3.3%)
Aspartate Aminotransferase increased	2 (2.2%)	3 (3.3%)
Blood creatine phosphokinase increased	1 (1.1%)	5 (5.5%)
Blood creatinine increased	1 (1.1%)	1 (1.1%)
Heart rate decreased	1 (1.1%)	0 (0.0%)
Injury, poisoning and procedural complications		
Excoriation	0 (0.0%)	2 (2.2%)
Intentional overdose	0 (0.0%)	1 (1.1%)
General disorders administration site conditions		
Catheter site haematoma	1 (1.1%)	1 (1.1%)
Catheter site pain	1 (1.1%)	0 (0.0%)
Catheter site oedema	2 (2.2%)	1 (1.1%)
Feeling cold	0 (0.0%)	1 (1.1%)
Thirst	0 (0.0%)	1 (1.1%)
Fatigue	1 (1.1%)	1 (1.1%)
Gastrointestinal disorders		
Abdominal pain	2 (2.2%)	0 (0.0%)
Abdominal discomfort	0 (0.0%)	1 (1.1%)
Constipation	1 (1.1%)	1 (1.1%)

Diarrhoea	2 (2.2%)	1 (1.1%)
Dyspepsia	1 (1.1%)	0 (0.0%)
Nausea	2 (2.2%)	1 (1.1%)
Abdominal pain upper	0 (0.0%)	1 (1.1%)
Vomiting	3 (3.3%)*	1 (1.1%)*
Eye disorders		
Ocular hyperaemia	1 (1.1%)	0 (0.0%)
Total	26 (28.26%)	28 (30.77%)
Number of subject dosed	92	91

Table 9. Protocol Deviations, Fasting Bioequivalence Study (Adapted from firm's Study Report Body, Section 10.2 Protocol Deviations)

Study No. ATOR-IMTB-05EB05-2FA (AQ4221)		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
In Period 1, the subject did not return to the clinic for the 72-hour ambulatory visit.	01	--
In Period 2, the subject did not return to the clinic for the 72-hour ambulatory visit.	14	--
In Period 2, the subject did not return to the clinic for the 72-hour ambulatory visit, but came back for all lab tests approximately two weeks later.	98	--
In Period 2, these subjects did not receive Creatine Kinase (CK) testing.	56	49, 54, 57

* Subjects #23, #39 and #80 and #77.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Ninety-eight (98) subjects were dosed with the respective test and reference product, and 85 subjects completed the study. There were 13 subjects (Subject #8, #16, #23, #37, #39, #55, #65, #75, #77, #79, #80, #98 and #100) who were withdrawn from the fasting BE study due to various reasons in either Period 1 or 2 when administered with the test or reference product.
- Subject #77 experienced two serious adverse events after taking the reference product. The subject experienced an overdose 136 hours post dosing as well as a seizure 147 hours post-dosing following intake of 70 tablets of "Sleep Eze". The subject was given gastric lavage / charcoal by naso-gastric tube for the overdose and diazepam to counter-act the seizure. These events were judged by the firm as moderate and not related to the study drug. The subject was withdrawn from the fasting BE study.

- Subjects #23, #39 and #80 were dropped from the fasting study in the respective Period 1 and 2 due to gastroenteritis / vomiting after administration of the test drug product.
- The firm's handling of dropouts, adverse events and protocol deviation is acceptable.
- There were some blood sampling time deviations during fasting bioequivalence study. The firm used actual sampling times for its PK calculation.

4.1.1.3 Bioanalytical Results

Table 10. Assay Validation – Within the Fasting Bioequivalence Study

Fasting Bioequivalence Study No.: ATOR-IMTB-05EB05-2FA (AQ4221) Analyte Name: Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	1.000	5.000	10.000	20.000	40.000	60.000	80.000	100.000
Inter day Precision (%CV)	2.0	3.5	3.3	3.0	2.7	2.2	2.1	2.5	2.4	3.2
Inter day Accuracy (%Dev)	0.0	0.0	2.2	3.1	1.0	1.1	1.7	-0.3	-3.3	-5.3
Linearity	0.9948 – 0.9997									
Linearity Range (ng/mL)	0.100 – 100.000									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	0.300	36.000	72.000
Inter day Precision (%CV)	4.5	3.3	4.1
Inter day Accuracy (%Dev)	3.3	0.2	-4.1

Fasting Bioequivalence Study No.: ATOR-IMTB-05EB05-2FA (AQ4221) Analyte Name: 2-Hydroxy-Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.250	0.500	2.500	5.000	10.000	20.000	40.000	60.000	80.000	100.000
Inter day Precision (%CV)	2.0	3.6	3.3	2.9	2.4	2.3	2.1	2.1	2.5	3.1
Inter day Accuracy (%Dev)	-0.4	0.6	0.0	1.9	-0.4	0.6	2.0	0.5	-1.6	-3.2
Linearity	0.9971 – 0.9996									
Linearity Range (ng/mL)	0.250 – 100.000									
Sensitivity/LOQ (ng/mL)	0.250									

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	0.750	36.000	72.000

Inter day Precision (%CV)	3.9	2.8	3.9
Inter day Accuracy (%Dev)	9.3	5.7	2.3

Fasting Bioequivalence Study No.: ATOR-IMTB-05EB05-2FA (AQ4221) Analyte Name: 4-Hydroxy-Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.125	0.250	1.250	2.500	5.000	10.000	20.000	30.000	40.000	50.000
Inter day Precision (%CV)	2.4	4.0	3.4	2.5	2.4	2.7	1.7	2.0	2.7	2.9
Inter day Accuracy (%Dev)	0.0	0.4	-0.7	2.8	0.3	0.7	1.0	0.3	-1.0	-3.4
Linearity	0.9969 – 0.9998									
Linearity Range (ng/mL)	0.125 – 50.000									
Sensitivity/LOQ (ng/mL)	0.125									

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	0.375	18.000	36.000
Inter day Precision (%CV)	5.5	2.7	3.5
Inter day Accuracy (%Dev)	2.7	0.2	-2.3

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (22.4%)
Were chromatograms serially or randomly selected?	Serially selected.

Comments on Chromatograms:

Acceptable.

Table 11. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ABM-BL-0154	04/25/07	Routine Batch Sample Analysis

Table 12. Additional Comments on Repeat Assays

Were all SOPs followed?	The reviewer comment(s) regarding the reassay samples will be provided after the firm responds the deficiency comments
Did recalculation of PK parameters change the study outcome?	Please see the above comments
Does the reviewer agree with the outcome of	Please see the above comments

the repeat assays?	
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Inadequate for the reasons listed in the Deficiency section.

4.1.1.4 Pharmacokinetic Results

Please note that the information below is obtained based on the assumption that the firm's repeated assays are acceptable, and the reviewer used the firm's repeated assay values for the calculation. The PK parameter calculation results may change upon the DBE's receipt of additional information and re-evaluation of the firm's repeated assays.

Table 13. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in **Table 17a-c** and **Figure 1a-c**

Fasting Bioequivalence Study, Study No. AQ4221 Atorvastatin									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr*ng/ml)	179.83	44.67	61.09	377.75	171.45	48.62	59.11	522.60	1.05
AUC∞ (hr *ng/ml)	181.98	44.39	68.05	385.05	173.63	48.37	61.54	530.17	1.05
Cmax (ng/ml)	38.83	46.98	5.16	95.26	38.46	50.15	11.51	121.01	1.01
Tmax* (hr)	1.33	.	0.50	5.00	0.75	.	0.33	5.00	1.78
Kel (hr^{-1})	0.10	18.15	0.03	0.14	0.10	16.96	0.05	0.14	1.03
T1/2 (hr)	6.98	35.99	4.94	27.23	7.04	19.42	4.79	14.28	0.99

Fasting Bioequivalence Study, Study No. AQ4221 2-Hydroxy-Atorvastatin									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	191.21	37.05	35.34	433.74	184.23	36.30	56.96	391.48	1.04
AUC∞ (hr *ng/ml)	195.08	36.18	49.64	436.45	188.11	35.44	62.91	394.07	1.04
Cmax (ng/ml)	33.03	50.87	2.24	92.31	31.32	49.14	5.06	91.34	1.05
Tmax* (hr)	1.33	.	0.75	7.00	1.00	.	0.50	5.00	1.33
Kel (hr^{-1})	0.10	17.07	0.03	0.13	0.09	17.27	0.05	0.14	1.03
T1/2 (hr)	7.47	28.92	5.36	23.95	7.57	18.61	5.03	13.76	0.99

Fasting Bioequivalence Study, Study No. AQ4221 4-Hydroxy-Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	20.79	55.96	2.37	53.60	19.42	54.19	2.20	45.13	1.07
AUC∞ (hr *ng/ml)	24.47	47.39	4.46	55.68	22.82	46.22	3.26	51.34	1.07
Cmax (ng/ml)	1.22	63.02	0.23	4.07	1.16	65.01	0.23	3.99	1.05
Tmax* (hr)	7.00	.	0.75	16.00	9.00	.	0.50	16.00	0.78
Kel (hr^{-1})	0.06	40.30	0.01	0.19	0.06	37.78	0.01	0.13	1.01
T1/2 (hr)	14.16	69.49	3.67	87.72	13.73	46.89	5.41	48.66	1.03

Table 14. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. AQ4221 Atorvastatin				
Parameter (units)	Test	Reference	Ratio (%)	90% C.I.
AUC0-t (hr *ng/ml)	166.770	158.556	105.2%	101.0 – 109.5%
AUC∞ (hr *ng/ml)	169.856	161.683	105.1%	101.2 – 109.1%
Cmax (ng/ml)	36.054	35.814	100.7%	92.7 – 109.3%

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. AQ4221 2-Hydroxy-Atorvastatin				
Parameter (units)	Test	Reference	Ratio (%)	90% C.I.
AUC0-t (hr *ng/ml)	178.294	173.302	102.9%	97.2 – 108.9%
AUC∞ (hr *ng/ml)	183.703	179.579	102.3%	97.2 – 107.7%
Cmax (ng/ml)	29.105	28.500	102.1%	92.9 – 112.2%

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. AQ4221 4-Hydroxy-Atorvastatin				
Parameter (units)	Test	Reference	Ratio (%)	90% C.I.
AUC0-t (hr *ng/ml)	17.954	16.664	107.7%	100.3 – 115.7%
AUC∞ (hr *ng/ml)	24.410	22.905	106.6%	100.5 – 113.0%
Cmax (ng/ml)	1.046	0.976	107.1%	97.4 – 117.9%

Table 15. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AQ4221 Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	166.74	158.53	1.05	100.84	109.70
AUC∞ (hr *ng/ml)	169.04	160.64	1.05	101.20	109.41
Cmax (ng/ml)	36.05	35.81	1.01	92.43	109.64

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AQ4221 2-Hydroxy-Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	178.27	173.30	1.03	97.00	109.09
AUC∞ (hr *ng/ml)	182.78	177.43	1.03	97.65	108.68
Cmax (ng/ml)	29.10	28.50	1.02	92.62	112.60

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AQ4221 4-Hydroxy-Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	17.95	16.66	1.08	100.08	116.00
AUC∞ (hr *ng/ml)	22.04	20.39	1.08	103.23	113.18
Cmax (ng/ml)	1.05	0.98	1.07	97.05	118.29

Table 16. Additional Study Information, Fasting Study No. AQ4221

Atorvastatin

Root mean square error, AUC0-t	0.1591	
Root mean square error, AUC∞	0.1474	
Root mean square error, Cmax	0.3227	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	85	85
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	85	0.99	0.77	1.00
Reference	85	0.99	0.96	1.00

2-Hydroxy-Atorvastatin

Root mean square error, AUC0-t	0.2221	
Root mean square error, AUC∞	0.2023	
Root mean square error, Cmax	0.3693	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	85	85
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	85	0.97	0.71	0.99
Reference	85	0.98	0.91	0.99

4-Hydroxy-Atorvastatin

Root mean square error, AUC0-t	0.2791	
Root mean square error, AUC∞	0.1740	
Root mean square error, Cmax	0.3742	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	85	85
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	85	0.82	0.26	0.97
Reference	85	0.82	0.31	0.96

Comments on Pharmacokinetic and Statistical Analysis:

- Subjects enrolled in this fasting BE study were dosed in different days and divided into three groups (Group 1-P1: 02/01/2008 and P2: 02/08/2008 for Subject #s 01-44; Group 2-P1: 02/02/2008 and P2: 02/09/2008 for Subject #s 45-78, and Group 3- P1: 02/23/2008 and P2: 03/01/2008 for Subject #s 89-106). The reviewer used the model GRP SEQ SEQ*GRP SUB (SEQ*GRP) PER (GRP) TRT TRT*GRP for statistical analysis. There was no significant TRT*GRP effect ($p>0.1$) for AUC0-t, AUC∞ and Cmax. Therefore, this term was dropped from subsequent analysis.

- Furthermore, the firm conducted the new fasting BE study in a single clinical center and the subjects were recruited from the same population (healthy volunteers) and were randomized to treatments based on randomization schedule outlined in the study protocol. Therefore, the group effect was not considered as a variable in the statistical analysis, and the data could be treated as if all subjects were dosed together.

- The firm assayed the plasma concentration data for atorvastatin, 2-hydroxy-atorvastatin, and 4-hydroxy-atorvastatin. The firm also provided the plasma profiles for atorvastatin, 2-hydroxy-atorvastatin, and 4-hydroxy-atorvastatin.

- The 90% CIs of LnAUCt, LnAUC∞ and LnCmax for the respective atorvastatin 2-hydroxy-atorvastatin and 4-hydroxy-atorvastatin calculated by the reviewer agree with the firm's calculations and are within 80% - 125% criteria for BE.

- It was noted that there was only one subject (Subject #30) for the test product in 2-hydroxy-atorvastatin assay, and four subjects (Subject #1, #7, #30 and #40) for the respective reference and test product in 4-hydroxy-atorvastatin assay, whose AUCt/AUC∞ ratios were much lower than 0.8 and who had very flat elimination phases (the last 3 to 5 concentration time points approximately reached zero). Since the sampling times for these subjects are adequate, thus they were included in the final statistical analysis by the reviewer.

- It was also noted that the median Tmax of atorvastatin of the test product (1.33 hrs; range: 0.5-5.0 hrs) is significantly different than that of the reference product (0.75 hrs; range: 0.33-5.0 hrs). Since the half life for atorvastatin is around 14 hours, therefore the onset of the peak drug concentration is less clinically meaningful under chronic dosing and steady-state conditions.

- Data from reviewer's calculation was generated using SAS code "CALCKE".

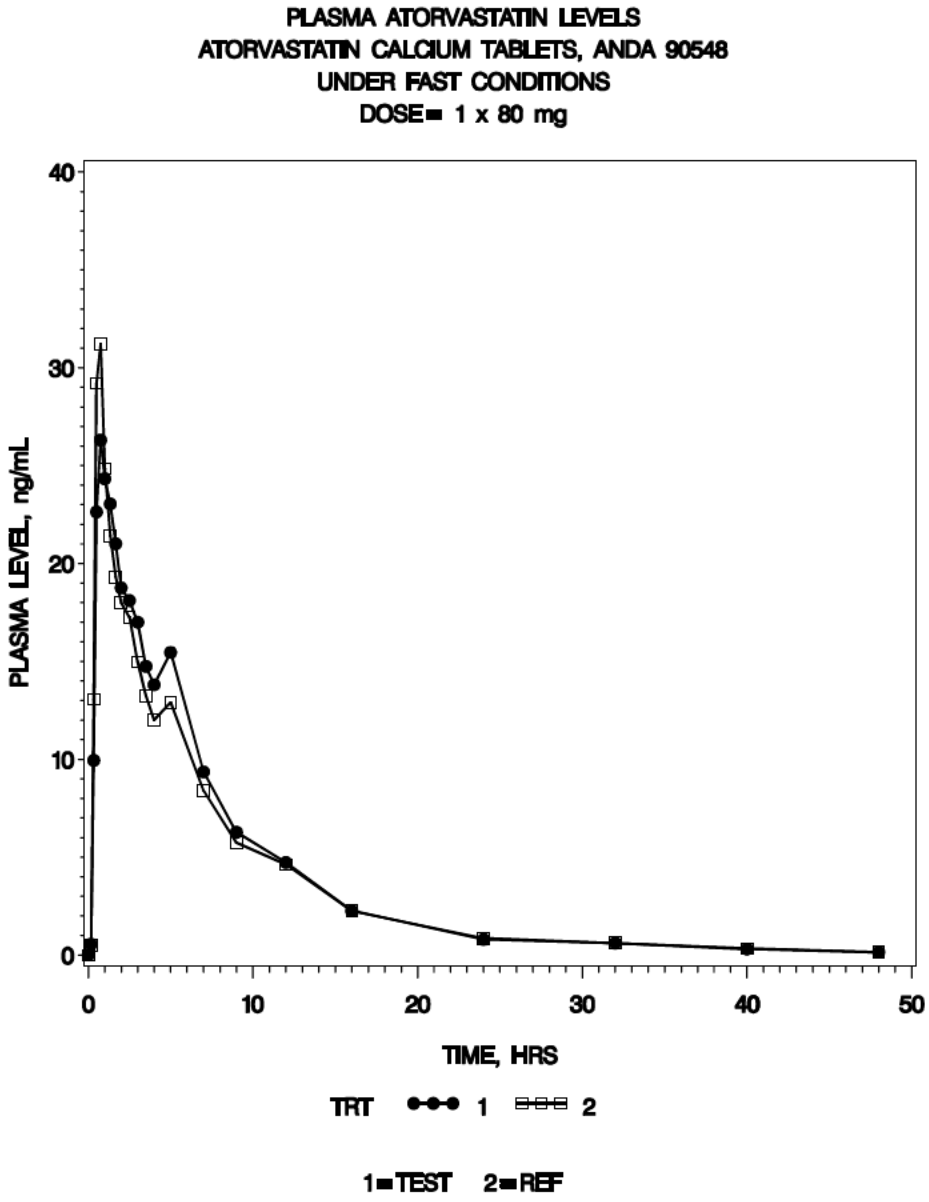
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The firm's in vivo BE study under fasting condition is **inadequate** due to the deficiencies listed in Section 3.9 (Deficiency Comments).

Table 17a. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n=85)		Reference (n=85)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.56	265.26	0.49	310.52	1.15
0.33	9.95	108.81	13.05	102.79	0.76
0.50	22.64	82.11	29.21	65.72	0.77
0.75	26.31	71.61	31.21	60.36	0.84
1.00	24.33	68.14	24.85	56.36	0.98
1.33	23.04	65.96	21.41	61.92	1.08
1.67	21.01	61.06	19.31	63.18	1.09
2.00	18.75	61.51	17.99	62.10	1.04
2.50	18.11	57.94	17.26	69.17	1.05
3.00	17.00	67.82	14.99	66.01	1.13
3.50	14.75	63.94	13.26	67.18	1.11
4.00	13.81	70.99	12.00	64.22	1.15
5.00	15.46	66.67	12.90	54.54	1.20
7.00	9.36	55.98	8.39	53.89	1.12
9.00	6.27	57.10	5.74	53.33	1.09
12.00	4.73	56.48	4.62	58.04	1.02
16.00	2.27	66.53	2.25	62.22	1.01
24.00	0.80	64.51	0.87	66.20	0.92
32.00	0.61	77.22	0.61	63.52	1.00
40.00	0.31	76.28	0.35	70.84	0.91
48.00	0.15	99.62	0.17	85.72	0.87

Figure 1a. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



Reviewer's Comments: It is noticed that the concentration profiles of atorvastatin for the test and reference product showed two peaks. However, the original RLD did not appear to show the same concentration profile characteristics (Enterprise Research: http://fdaesearch.fda.gov:81/SecureES/loadNativeDocument.do?theId=16809223&theLib=bph_lib#xml=http://fdaesearch.fda.gov:81/SecureES/loadPdfDocument.do?theId=16809223&theLib=bph_lib). Per the drug product labeling, atorvastatin does not appear to undergo entrohepatic recirculation (see PK/PD Information section). The reviewer also noticed that concentration profiles in other ANDAs under review (ANDAs 78733 & 77575) for the same drug product show the same profile characteristics as that of the current application (e.g., double peaks).

Table 18b. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

2-Hydroxy-Atorvastatin					
Time (hr)	Test (n=85)		Reference (n=85)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.00	921.95	0.02	748.71	0.26
0.33	1.73	145.61	2.93	157.13	0.59
0.50	8.91	104.63	13.00	93.52	0.69
0.75	18.67	81.26	24.41	65.33	0.76
1.00	21.71	73.29	24.83	60.38	0.87
1.33	23.77	76.09	23.20	55.55	1.02
1.67	22.90	68.70	21.62	53.61	1.06
2.00	20.83	63.80	20.36	52.82	1.02
2.50	19.81	56.12	19.61	51.76	1.01
3.00	18.45	55.28	17.61	50.63	1.05
3.50	16.76	50.72	16.11	52.53	1.04
4.00	15.69	51.09	14.63	51.62	1.07
5.00	14.93	45.95	13.31	43.54	1.12
7.00	10.05	45.00	9.07	44.68	1.11
9.00	7.66	41.81	7.03	42.19	1.09
12.00	5.40	38.26	5.07	38.33	1.07
16.00	2.76	41.99	2.63	38.50	1.05
24.00	1.06	41.25	1.05	36.76	1.01
32.00	0.78	43.73	0.76	38.17	1.03
40.00	0.39	57.37	0.41	54.27	0.96
48.00	0.12	140.15	0.14	122.83	0.88

Figure 2b. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

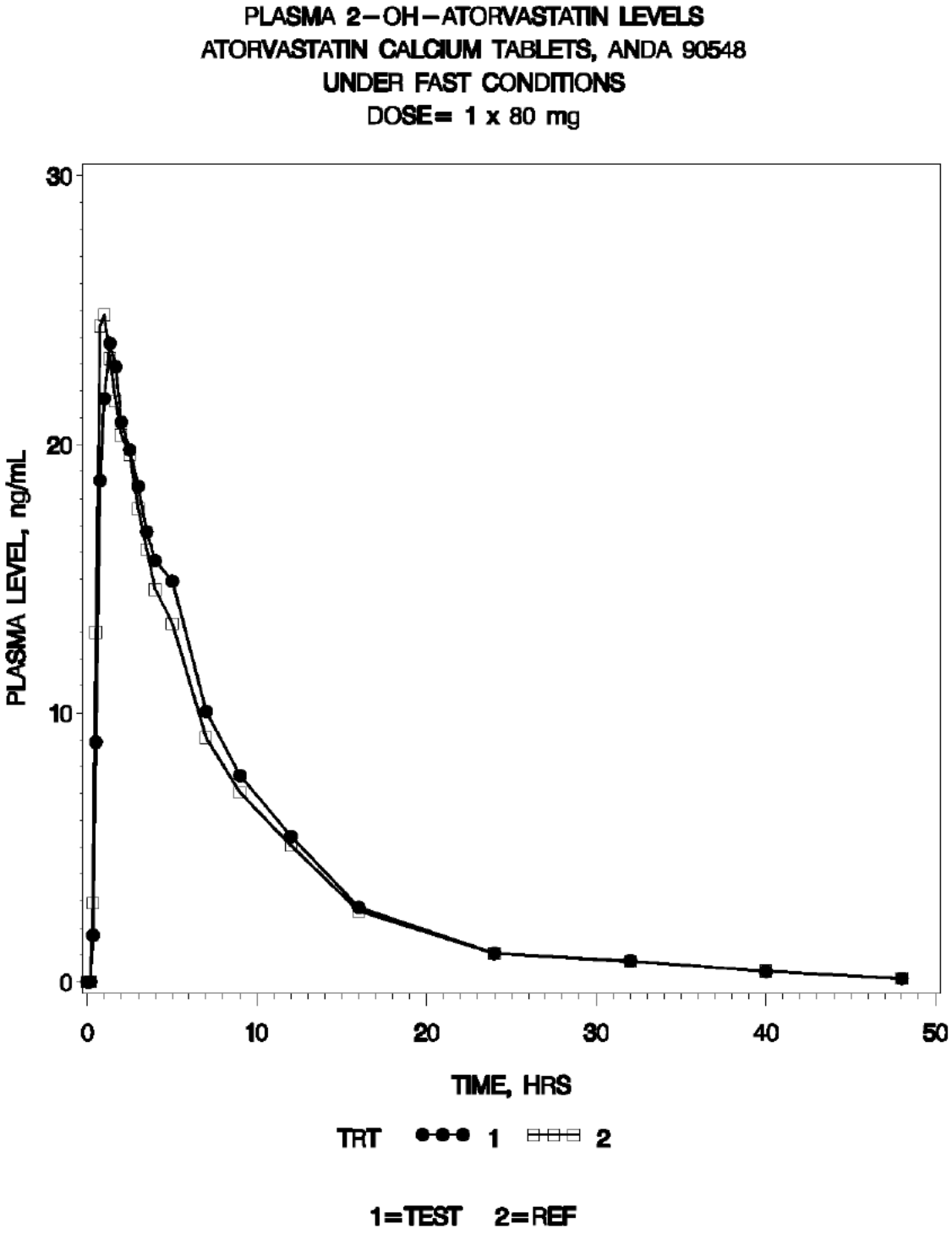
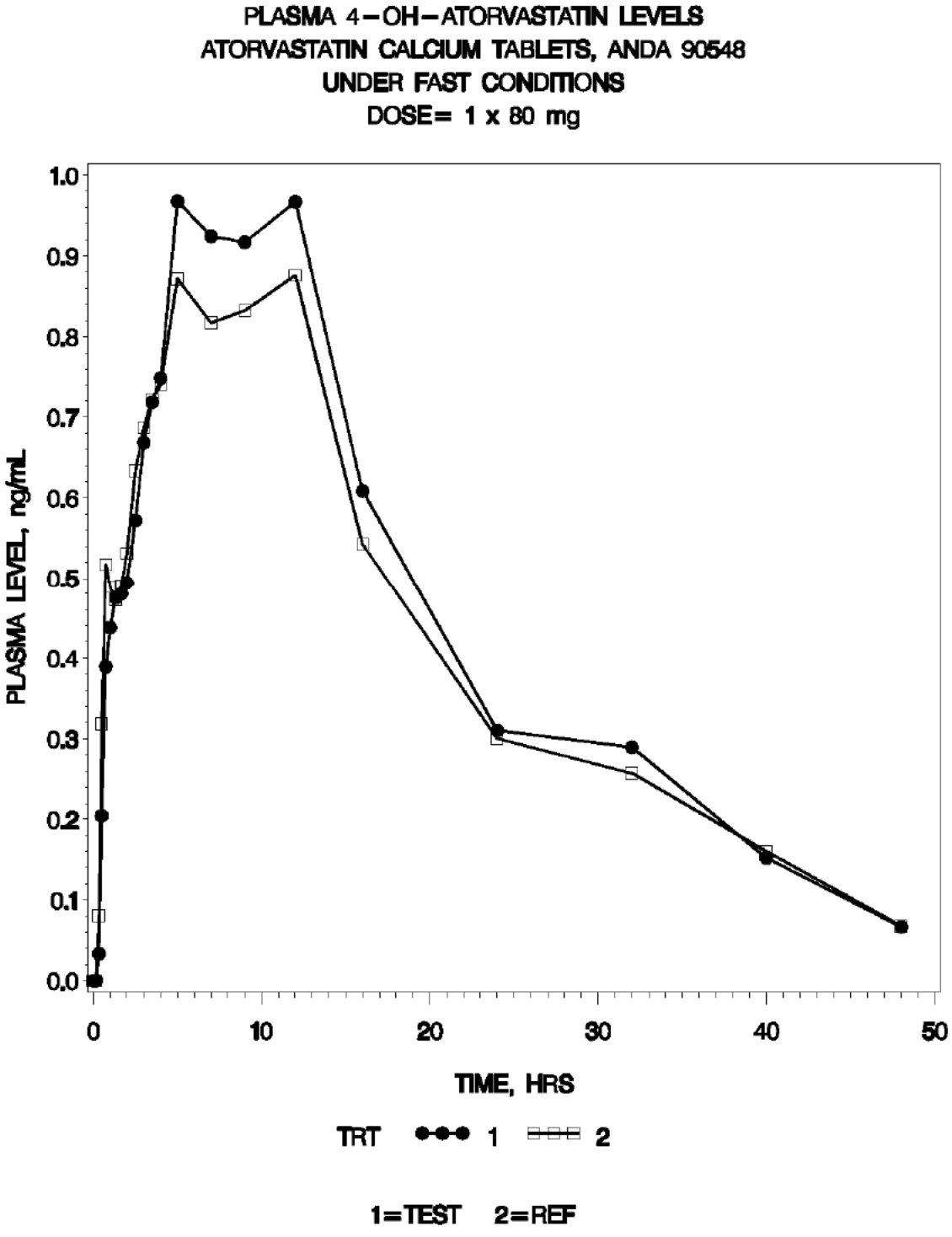


Table 19c. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

4-Hydroxy-Atorvastatin					
Time (hr)	Test (n=85)		Reference (n=85)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.00	.	0.00	.	.
0.33	0.03	310.76	0.08	263.54	0.41
0.50	0.20	147.42	0.32	129.99	0.64
0.75	0.39	118.87	0.52	96.88	0.75
1.00	0.44	105.72	0.49	92.08	0.89
1.33	0.48	88.29	0.47	90.39	1.00
1.67	0.48	80.54	0.49	94.46	0.98
2.00	0.49	84.37	0.53	90.46	0.93
2.50	0.57	80.14	0.63	90.97	0.90
3.00	0.67	82.45	0.69	87.09	0.97
3.50	0.72	83.73	0.72	89.73	0.99
4.00	0.75	78.93	0.74	85.41	1.01
5.00	0.97	73.32	0.87	68.68	1.11
7.00	0.92	70.43	0.82	66.48	1.13
9.00	0.92	62.02	0.83	59.85	1.10
12.00	0.97	55.60	0.88	57.17	1.10
16.00	0.61	56.58	0.54	49.02	1.12
24.00	0.31	50.83	0.30	53.66	1.03
32.00	0.29	58.25	0.26	53.51	1.12
40.00	0.15	83.42	0.16	72.36	0.95
48.00	0.07	144.52	0.07	135.37	0.98

Figure 3c. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 20. Study Information

Study Number	ATOR-IMTB-05EB03-2FE (AQ3681)
Study Title	Comparative, Randomized, 2-Way Crossover Bioavailability Study of Atorvastatin Calcium Tablets (Apotex) and Lipitor Tablets (Pfizer), (USA) Under Fed Conditions
Clinical Site (Name & Address)	Apotex Inc. BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario 416-749-9300
Principal Investigator	Dr. Rai, M.D.
Dosing Dates	Period 1 Dose – January 19, 2008 Period 2 Dose – January 26, 2008
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	January 30, 2008 – February 14, 2008
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	January 19, 2008 – February 14, 2008 26 days

Table 21. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium Tablets	Lipitor®
Manufacturer	Apotex Inc.	Parke Davis*
Batch/Lot No.	FD051-317	24856V
Manufacture Date	October 22, 2007	
Expiration Date		December 2009
Strength	80 mg	80 mg
Dosage Form	Film Coated Tablets	Film Coated Tablets
Bio-Batch Size	(b) (4)	
Production Batch Size	(b) (4)	

	(b) (4)	
Potency (Assay)	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	100.6%, 0.9%	
Dose Administered	1 x 80 mg	1 x 80 mg
Route of Administration	Oral	Oral

*A division of Pfizer Inc.

Table 22. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	54 dosed, 49 completed and 49 analyzed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 1, 2, 5, 6, 11, 12, 14, 15, 17, 20, 22, 23, 27, 28, 29, 31, 35, 36, 38, 39, 41, 44, 46, 47, 50, 51, 53, 54 BA: 3, 4, 7, 8, 9, 10, 13, 16, 18, 19, 21, 24, 25, 26, 30, 32, 33, 34, 37, 40, 42, 43, 45, 48, 49, 52
Blood Sampling Times	Predose, 0.1667, 0.3333, 0.5, 0.75, 1.00, 1.3333, 1.6667, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 9.00, 12.00, 16.00, 24.00, 32.00, 40.00 and 48.00 hours postdose.
Blood Volume Collected/Sample	6 ml
Blood Sample Processing/Storage	Blood samples were drawn by direct venipuncture using vacuum tubes containing sodium heparin, an anticoagulant, then collected into pre-chilled collection tubes, immediately inverted manually and placed into an ice bath. The plasma samples were separated by centrifugation at ~3500 rpm for 10 minutes under refrigerated conditions and transferred into labeled polypropylene snap cap storage tubes. The plasma obtained from the post-dose samples were divided into two portions, transferred into labeled polypropylene snap cap storage tubes and stored in a -30 ± 5°C set point freezer pending for later bioanalysis.
IRB Approval	Approved on 03/23/2007
Informed Consent	Yes
Length of Fasting Before Meal	The subjects were fasted 10 hours overnight. A standard high fat breakfast was given 30 minutes prior to dosing.
Length of Confinement	At least 10 hours proceeding dosing and 48 hours following each dose
Safety Monitoring	Blood pressure, body temperature, heart rate were measured 10 hours before dosing, and 48 and 72 hours postdose during each study period. Also, physical examination recording was done during check-in and discharge of each study period. A clinical laboratory examination of CK, ALT, AST and creatinine was done at 24 and 72 hours post-dose. Adverse events were collected and reports were tabulated.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 23. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. ATOR-IMTB-05EB03 – 2FE (AQ3681)			
		Treatment Groups	
		Test Product N =49	Reference Product N =49
Age (years)	Mean ± SD	35.63 ± 9.13	35.63 ± 9.13
	Range	21-54	21-54
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 39	28 (57.1%)	28 (57.1%)
	40 – 64	21 (42.9%)	21 (42.9%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	49 (100.0%)	49 (100.0%)
	Female	0 (0.0%)	0 (0.0%)
Race	Asian	2 (4.1%)	2 (4.1%)
	Black	4 (8.2%)	4 (8.2%)
	Caucasian	30 (61.2%)	30 (61.2%)
	Hispanic or Latino	12 (24.5%)	12 (24.5%)
	Multi-racial	0 (0.0%)	0 (0.0%)
	Aboriginal	1 (2.0%)	1 (2.0%)
BMI	Mean + SD	25.65 ± 2.37	25.65 ± 2.37
	Range	21.9 – 29.7	21.9 – 29.7

Table 24. Dropout Information, Fed Bioequivalence Study

Study No. ATOR-IMTB-05EB03-2FE			
Subject No.	**Reason**	**Period**	**Replaced?**
04	Sore throat, Tender cervical nodes, Enlarged cervical node redness to throat-Reference 07:00 on 01/26/08	Inter-period	No
15	Out of spec alanine transaminase-Test-07:12 on 01/26/08	Inter-period	No
47	Out of spec alanine transaminase-Test-07:31 on 01/26/08	Inter-period	No
48	No show for Period 2 check-in-Reference-Period 2 check-in on 01/25/08	Inter-period	No
50	No show for Period 2 check-in-Test- Period 2 check-in on 01/25/08	Inter-period	No

Table 25. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Study No. ATOR-IMTB-05EB03-2FE	
	Test	**Reference**
Respiratory, thoracic and mediastinal disorder		
Pharyngolaryngeal pain	1 (1.92 %)	2 (3.92%)
Pharyngolaryngeal discomfort	1 (1.92 %)	0
Pharyngeal erythema	1 (1.92 %)	1 (1.96%)
Nasal congestion	0	2 (3.92%)
Gastrointestinal disorder		
Diarrhoea	2 (3.85%)	1 (1.96%)
Flatulence	1 (1.92 %)	0
Nausea	2 (3.85%)	1 (1.96%)
Vomiting	0	2 (3.92%)
Abdominal pain	0	1 (1.96%)
Abdominal distension	0	1 (1.96%)
General disorders and administration site conditions		
Thirst	1 (1.92 %)	0
Catheter site discomfort	1 (1.92 %)	0
Venipuncture site swelling	1 (1.92 %)	0
Vessel puncture site pain	1 (1.92 %)	0
Catheter site oedema	1 (1.92 %)	2 (3.92%)

Asthenia	0	1 (1.96%)
Vessel puncture site haematoma	0	1 (1.96%)
Musculoskeletal and connective tissue disorder		
Neck pain	0	1 (1.96%)
Pain in extremity	0	1 (1.96%)
Blood and lymphatic system disorders		
Lymphadenopathy	0	1 (1.96%)
Cardiac disorder		
Electrocardiogram-QT prolonged	0	1 (1.96%)
Nervous system disorder		
Somnolence	1 (1.92 %)	3 (5.88%)
Dizziness	0	2 (3.92%)
Headache	0	2 (3.92%)
Skin and subcutaneous tissue disorder		
Hyperhidrosis	0	1 (1.96%)
Investigations		
Alanine aminotransferase increased	6 (11.54%)	3 (5.88%)
Blood creatine phosphokinase increased	2 (3.85%)	1 (1.96%)
Aspartate aminotransferase increased	2 (3.85%)	1 (1.96%)
Blood pressure increased	1 (1.92 %)	3 (5.88%)
Heart rate increased	0	1 (1.96%)
Total	18 (34.62%)	18 (35.29%)
Number of subject dosed	52	51

Table 26. Protocol Deviations, Fed Bioequivalence Study (Adapted from firm's Study Report Body, Section 10.2 Protocol Deviations)

Study No. ATOR-IMTB-05EB03 – 2FE (AQ3681)		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
In Period 2, the subject was found lying down for approximately 15 minutes during Posture and Physical Activity restriction period after dosing.	30	--
(b) (4), who is listed as the Qualified Investigator, tendered his resignation on (b) (4), and Dr. Gurinder Rai has accepted the role of Principal	All subjects except Subject 04 and 48	All subjects except Subject 15, 47 and 50.

Investigator on the same day.		

Comments on Adverse Events/Protocol Deviations:

- Fifty-four (54) subjects were dosed with the respective test and reference product, and 49 subjects completed the study. There were five subjects (Subject #4, #15, #47, #48 and #50) who were withdrawn from the fed BE study either in Period 1 or 2. Subject #4 who developed sore throat, cervical lymph node tenderness and enlargement approximately 95 hours after dosing with the reference drug, and experienced vomiting and diarrhea approximately 150 hours after dosing with the same drug in Period 1, was withdrawn from the fed BE study.
- Subject #30 experienced vomiting approximately 20 hours after the administration of the reference product in Period 1, which occurred after 2 times median Tmax of the time duration for the drug product. This subject was included in the fed BE study.
- No severe adverse event of the drug occurred.
- The firm's handling of dropouts, adverse events and protocol deviation is acceptable.
- There were some blood sampling time deviations during fasting bioequivalence study. The firm used actual sampling times for its PK calculation.

4.1.2.3 Bioanalytical Results

Table 27. Assay Validation – Within the Fed Bioequivalence Study

Fed Bioequivalence Study No.: ATOR-IMTB-05EB03-2FE (AQ3681) Analyte Name: Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	1.000	5.000	10.000	20.000	40.000	60.000	80.000	100.000
Inter day Precision (%CV)	2.0	3.5	2.6	2.5	3.3	2.0	1.9	2.5	2.7	2.1
Inter day Accuracy (%Dev)	0.0	0.5	0.6	-0.3	-1.1	1.4	2.6	1.1	-0.5	-4.0
Linearity	0.9974 – 0.9996									
Linearity Range (ng/mL)	0.100 – 100.000									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	0.300	36.000	72.000
Inter day Precision (%CV)	3.6	2.4	2.5
Inter day Accuracy (%Dev)	2.3	-0.1	-2.9

Fed Bioequivalence Study No.: ATOR-IMTB-05EB03-2FE (AQ3681) Analyte Name: 2-Hydroxy-Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.250	0.500	2.500	5.000	10.000	20.000	40.000	60.000	80.000	100.000
Inter day Precision (%CV)	1.6	3.6	2.7	2.6	2.8	2.5	2.3	2.7	2.8	3.2
Inter day Accuracy (%Dev)	0.8	-0.8	-1.5	-1.5	-1.5	0.4	2.0	2.1	1.2	-5.3
Linearity	0.9969 – 0.9998									
Linearity Range (ng/mL)	0.250 – 100.000									
Sensitivity/LOQ (ng/mL)	0.250									

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	0.750	36.000	72.000
Inter day Precision (%CV)	4.1	3.1	3.1
Inter day Accuracy (%Dev)	7.9	5.5	3.8

Fed Bioequivalence Study No.: ATOR-IMTB-05EB03-2FE (AQ3681) Analyte Name: 4-Hydroxy-Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.125	0.250	1.250	2.500	5.000	10.000	20.000	30.000	40.000	50.000
Inter day Precision (%CV)	2.4	4.0	3.1	2.7	2.6	2.1	1.8	2.5	2.5	2.2
Inter day Accuracy (%Dev)	0.0	0.4	0.0	0.7	-1.3	-0.5	0.5	0.9	0.6	-1.2
Linearity	0.9979 – 0.9998									
Linearity Range (ng/mL)	0.125 – 50.000									
Sensitivity/LOQ (ng/mL)	0.125									

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	0.375	18.000	36.000
Inter day Precision (%CV)	5.0	2.7	2.9
Inter day Accuracy (%Dev)	1.9	-0.3	-1.5

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (24.5%)
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms:

Acceptable.

Table 28. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ABM-BL-0154	04/25/07	Routine Batch Sample Analysis

Table 29. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Acceptable.

4.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in **Table 34a-c** and **Figure 2a-c**

Fed Bioequivalence Study, Study No. AQ3681 Atorvastatin									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr*ng/ml)	160.04	45.85	64.58	409.23	160.32	44.07	67.73	351.97	1.00
AUC∞ (hr *ng/ml)	161.85	45.54	66.29	412.44	162.21	43.71	69.85	353.11	1.00
Cmax (ng/ml)	37.36	69.02	8.71	142.73	35.69	72.47	7.80	131.76	1.05
Tmax* (hr)	1.67	.	0.50	5.00	1.33	.	0.50	5.00	1.25
Kel (hr^{-1})	0.10	13.38	0.07	0.12	0.09	13.09	0.05	0.12	1.04
T1/2 (hr)	7.33	14.24	5.74	10.17	7.64	15.62	5.93	12.93	0.96

Fed Bioequivalence Study, Study No. AQ3681 2-Hydroxy-Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	149.62	37.74	75.52	312.18	142.26	36.45	75.18	260.56	1.05
AUC∞ (hr *ng/ml)	153.70	36.89	80.27	315.59	146.53	35.23	81.52	264.96	1.05
Cmax (ng/ml)	21.63	56.19	7.66	70.82	18.94	46.30	7.55	38.74	1.14
Tmax* (hr)	2.00	.	0.75	6.00	2.00	.	0.75	5.00	1.00
Kel (hr^{-1})	0.09	14.06	0.06	0.12	0.09	14.87	0.05	0.11	1.04
T1/2 (hr)	7.85	15.29	6.01	11.18	8.18	17.34	6.07	14.39	0.96

Fed Bioequivalence Study, Study No. AQ3681 4-Hydroxy-Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	19.21	58.25	4.13	51.70	18.16	57.72	4.97	49.95	1.06
AUC∞ (hr *ng/ml)	22.85	50.36	5.16	55.70	21.47	50.16	6.05	51.91	1.06
Cmax (ng/ml)	1.41	72.32	0.39	5.04	1.25	70.36	0.30	4.33	1.13
Tmax* (hr)	5.00	.	0.75	16.00	5.00	.	0.75	16.00	1.00
Kel (hr^{-1})	0.06	46.61	0.02	0.20	0.06	43.95	0.02	0.19	1.04
T1/2 (hr)	13.57	42.49	3.54	40.29	13.84	34.90	3.71	32.50	0.98

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. AQ3681 Atorvastatin				
Parameter (units)	Test	Reference	Ratio (%)	90% C.I.
AUC0-t (hr *ng/ml)	146.498	146.562	100.0%	95.7 – 104.4%
AUC∞ (hr *ng/ml)	149.248	149.634	99.7%	95.5 – 104.2%
Cmax (ng/ml)	30.709	29.242	105.0%	93.7 – 117.7%

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. AQ3681 2-Hydroxy-Atorvastatin				
Parameter (units)	**Test**	**Reference**	**Ratio (%)**	**90% C.I.**
AUC0-t (hr *ng/ml)	140.379	134.085	104.7%	101.0 – 108.5%
AUC∞ (hr *ng/ml)	146.134	141.854	103.0%	99.0 – 107.2%
Cmax (ng/ml)	18.956	17.100	110.9%	101.4 – 121.2%

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. AQ3681 4-Hydroxy-Atorvastatin				
Parameter (units)	**Test**	**Reference**	**Ratio (%)**	**90% C.I.**
AUC0-t (hr *ng/ml)	16.577	15.759	105.2%	100.6 – 110.0%
AUC∞ (hr *ng/ml)	21.765	21.031	103.5%	99.2 – 107.9%
Cmax (ng/ml)	1.149	1.042	110.3%	101.7 – 119.5%

Table 32. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. AQ3681 Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	146.48	146.57	1.00	95.65	104.41
AUC∞ (hr *ng/ml)	148.30	148.53	1.00	95.61	104.28
Cmax (ng/ml)	30.71	29.24	1.05	93.74	117.65

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. AQ3681 2-Hydroxy-Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	140.37	134.07	1.05	101.01	108.52
AUC∞ (hr *ng/ml)	144.61	138.64	1.04	100.76	107.99
Cmax (ng/ml)	18.96	17.10	1.11	101.38	121.21

Atorvastatin, 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. AQ3681 4-Hydroxy-Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	16.58	15.76	1.05	100.60	110.01
AUC∞ (hr *ng/ml)	20.42	19.25	1.06	100.75	111.62
Cmax (ng/ml)	1.15	1.04	1.10	101.70	119.54

Table 33. Additional Study Information, Fed Study No. AQ3681

Atorvastatin

Root mean square error, AUC0-t	0.1291	
Root mean square error, AUC∞	0.1279	
Root mean square error, Cmax	0.3351	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	49	49
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	49	0.99	0.97	1.00
Reference	49	0.99	0.97	1.00

2-Hydroxy-Atorvastatin

Root mean square error, AUC0-t	0.1057	
Root mean square error, AUC∞	0.1023	
Root mean square error, Cmax	0.2635	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	49	49
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	49	0.97	0.94	0.99
Reference	49	0.97	0.92	0.99

4-Hydroxy-Atorvastatin

Root mean square error, AUC0-t	0.1320	
Root mean square error, AUC∞	0.1510	
Root mean square error, Cmax	0.2383	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	49	49
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	49	0.83	0.24	0.95
Reference	49	0.82	0.60	0.96

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer utilized a CALCKE SAS program which used the 2nd last time point and the 5th last time points to calculate terminal Kel for all subjects. The firm used individually calculated Kel for each subject.

- The AUCi values calculated by the reviewer are slightly different from those by the firm probably because the former used 2-5 endpoints for calculating the Kel for all subjects while the latter reports the individually calculated Kel and AUCi values. The difference in the AUCi estimation method appeared to result in small differences in the firm-calculated and reviewer-calculated AUCi and Kel values.

- It was noted that there were four subjects (Subject #11, #26, #34 and #35) for the respective test and reference product in 4-hydroxy-atorvastatin assay, whose AUCt/AUC∞ ratios were much lower than 0.8 and who had very flat elimination phases (the last 3 to 5 concentration time points approximately reached zero). Since the sampling times for these subjects are adequate, thus they were included in the final statistical analysis by the reviewer.

- All data from reviewer's calculation were generated using SAS code "CALCKE".

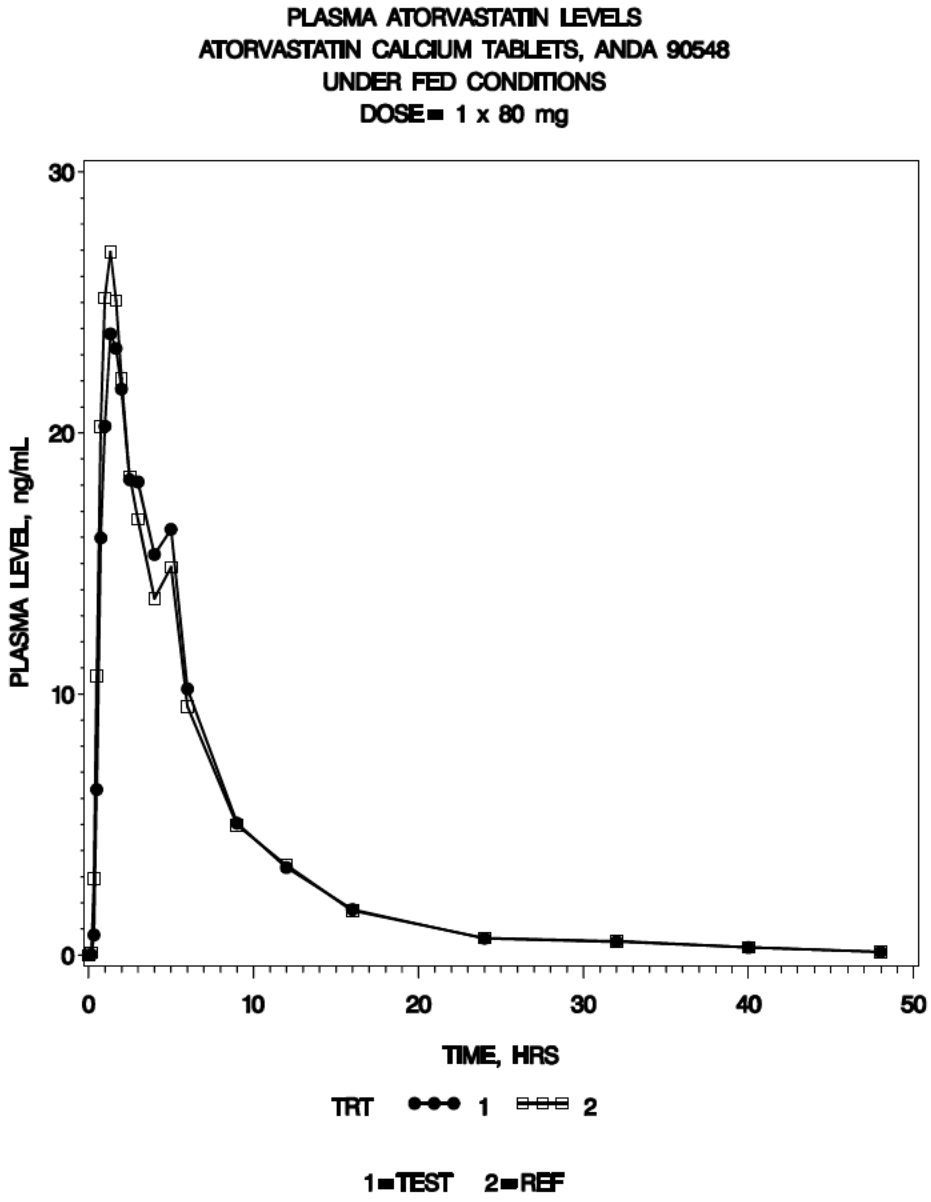
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The firm's in vivo BE study under fed condition is **adequate.**

Table 34a. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n=49)		Reference (n=49)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.02	275.30	0.09	223.57	0.23
0.33	0.77	209.09	2.93	229.73	0.26
0.50	6.34	247.18	10.69	193.09	0.59
0.75	15.98	171.06	20.26	119.44	0.79
1.00	20.26	118.03	25.18	76.02	0.80
1.33	23.80	87.87	26.94	73.28	0.88
1.67	23.24	77.50	25.07	69.43	0.93
2.00	21.68	78.68	22.08	59.55	0.98
2.50	18.21	70.77	18.34	55.07	0.99
3.00	18.13	69.12	16.69	58.56	1.09
4.00	15.35	54.64	13.66	52.47	1.12
5.00	16.31	46.91	14.86	49.55	1.10
6.00	10.20	40.77	9.53	43.16	1.07
9.00	5.06	43.95	4.98	51.10	1.02
12.00	3.35	37.88	3.44	45.26	0.97
16.00	1.75	44.54	1.70	51.33	1.03
24.00	0.64	45.01	0.65	45.60	0.98
32.00	0.51	49.52	0.54	46.32	0.96
40.00	0.29	49.09	0.29	43.32	0.99
48.00	0.12	75.81	0.13	68.87	0.92

Figure 2a. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



Reviewer's Comments: It is noticed that the concentration profiles of atorvastatin for the test and reference product showed two peaks. However, the original RLD did not appear to show the same concentration profile characteristics (Enterprise Research: http://fdaesearch.fda.gov:81/SecureES/loadNativeDocument.do?theId=16809223&theLib=bph_lib#xml=http://fdaesearch.fda.gov:81/SecureES/loadPdfDocument.do?theId=16809223&theLib=bph_lib). Per the drug product labeling, atorvastatin does not appear to undergo entrohepatic recirculation (see PK/PD Information section). The reviewer also noticed that concentration profiles in other ANDAs under review (ANDAs 78733 & 77575) for the same drug product show the same profile characteristics as that of the current application (e.g., double peaks).

Table 34b. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

2-Hydroxy-Atorvastatin					
Time (hr)	Test (n=49)		Reference (n=49)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.00	.	0.00	.	.
0.33	0.03	410.26	0.24	281.90	0.11
0.50	1.07	237.56	2.15	181.58	0.50
0.75	5.44	214.67	6.97	125.06	0.78
1.00	8.79	148.73	11.16	78.49	0.79
1.33	11.81	96.14	13.94	56.35	0.85
1.67	12.74	77.62	14.33	59.47	0.89
2.00	12.92	71.11	13.57	53.34	0.95
2.50	12.10	64.24	12.58	49.59	0.96
3.00	13.36	60.53	12.56	50.24	1.06
4.00	14.92	53.16	12.84	48.28	1.16
5.00	15.37	44.97	13.34	43.08	1.15
6.00	10.93	44.48	9.63	40.31	1.13
9.00	6.48	38.31	6.13	41.03	1.06
12.00	4.30	37.23	4.12	35.70	1.04
16.00	2.29	41.62	2.10	35.01	1.09
24.00	0.90	37.33	0.88	37.14	1.02
32.00	0.71	38.11	0.71	32.05	1.00
40.00	0.41	49.70	0.37	54.82	1.09
48.00	0.10	168.05	0.12	138.35	0.85

Figure 2b. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

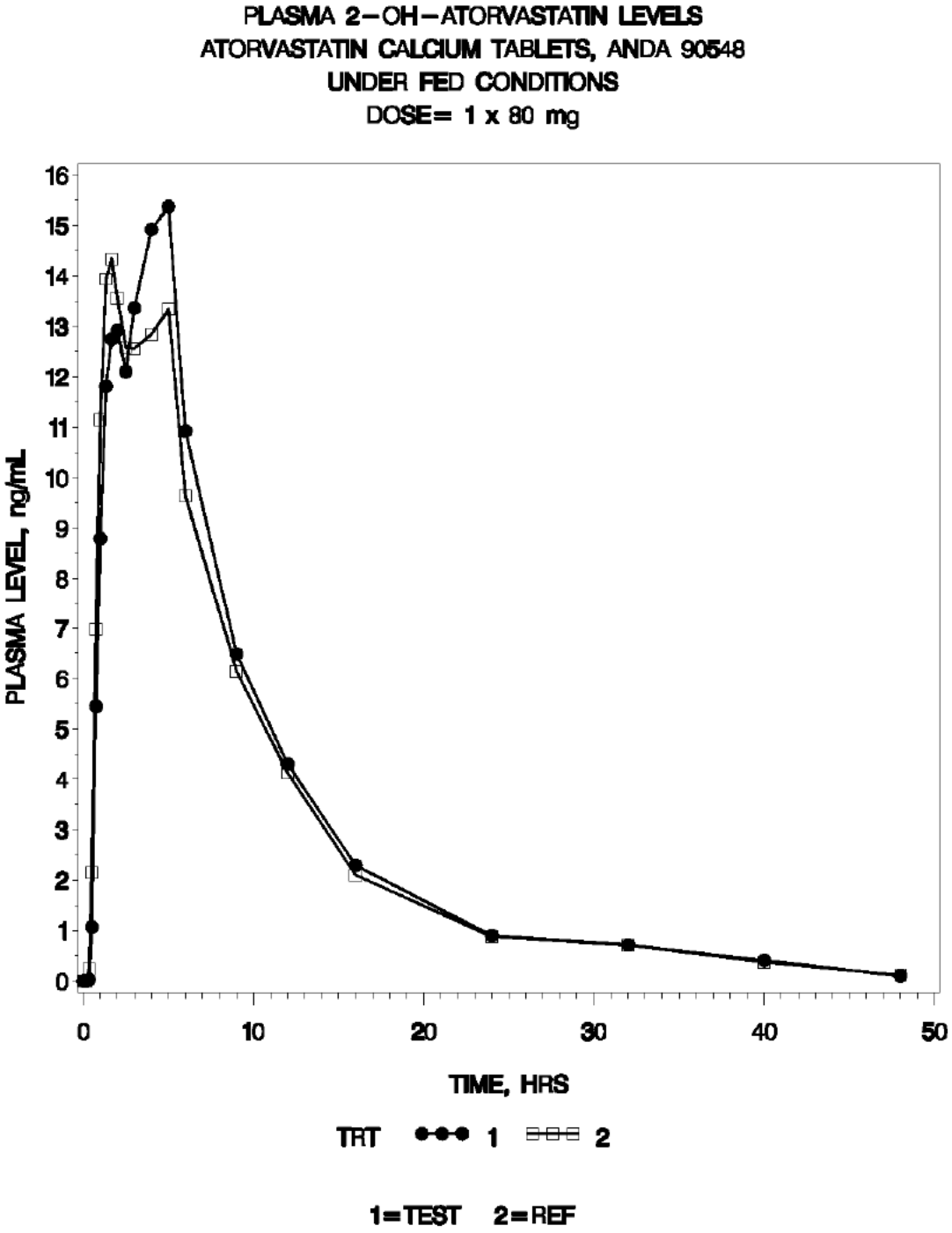
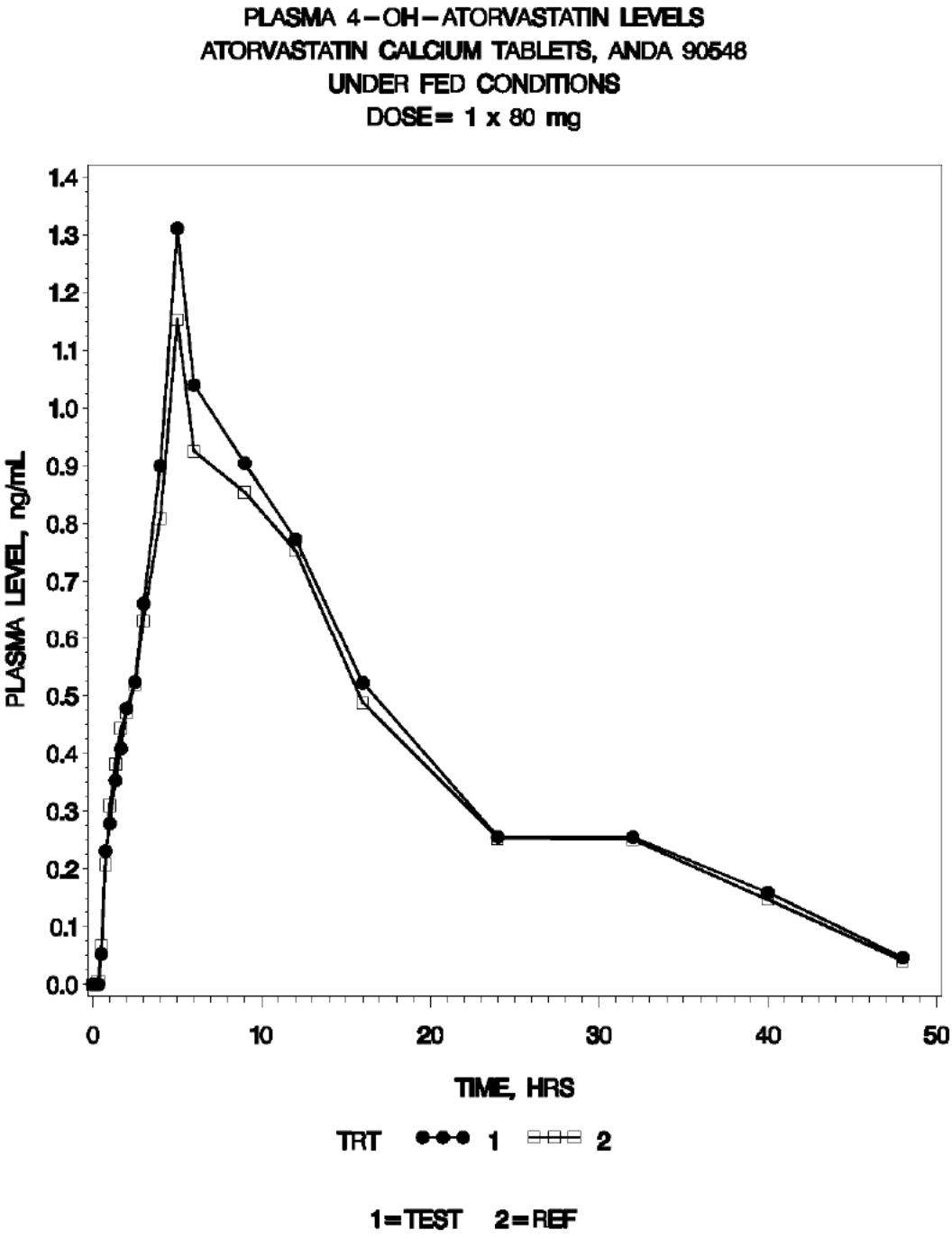


Table 34c. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

4-Hydroxy-Atorvastatin					
Time (hr)	Test (n=49)		Reference (n=49)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.00	.	0.00	.	.
0.33	0.00	.	0.01	490.12	0.00
0.50	0.05	376.10	0.07	289.16	0.78
0.75	0.23	331.82	0.21	198.01	1.11
1.00	0.28	211.41	0.31	130.09	0.90
1.33	0.35	119.15	0.38	111.03	0.92
1.67	0.41	104.07	0.44	103.49	0.92
2.00	0.48	97.35	0.47	96.14	1.02
2.50	0.52	91.53	0.52	94.89	1.01
3.00	0.66	88.11	0.63	94.64	1.05
4.00	0.90	80.61	0.81	87.87	1.11
5.00	1.31	68.60	1.15	76.83	1.14
6.00	1.04	63.63	0.92	66.39	1.12
9.00	0.90	60.47	0.85	58.55	1.06
12.00	0.77	48.60	0.75	50.70	1.03
16.00	0.52	49.98	0.49	51.04	1.07
24.00	0.25	54.66	0.25	54.12	1.01
32.00	0.25	52.15	0.25	52.22	1.02
40.00	0.16	72.33	0.15	72.22	1.08
48.00	0.05	185.37	0.04	194.20	1.13

Figure 2c. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data (Adapted from firm's Table 6 Formulation Data)

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet			
	10 mg	20 mg	40 mg	80 mg	10 mg	20 mg	40 mg	80 mg
[redacted]								
Atorvastatin Calcium Propylene Glycol Solvate								
Calcium Acetate								
Croscarmellose Sodium								
Sodium Carbonate, [redacted]								
Microcrystalline Cellulose [redacted]								
Magnesium Stearate, Vegetable Source								
Colloidal Silicon Dioxide								
[redacted]								
[redacted]								
[redacted]								
Hydroxypropyl Cellulose [redacted]								
Polyethylene Glycol [redacted]								
Titanium Dioxide								
[redacted]								
[redacted]								
[redacted]								

Inactive Ingredients:

Ingredient (mg)	*Maximum amount/day based on MDD of Atorvastatin Amount (mg)				Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit or Justified with MDD	Test formulation Below or Exceed FDA IIG
	10mg	20mg	40mg	80 mg		
Calcium Acetate						(b) (4)
Croscarmellose Sodium						
Sodium Carbonate, (b) (4)						
Microcrystalline Cellulose (b) (4)						
Magnesium Stearate						
Colloidal Silicon Dioxide						
(b) (4)						
Hydroxypropyl Cellulose (b) (4)						
Polyethylene Glycol (b) (4)						
Titanium Dioxide						

*MDD of Atorvastatin is 80 mg/day

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A

Reviewer's Comments on Formulation:

- As per Chemistry Review of the current ANDA [DARRTS – 3/18/2009: REV-QUALITY-03 (General Review)], *"Based on the drug substance, strength, route of administration and dosage form, the proposed ANDA product is pharmaceutically equivalent to the RLD. There is no issue with pharmaceutical equivalence based on the fact that the RLD drug substance is a trihydrate and the proposed drug substance is a propylene glycol solvate based on current polymorph guidance".*

- The amounts of all inactive ingredients in the tablet except "calcium acetate" (see comment below) are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products, based on MDD.

- Per the OGD's consultation from the Pharmacology/Toxicology Division of the Office of New Drugs [DARRTS – 4/28/2009: REV-NONCLINICAL-03 (General Review)]**,** it was recommended that *"sponsor by providing justification, and available literature references has qualified the amounts of calcium acetate in atorvastatin calcium in ANDA 90-548. Based on the review of previous Pharmacology/toxicity data on PhosLo tablets (i.e. calcium acetate as API in NDA19-976 and NDA 21-160), this reviewer agrees that it is unlikely that the calcium acetate contained in Apotex Atorvastatin tablets would produce a pharmacological phosphate-binding effect. Thus, from the pharmacology/toxicity point of view, the proposed levels of calcium acetate in ANDA 90-548 are qualified".*

- The Per CFR 21, Part 73, "Listing of Color Additive Exempt From Certification, Subpart B-Drugs", Titanium dioxide "*may be used for coloring ingested and externally applied drugs generally, in amounts consistent with good manufacturing practice. External application includes use in the area of the eye."* (CFR21. 73.1575)

- The formulation of 10 mg, 20 mg and 40 mg strength products are proportionally similar to the formulation of the 80 mg biostudy strength product.

- The formulations are acceptable.

4.3 Dissolution Data

Dissolution Review Path	DARRTS: 11/25/2008 REV-BIOEQ-02 (Dissolution Review)

Table 34. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate buffer, pH 6.8.
	Volume:	900 mL
	Temperature:	37 ^{0}C ± 5 ^{0}C
Firm's Proposed Specifications	Q= (b)(4) % in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

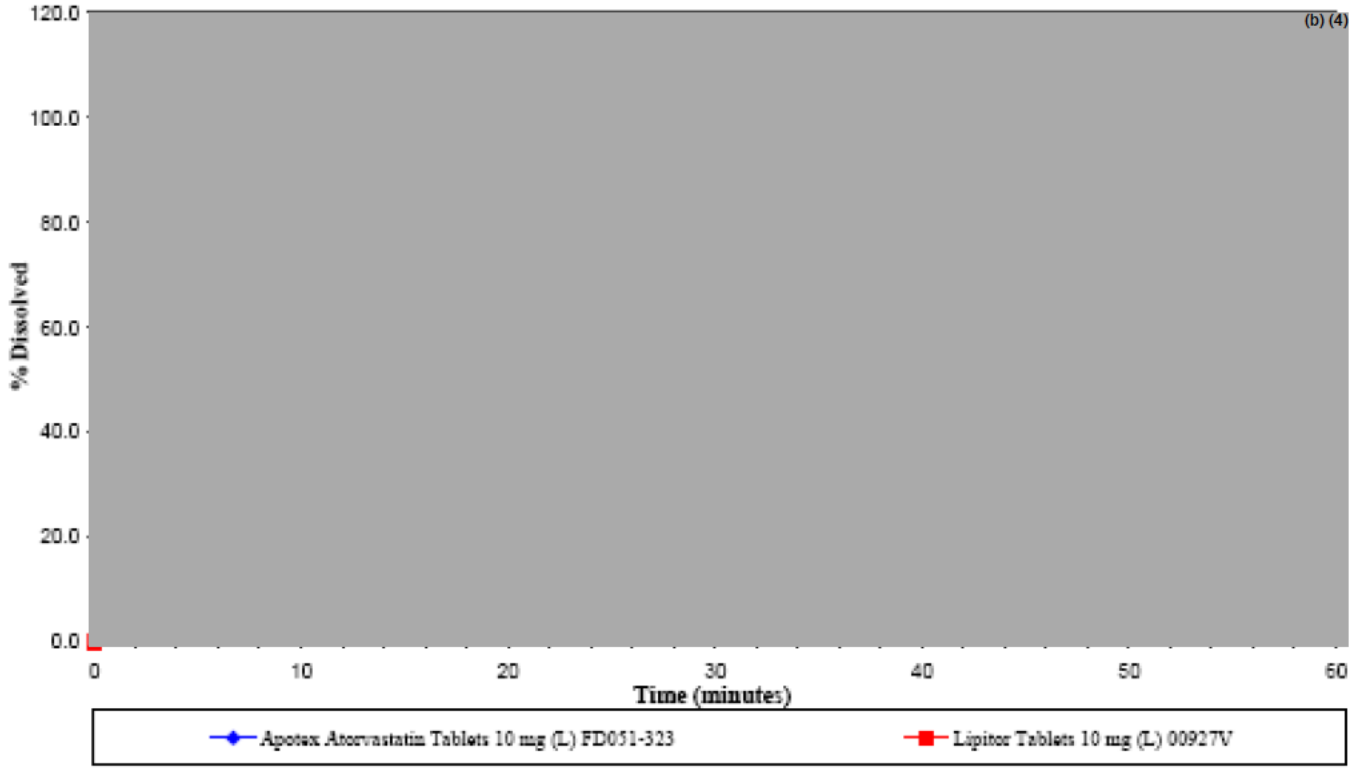
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report No: (Repeated study) ator_imtb_02_u_cds_03 (Comparative Dissolution Report)	12/02/2008	Test Product Atorvastatin Calcium Tablets (FD051-323) (Manufactured: October 2007)	10 mg Tablet	12	Mean	71	95	98	99	100	100	100	Attachment 1, the current amendment
					Range	(b) (4)							
					%CV	6	1	1	1	1	1	1	
	12/02/2008	Reference Product Lipitor ® Tablets (00927V) (Exp. 01/2010)	10 mg Tablet	12	Mean	89	97	99	100	101	101	101	Attachment 1, the current amendment
					Range	(b) (4)							
					%CV	4	2	2	3	2	2	2	

Table 1: Atorvastatin 10 mg Tablets Lot # FD051-323, Apotex Inc.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5	[redacted]											(b) (4)	(b) (4)	71	6
10														95	1
15														98	1
20														99	1
30														100	1
45														100	1
60														100	1

Table 2: Lipitor 10 mg Tablets Lot# 00927V, Pfizer Ireland Pharmaceuticals, Expiry Date: 01/2010.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5	[redacted]											(b) (4	(b) (4)	89	4
10														97	2
15														99	2
20														100	3
30														101	2
45														101	2
60														101	2



Method: USP apparatus #2, 75 rpm
Medium: 900 ml phosphate buffer pH 6.8

Dissolution Conditions	**Apparatus:**	USP II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate buffer, pH 6.8.
	Volume:	900 mL
	Temperature:	37 ^{0}C ± 5 ^{0}C
Firm's Proposed Specifications	Q [(b) (4)]% in [(b) (4)] minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report No: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Nov., 2007	Test Product Atorvastatin Calcium Tablets (FD051-326) (Manufactured: October 2007)	20 mg Tablet	12	Mean	58	90	96	97	99	99	99	5.3.1.3
					Range	[(b) (4)]							
					%CV	8	1	1	1	1	1	1	
	Jan., 2008	Reference Product Lipitor ® Tablets (0533077) (Exp. 06/2010)	20 mg Tablet	12	Mean	92	98	99	100	100	100	100	5.3.1.3
					Range	[(b) (4)]							
					%CV	2	1	1	1	1	1	1	

Dissolution Conditions	**Apparatus:**	USP II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate buffer, pH 6.8.
	Volume:	900 mL
	Temperature:	37 ^{0}C ± 5 ^{0}C
Firm's Proposed Specifications	Q= (b)(4)% in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report No: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Oct., 2007	Test Product Atorvastatin Calcium Tablets (FD051-329) (Manufactured: October 2007)	40 mg Tablet	12	Mean	68	94	98	99	100	101	101	5.3.1.3
					Range	(b)(4)							
					%CV	8	1	2	2	2	2	2	
	Jan., 2008	Reference Product Lipitor ® Tablets (0490067) (Exp. 05/2010)	40 mg Tablet	12	Mean	92	97	99	99	100	100	100	5.3.1.3
					Range	(b)(4)							
					%CV	3	1	1	1	1	1	1	

Dissolution Conditions	**Apparatus:**	USP II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate buffer, pH 6.8.
	Volume:	900 mL
	Temperature:	37 ^{0}C ± 5 ^{0}C
Firm's Proposed Specifications	Q=(b)(4)% in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**							**Study Report Location**
						5	**10**	**15**	**20**	**30**	**45**	**60**	
Study Report No: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Oct., 2007	Test Product Atorvastatin Calcium Tablets (FD051-317) (Manufactured: October 2007)	80 mg Tablet	12	Mean	62	90	94	96	98	98	99	5.3.1.3
					Range	(b)(4)							
					%CV	6	1	2	1	1	1	1	
	Aug., 2007	Reference Product Lipitor ® Tablets (24856V) (Exp. 12/2009)	80 mg Tablet	12	Mean	82	94	96	98	99	100	100	5.3.1.3
					Range	(b)(4)							
					%CV	4	2	2	2	1	1	1	

Reviewer's notes on dissolution testing:

- There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution data with the FDA-recommended method were acceptable for the 20 mg, 40 mg and 80 mg strengths. However, for the 10 mg strength test product, one tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. The firm was asked to repeat the dissolution testing using the FDA-recommended method for the 10 mg strength only [Reviewed in a separate report; DARRTS: 11/25/2008 REV-BIOEQ-02 (Dissolution Review)].

- On 12/24/2008, the firm submitted the repeated dissolution testing data for the strength of 10 mg of the test and reference product (see currently submitted data above). The firm's data for the additional dissolution testing on the 10 mg strength tablets is acceptable.

- However, the firm's specification [(b) (4)% (Q) in (b) (4)minutes] differs from the one recommended by the FDA [(b) (4)% (Q) in 15 minutes]. The firm should acknowledge for the acceptance of the FDA-recommended specification.

- Therefore, the dissolution testing is **inadequate**.

4.4 SAS Output

4.4.1 Fasting Study Data

FAST CONCENTRATION DATASET FOR ATORVASTATIN

(b) (4)



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BIOEQUIVALENCE DEFICIENCIES

ANDA: 090548

APPLICANT: Apotex Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. For your fasting study (Study No. AQ4221), there was discrepancy between the numbers of sample reassays for code B (29 for the test product and 23 from the reference product per your CTD summary for "Reanalysis of Study Samples") and those for the same code in the reassay individual data submitted (50 for the test product and 40 for the reference product; Appendix 16.5.1.8.6.1 & 2 Summary of Repeat Assays Study AQ4221). You should provide explanation(s) for the discrepancy. Also, you are advised to provide a table listing all the original (if any) and repeat values for samples that were reassayed for the reason of "Analysis incomplete".

2. Your dissolution testing data are acceptable. However, your proposed specification of NLT (b)(4)%(Q) in (b)(4) minutes is not acceptable. Based on the dissolution data submitted, the DBE recommends a more appropriate specification. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

   The dissolution should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37 ± 0.5 ^{0}C, using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) amount of the labeled Atorvastatin Calcium is dissolved in **15** minutes.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 090548

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10084	8/7/2008	Bioequivalence Study	Fasting Study	1	1
10084	8/7/2008	Bioequivalence Study	Fed Study	1	1
10084	8/7/2008	Other	Dissolution Waiver	1	1
10084	8/7/2008	Other	Dissolution Waiver	1	1
10084	8/7/2008	Other	Dissolution Waiver	1	1
				Bean Total:	5

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90548	ORIG-1		ATORVASTATIN CALCIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI GONG
01/27/2010

BING V LI
01/27/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
01/28/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90-548	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength (s)	EQ. 10 mg, 20 mg, 40 mg and 80 mg Base	
Applicant Name	Apotex Inc.	
Address	150 Signet Drive, Toronto, Ontario, M9L 1T9, Canada	
Applicant's Point of Contact	Kiran Krishnan	
Contact's Phone Number	954-384-3986	
Contact's Fax Number	416-401-3809	
Submission Date(s)	Aug. 6, 2008	
First Generic	No	
Reviewer	Xiaojian Jiang, Ph.D.	
Study Number (s)	ATOR-IMTB-05EB05-2FA-(2) (AQ4221)	ATOR-IMTB-05EB03-2FE (AQ3681)
Study Type (s)	Fasting	Fed
Strength(s)	80 mg	80 mg
Clinical Site and Address	Apotex Inc. BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario	
Analytical Site and Address	(b) (4)	
OUTCOME DECISION	**Incomplete**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable for the 20 mg, 40 mg and 80 mg strengths. The test product of these strengths meets the data driven FDA-recommended specification of NLT (b)(4)% (Q) in 15 min at the S1 level. However, for the 10 mg strength test product, one tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. In addition, the 10 mg test product does not meet the specification of NLT (b)(4)% (Q) in 15 min. To confirm the firm's data, the firm should repeat the dissolution testing using the FDA-recommended method for the 10 mg strength only. The DBE will set the specification for the test product after reviewing the additional dissolution data.

Note: The current "on-the-file" specification for this product is NLT (b)(4)% (Q) in 15 min.

The Long Term Storage Stability (LTSS) of 99 days is sufficient to cover the maximum storage time of the study samples (45 days).

Both clinical and analytical sites were inspected on 2/21/2008. No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Internal Dissolution Database

Atorvastatin Calcium

Dosage Form: Tablet

Medium: 0.05 M Phosphate buffer, pH 6.8

Apparatus: II (Paddle)

Speed/RPMs: 75

Modify Date: 1/15/2004

Sampling Times: 5, 10, 15 and 30

Volume: 900

Notes: From OCBP Review 2000 Update: 11/22/02 by NT

Specification: NLT (b)(4)%, 15 min

External Dissolution Database

Atorvastatin Calcium	Tablet	II (Paddle)	75	0.05 M Phosphate buffer, pH 6.8	900	5, 10, 15 and 30	01/15/2004

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP apparatus II
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate Buffer pH 6.8
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Q= (b) (4) % in (b) (4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)							Study Report Location
					5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
Study Report No.: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Nov. 2007	Atorvastatin Calcium Tablets (FD051-323) (Manufactured: October 2007)	10 mg Tablet	12	57	87	95	99	100	101	100	5.3.1.3
					(b) (4)							
					32	31	15	6	3	2	1	
	Jan. 2008	Lipitor ® Tablets (00927V) (Exp. 01/2010)	10 mg Tablet	12	5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
					92	98	99	99	100	100	100	
					(b) (4)							
					3	2	2	2	1	2	2	

* For the test 10 mg tablets, one tablet had unusual dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points (see below for the individual data).

Table 1: Atorvastatin 10 mg Tablets Lot # FD051-323, Apotex Inc.

Time (minutes)	% Dissolved														
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Mean	%RSD
5													(b) (4)	57	32
10														87	31
15														95	15
20														99	6
30														100	3
45														101	2
60														100	1

Dissolution Conditions	**Apparatus:**	USP apparatus II
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate Buffer pH 6.8
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Q= (b) (4) % in (b) (4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)							Study Report Location
					5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
Study Report No.: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Nov. 2007	Atorvastatin Calcium Tablets (FD051-326) (Manufactured: October 2007)	20 mg Tablet	12	58	90	96	97	99	99	99	5.3.1.3
											(b) (4)	
					8	1	1	1	1	1	1	
	Jan. 2008	Lipitor ® Tablets (0533077) (Exp. 06/2010)	20 mg Tablet	12	5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
					92	98	99	100	100	100	100	
											(b) (4)	
					2	1	1	1	1	1	1	

Dissolution Conditions	**Apparatus:**	USP apparatus II
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate Buffer pH 6.8
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Q= (b)(4)% in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)							Study Report Location
					5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
Study Report No.: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Oct. 2007	Atorvastatin Calcium Tablets (FD051-329) (Manufactured: October 2007)	40 mg Tablet	12	68	94	98	99	100	101	101	5.3.1.3
					(b) (4)							
					8	1	2	2	2	2	2	
	Jan. 2008	Lipitor ® Tablets (0490067) (Exp. 05/2010)	40 mg Tablet	12	5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
					92	97	99	99	100	100	100	
					(b) (4)							
					3	1	1	1	1	1	1	

Dissolution Conditions	**Apparatus:**	USP apparatus II
	Speed of Rotation:	75 rpm
	Medium:	0.05 M Phosphate Buffer pH 6.8
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Q= (b)(4)% in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	Apotex Inc. (Signet site) 150 Signet Drive Toronto, Ontario M9L 1T9 Canada	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)							Study Report Location
					5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
Study Report No.: ator_imtb_02_u_cds_02 (Comparative Dissolution Report)	Oct. 2007	Atorvastatin Calcium Tablets (FD051-317) (Manufactured: October 2007)	80 mg Tablet	12	62	90	94	96	98	98	99	5.3.1.3
					(b) (4)							
					6	1	2	1	1	1	1	
	Aug. 2007	Lipitor ® Tablets (24856V) (Exp. 12/2009)	80 mg Tablet	12	5 Mean Range %RSD	10 Mean Range %RSD	15 Mean Range %RSD	20 Mean Range %RSD	30 Mean Range %RSD	45 Mean Range %RSD	60 Mean Range %RSD	
					82	94	96	98	99	100	100	
					(b) (4)							
					4	2	2	2	1	1	1	

II. COMMENTS:

The firm's dissolution testing data with the FDA-recommended method are acceptable for the 20 mg, 40 mg and 80 mg strengths. The test product of these strengths meets the data driven FDA-recommended specification of NLT (b)(4)% (Q) in 15 min at the S1 level. However, for the 10 mg strength test product, one tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. In addition, the 10 mg test product does not meet the specification of NLT (b)(4)% (Q) in 15 min. The firm's proposed specification is (b)(4)% (Q) in (b)(4) min for all of their test strengths, which is different from the data-driven specification.

To confirm firm's data, the firm should be advised to repeat the dissolution testing using the FDA-recommended method for the 10 mg strength only. The DBE will set the specification for the test product after reviewing the additional dissolution data.

III. DEFICIENCY COMMENT:

The firm should repeat the dissolution testing using the FDA-recommended method for the 10 mg strength only.

IV. RECOMMENDATION:

The *in vitro* dissolution testing conducted by the firm on its test and reference products is incomplete. The firm should repeat dissolution testing using the FDA-recommended specification for the 10 mg strength only. The dissolution testing should be conducted in 900 ml of 0.05 M Phosphate Buffer, pH 6.8 at 37°C using USP apparatus II (paddle) at 75 rpm. The DBE will set the specification for the test product after reviewing the additional dissolution data.

BIOEQUIVALENCE DEFICIENCY

ANDA: 90-548

APPLICANT: Apotex Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, EQ. 10 mg, 20 mg, 40 mg and 80 mg Base

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and the waiver request will be conducted at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable for the 20 mg, 40 mg and 80 mg strengths. Your dissolution testing data for the 10 mg strength are incomplete. One tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. To confirm your data, please repeat the dissolution testing using the FDA-recommended method on the 10 mg strength test and reference products only. The DBE will set the specification for the test product after reviewing the additional dissolution data. The dissolution testing should be conducted in 900 mL of 0.05M Phosphate buffer at pH 6.8 using a Paddle (USP apparatus II) at 75 rpm.

Please include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested. Also, please provide the date(s) of the dissolution testing and resubmit the dissolution testing data summary table containing the newly obtained data.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

VI. *Completed Assignment for 90548 ID: 6867*

Reviewer: Jiang, Xiaojian **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6867	8/6/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Xiaojian Jiang
11/23/2008 11:19:41 AM
BIOPHARMACEUTICS

Utpal Munshi
11/24/2008 12:09:25 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
11/25/2008 08:55:03 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090548

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 33	PM: Bob Gaines

Electronic ANDA: Yes ☒ No ☐

ANDA #:090548
Firm Name:Apotex Corp.
ANDA Name:Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base)
RLD Name:Lipitor by Pfizer Inc.

Electronic AP Routing Summary Located:
V:\Chemistry Division III\Team 33\Electronic AP Summary\90548.ap.doc

AP/TA Letter Located:
V:\Chemistry Division III\Team 33\PM Folder\Approval Letters\AP Letters\90548.apltr.DOC

Project Manager Evaluation: **Date: 5/16/12 Initials:** RG

☒ Previously reviewed and tentatively approved --- Date 4/24/12
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 5/2/08	Date of Application 5/1/08	Date Acceptable for Filing 11/3/08
Patent Certification (type) P-IV	Date Patent/Excl. expires 6/8/17	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ **DMF#:** 21574 (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 5/15/12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 6/8/10 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 4/18/12 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:
☒ Labeling Endorsement, Date emailed: 5/16/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 5/21/12

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 5/18/2012**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Lipitor NDA# 20-702 Date Checked Granted. Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☒ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP
☐ OTHER:

Comments:Tentative Approval granted to this ANDA on 4/24/2012. The reason cited for TA at that time was another applicant's eligibility for 180 day exclusivity. Apotex has provided PIV certs to the '104, '156 and '971 patents and they were not sued on any of these patents after providing notice to the appropriate parties. Therefore, none of these three patents is a barrier to the approval of this ANDA.
Ranbaxy, the sponsor of ANDA 76-477, was awarded 180 day exclusivity for all strengths of Atorvastatin Calcium Tablets. Ranbaxy triggered their 180 day exclusivity period with commercial marketing and this exclusivity will expire on 5/28/2012 (this date is a Monday but is a Federal holiday) for all 4 strengths.
This ANDA is eligible for Full Approval on or after Tuesday the 29th of May as at that time all claims to 180 day exclusivity will have elapsed.

2. ***Labeling Endorsement***

Reviewer, BT:
Date5/17/12
InitialsBT/RG for

Labeling Team Leader, RW:
Date5/17/12
InitialsRW/RG for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, May 17, 2012 9:04 AM
To: Turner, Betty; Gaines, Robert
Subject: RE: ANDA 90548
I concur

From: Turner, Betty
Sent: Wednesday, May 16, 2012 2:55 PM
To: Gaines, Robert
Cc: Wu, Ruby (Chi-Ann)
Subject: RE: ANDA 90548
Hi Bob,

I have checked the OB, Drugs@fda website, USP, DARRTS, REMS and Medwatch and there are no changes since last labeling review was completed. I have attached the latest Labeling AP Summary for your records.

Thanks,

Betty

From: Gaines, Robert
Sent: Wednesday, May 16, 2012 1:30 PM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 90548
Good afternoon Betty and Ruby.
The subject Atorvastatin application is ready for approval on 5/29/12. Please provide the labeling endorsement.
Thanks
Bob
<< File: 90548.apltr.DOC >> << File: 90548 label rev.pdf >>

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 21May2012**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 5/22/12**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 5/25/12**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. Ranbaxy's ANDA 76-477 for this drug product was approved on November 30, 2011.

OGD Office Management Evaluation

6. Peter Rickman **Date 5/25/12**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: This ANDA was granted tentative approval on April 24, 2012. Final approval of this ANDA was blocked at that time by Ranbaxy's 180-day generic drug exclusivity for Atovastatin Calcium Tablets under ANDA 76-477. Ranbaxy's 180-day exclusivity will expire on May 28, 2012. With the expiration of Ranbaxy's 180-day exclusivity, Apotex's ANDA becomes eligible for final approval.

Final-printed labeling (FPL) remains acceptable for final approval (Approval Summary #4) 4/18/12, as endorsed 5/17/12. No REMS is required.

CMC remains acceptable for final approval - (Chemistry Review #5 - Addendum #1) 5/15/12.

AND/OR

7. Robert L. West **Date 5/25/12**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☒ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 4/23/12 (Verified 5/25/12). No "OAI" Alerts noted.

Apotex provided paragraph IV certifications to the '104, '156 and '971 patents, but was not sued within the 45-day period. There are no additional unexpired patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for final approval upon expiration of Ranbaxy's 180-day generic drug exclusivity for this drug product on May 28, 2012. Since May 28, 2012 occurs on a non-work day, final approval of this ANDA will occur on May 29, 2012.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments:
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments: RLWest for Keith Webber, Ph.D. 5/25/12.

9. Project Manager
Date 5/29/12
Initials RG

Check Communication and Routing Summary into DARRTS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT T GAINES
05/29/2012

APOTEX
ADVANCING GENERICS

May 09, 2012

Mr. Raghu Sammy
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Dear Mr. Raghu Sammy:

Re: TELEPHONE AMENDMENT
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg; ANDA No. 090548

Apotex Inc. is hereby submitting a Telephone Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, ANDA No. 090548 submitted in response to the telephone call received by Kiran Krishnan on May 08, 2012.

At this time, we would like to withdraw the submitted [redacted] (b) (4) with respect to the alternative drug product manufacturing facility. In addition, Apotex Inc. hereby commits to adhere the Guidance for Industry – *Changes to an Approved NDA or ANDA* and the appropriate reporting category for any post approval changes.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp. at telephone number (954) 384-3986 or fax number (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

RECORD OF TELEPHONE CONVERSATION

Background Information:	**DATE:** May 8, 2012
The ANDA was tentatively approved on April 24, 2012. However, the firm in the (b) (4) proposes a reporting category for alternate manufacturing site as a CBE-0, which is not approvable in its current form **FDA:** We note that you have submitted a (b) (4) in your ANDA. Please be aware that we are not approving it in its current form. Please submit these changes as an appropriate supplement when the changes are going to be implemented.	**ANDA NUMBER:** 90548
	TELECON INITIATED BY: **APPLICANT** **FDA**
	MADE: **BY TELEPHONE** **IN PERSON**
	PRODUCT NAME: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg
	FIRM NAME: Apotex Inc.
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: **FDA (OGD):** Dr. Raghu Samy, CMC Reviewer **Firm:** Kiran Krishnan – Director, North American Regulatory Affairs
	TELEPHONE NUMBER: 954-384-3986
	SIGNATURES: Raghu Samy

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAGHU SAMY
05/08/2012

APOTEX
ADVANCING GENERICS

April 25, 2012

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Dear Sir/ Madam:

Re: MINOR AMENDMENT - FINAL APPROVAL REQUESTED
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg; ANDA No. 090548

Apotex Inc. is hereby submitting a Minor Amendment – Final Approval Requested for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg (ANDA No. 09054) as outlined in the FDA Tentative Approval Letter dated April 24, 2012. We are requesting for final approval on May 28, 2012.

The basis of this request for final approval is that the 180-day exclusivity held by Ranbaxy Labs Ltd. will expire on May 28, 2012 as listed in the Electronic Orange Book.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3809.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

ROUTING SHEET

☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 33	PM: Bob Gaines

Electronic ANDA: Yes ☒ No ☐

ANDA #:090548
Firm Name:Apotex Inc.
ANDA Name:Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
RLD Name:Lipitor by Pfizer

Electronic AP Routing Summary Located:
V:\Chemistry Division III\Team 33\Electronic AP Summary\90548.ta.doc

AP/TA Letter Located:
V:\Chemistry Division III\Team 33\PM Folder\Approval Letters\TA Letters\90548.taltr.DOC

Project Manager Evaluation: **Date: 9/9/11 Initials:** RG

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 5/2/08	Date of Application 5/1/08	Date Acceptable for Filing 11/3/08
Patent Certification (type) P-IV	Date Patent/Excl. expires 6/8/17	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** 21574 (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☒ Pending ☐ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) _____ Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 6/8/10 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 11/18/11 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:
☒ Labeling Endorsement, Date emailed: 11/22/11 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☒ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 11/28/2011**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Lipitor NDA# 20-702 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	

Type of Letter:
☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP
☐ OTHER:

Comments:ANDA submitted on 5/2/2008, BOS=Lipitor NDA 20-702, PIII to '893, PIV to '995, '104, '156 and '971 patents. RTR issued on 7/23/2008. ANDA ack for filing for the 10 mg, 20 mg, 40 mg and 80 mg strengths with a PIV certification on 8/7/2008 (LO dated 11/3/2008). Patent Amendment rec'd on 11/6/2008-notice sent via Fed Ex to Connoly Bove in Wilmington DE with notice delivered on 11/5/2008, notice sent via Fed Ex to Pfizer Inc. in NY, NY with notice delivered on 11/5/2008, notice sent via Fed Ex to Warner-Lambert in Ann Arbor MI with notice delivered on 11/5/2008, notice sent via Fed Ex to Warner Lambert in Morris Plains, NJ with notice delivered on 11/5/2008. Patent Amendment rec'd on 1/16/2009-CA 08-CV-7231 filed in the Northern D of IL Eastern District on 12/17/2008 for infringement of the '995. Patent Amendment rec'd on 3/18/2009-PIV to '667 again on 3/19/2011, 3/20.
Patent Amendment rec'd on 5/19/2009-PIV to '810, again 5/20, 5/21, 5/22, 5/26, 5/27, 5/28, 5/29, 6/1, 6/2, 6/3, 6/4, 6/5, 6/8, 6/9, 6/10, 6/11, 6/12, 6/15, 6/16, 6/17, 6/18, 6/19, 6/22 and 6/23/2009.
Patent Amendment rec'd on 5/27/2010-proof of notice for the '667: notice sent via Fed Ex to Pfizer in NY, NY with notice delivered on 3/18/2009(three addressees on NY, NY), notice sent to Connoly Bove in Wilmington DE with notice delivered on 3/18/2009, notice sent via Fed Ex to Warner Lambert in Morris Plains NJ with notice delivered on 3/18/2009, notice sent via Fed Ex to Warner Lambert in Ann Arbor MI with notice delivered on 3/18/2009, notice sent via Fed Ex to Pfizer Ireland in Dublin Ireland with notice delivered on 3/19/2009, CA 08-948 filed in the D of DA(first amended complaint) for infringement of the '667, complaint amended on 3/23/2009.
Patent Amendment rec'd on 9/7/2010-PIV to the '197, again 9/8, 9/9, 9/10, 9/13, 9/14, 9/15, 9/16, 9/17, 9/20, 9/21, 9/22, 9/23, 9/24, 9/27, 9/28, 9/29, 9/30, 10/1, 10/4, 10/5, 10/6, 10/7 and 10/8/2010. To date this patent is not listed in the OB.

Patent Amendment rec'd on 6/21/2011-PIV to the '614 firm submitted serial certifications on every business day for this patent until ending on 7/22/2011. To date this patent is not listed in the OB.
Patent Amendment rec'd on 8/3/2011-PIV to the '996, firm submitted serial certifications on every business day for this patent until ending on 9/2/2011. To date this patent is not listed in the OB.
Patent Amendment rec'd on 9/27/2011-PIV to the '376, firm submitted serial certifications on every business day for this patent until ending on 10/28/2011. To date this patent is not listed in the OB.

Apotex was sued by Pfizer with respect to the '995 and '667 patents which both expired on 6/28/2011. Apotex was not sued on the '104, '156 and '971 patents. ANDA is eligible for TA only as they are subject to Ranbaxy's 180 day exclusivity.

2. ***Labeling Endorsement***

Reviewer, AV:
Date 11/23/11
Initials RG for

Labeling Team Leader, JG:
Date 4/24/12
Initials rlw for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

Final-printed labeling (FPL) found acceptable for approval (Approval Summary #4) 4/18/12. No REMS is required./
RLWest 4/24/12.

concur.

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgement at this time.
It does not necessarily represent an advisory opinion or the formal position of FDA.
It does not bind or otherwise commit the Agency to the views expressed.

From: Vu, Thuyanh (Ann)
Sent: Wednesday, November 23, 2011 10:07 AM
To: Gaines, Robert; Grace, John F
Subject: RE: ANDA 90548 TA labeling endorsement

Please sign off for me. I checked DAARTS, Drugs@FDA and OB.

Thanks
Ann

From: Gaines, Robert
Sent: Wednesday, November 23, 2011 8:45 AM
To: Vu, Thuyanh (Ann); Grace, John F
Subject: ANDA 90548 TA labeling endorsement

Good morning Ann and John.

ANDA 90548, Atorvastatin by Apotex, is ready for tentative approval. Please provide the necessary labeling endorsement.

Thanks.

Bob

<< File: 90548 label rev.pdf >> << File: 90548.taltr.DOC >>

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read — **Date 28Nov2011**
OGD Regulatory Counsel — **InitialsDTR**

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Minor changes to TA letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 12/1/11**

Chemistry Div. **III (Sayeed)** **InitialsVAS**

Comments:cmc satisfactory.

5. ***First Generic Evaluation*** **First Generics Only**

Frank Holcombe **Date 4/24/12**
Assoc. Dir. For Chemistry **Initials rlw/for**

Comments: (First generic drug review)

N/A. Multiple ANDAs have been tentatively approved for this drug product. Ranbaxy's ANDA 76-744 for this drug product was approved on 11/30/11.

OGD Office Management Evaluation

6. Peter Rickman **Date 4/24/12**
Director, DLPS **Initials rlw/for**

Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 80 mg tablet strength found acceptable. In-vitro dissolution testing for all 4 tablet strengths also found acceptable. Waivers granted under 21 CFR 320.22(d)(2) for the 10 mg, 20 mg and 40 mg strengths. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 1/28/10, 6/8/10.

Labeling (in final-print format) found acceptable (Approval Summary #4) 4/18/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #5 - Addendum #1) 12/1/11.

AND/OR

7. Robert L. West **Date 4/24/12**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 4/23/12 (Verified 4/24/12). No "OAI" Alerts noted.

Apotex provided paragraph IV certifications to the '104, '156 and '971 patents, but was not sued within the 45-day period. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

Final approval for this ANDA is blocked by Ranbaxy's 180-day generic drug exclusivity for Atorvastatin Calcium Tablets under ANDA 76-477. Ranbaxy's 180-day generic drug exclusivity will expire on May 28, 2012.

Note: This ANDA was found approvable by OGD in December 2011. Issuance of the tentative approval letter has been delayed pending a recommendation from Office of Compliance.

This ANDA is recommended for tentative approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Keith Webber, Ph.D. 4/24/12.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 4/24/12
Initials RG

Check Communication and Routing Summary into DARRTS

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/s/

ROBERT T GAINES
04/24/2012

MEMORANDUM TO FILE

RE: Clarification of Post-Approval Comments to Firm.

On April 20, 2012, the firm was contacted and asked to make the following post-approval comments for ANDA 090548, Atorvastatin Calcium Tablets.

CONTAINER and CARTON LABELS:

- Revise the "Each tablet contains…" statement to read "*Each film-coated tablet contains…"
- Add an asterisk after the strength (e.g. 80 mg*) and before "*Each film-coated tablet contains…"

INSERT:

- **HOW SUPPLIED**- Add as the first sentence, "Atorvastatin calcium tablets are supplied as white, **oval, biconvex** film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin."

The above comments were communicated to Kiran Krishnan at KKrishna1@apotex.com and (954) 384-3986.

Betty Turner
Labeling Reviewer

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/s/

BETTY B TURNER
04/20/2012

APOTEX
ADVANCING GENERICS

March 21, 2012

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: **Gratuitous Labeling Amendment and Request for Tentative Approval**
ANDA No. 090548; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Apotex Inc. is hereby submitting a Gratuitous Labeling Amendment to ANDA 090548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This amendment is being submitted to update our prescribing information and patient information to match the RLD prescribing information and patient information approved on February 28, 2012.

Please refer to Addendum 1 for a description of the label revision and labels provided in this submission.

Upon satisfactory review of the revised labeling, Apotex Inc. would like to request tentative approval for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg, ANDA 090548. The review of the chemistry and bioequivalency portions of this ANDA have been completed and found to be acceptable.

A signed application form (FDA 356h) is provided.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been previously submitted.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (954) 349-4233, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

March 21, 2012.
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090548

Christine J. Siwik, Esq.
Rakoczy Molino Mazzochi Siwik LLP
6 West Hubbard Street., Suite 500
Chicago, IL 60654

Dear Ms. Siwik:

I write in response to your December 19, 2011 email to Steven Lynn, Acting Director, Office of Manufacturing and Product Quality (OMPQ), within the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA). This inquiry has been forwarded to me because it concerns a tentative approval issue specific to the Office of Generic Drugs. Specifically, you request that FDA grant immediate tentative approval of Apotex's Abbreviated New Drug Application (ANDA) 090548 for atorvastatin calcium tablets, or provide a statement of FDA's legal authority to deny such approval. At this time, the Agency denies the request for tentative approval due to the lack of an adequate current good manufacturing practices (cGMP) compliance assessment of Apotex's active pharmaceutical ingredient (API) facility.

The agency grants "tentative approval" when an ANDA meets the approval requirements of section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act, but cannot receive effective approval because the application is blocked by a patent or exclusivity. See 505(j)(5)(B)(iv)(II)(dd)(AA); see also 21 C.F.R § 314.107(b).

Section 505(j)(2)(A)(vi) requires an ANDA to contain, among other things, the items specified in clauses (B) through (F) of 505(b)(1). Section 505(b)(1)(D) requires that an application contain "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug[.]" See also 21 CFR § 314.94(a)(9). Similarly, section 505(j)(4)(A) states that an ANDA shall be approved unless "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity[.]" See also 21 CFR § 314.127(a)(1).

Thus, by statute, to assess whether ANDA 090548 is eligible for tentative approval, FDA must assess the cGMP compliance of the facilities and controls identified in the ANDA for the manufacture, processing and packing of the drug product. The Apotex Pharmachem facility produces the API that Apotex uses in its production of atorvastatin calcium tablets. As Steven Lynn described in his letter to Mr. Rakoczy dated December 9, 2011, FDA has determined that

an inspection of Apotex's API facility is necessary for FDA to properly evaluate cGMP compliance status for ANDA 090548, and that it would not be appropriate to rely upon an out-dated inspection or one conducted by a regulatory authority other than FDA. Apotex's ANDA 090548 will be eligible for tentative approval only after the Agency has inspected the facility and found that it is being operated pursuant to cGMP.

Please let me know if you have any questions.

Sincerely,

{See appended electronic signature page}

Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

KEITH O WEBBER
01/20/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2011

FROM: Robert L. West, Deputy Director, Office of Generic Drugs, CDER

TO: ANDA 078773 (Teva)
ANDA 077575 (Sandoz)
ANDA 090548 (Apotex)
ANDA 091226 (Mylan/Matrix)

SUBJECT: Pre-Launch Activities Importation Requests (PLAIRs); Atorvastatin ANDAs

The Agency is in the process of developing a Guidance regarding pre-launch activities importation requests (PLAIRs). In the past, requests to permit importation of such unapproved finished dosage form drug products have been reviewed and informally granted or denied.[1] Recently the Agency has sought to standardize the process regarding how a PLAIR should be submitted and the circumstances under which the Agency may grant a PLAIR. This memorandum, the purpose of which is to explain the background under which the PLAIRs for ANDA 078773 (Teva), ANDA 077575 (Sandoz), ANDA 090548 (Apotex) were granted, reflects much of the work that has been done in developing the Guidance.

BACKGROUND

To allow domestic drug manufacturers to prepare and position products for market launch in anticipation of NDA/ANDA approval, for many years FDA has used its enforcement discretion and permitted certain interstate shipments of unapproved products in finished dosage form. (Such shipments have been allowed under certain controls and restrictions; for example, products may only be shipped to facilities identified in a pending NDA or ANDA or to facilities owned and controlled by the applicant.) Because foreign firms must bring their products through Customs, such an informal scheme has certain drawbacks. FDA's PLAIR program allows, on a case-by-case basis, the importation and warehousing of finished drugs when an NDA or ANDA is pending. The PLAIR program was developed to formalize the Agency's historical use of enforcement discretion and to allow foreign and domestic manufacturers to operate on a more or less equal footing in their ability to prepare and position products for rapid market launch upon approval.

[1] Section 505(a) of the Federal Food, Drug, and Cosmetic Act (the Act) prohibits the introduction or delivery for introduction into interstate commerce of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." Section 801(a)(3) of the Act states that a drug may be refused admission into the United States if, among other things, it appears that it violates section 505 of the Act.

It is the choice of an applicant who has a pending NDA or ANDA whether or not to submit a PLAIR. The unapproved finished dosage form drug products should either be in final packaged form or require minimal further processing, such as final packaging and/or labeling. A PLAIR includes information such as the drug product name and how supplied, the NDA or ANDA number, the name and address of the foreign manufacturer of the finished drug product, the name and address of the U.S. consignee, the name and address of the warehouse or distribution facility controlled by or under contract with the applicant where the finished dosage form product in final packaged form will be stored pending approval. A PLAIR also should include a signed statement that neither the applicant nor its consignees or distributors will sell, offer for sale, or distribute the drug product in U.S. commerce until FDA has approved the NDA or ANDA. When finished dosage form drug product in bulk is imported for further processing, a PLAIR includes information regarding the facility where further processing activities will occur, including the name and address of the facility, a description of the further processing activities, and information about where the finished dosage form product in final packaged form will be stored pending approval.

An ANDA applicant should not submit a PLAIR until after FDA has determined that the chemistry, manufacturing, and control (CMC) portion is acceptable. For an ANDA that is tentatively approved, a PLAIR should be submitted no more than 60 days prior to the anticipated full approval. Applicants submit a PLAIR by e-mail and one PLAIR should be submitted for each NDA or ANDA. After review of the PLAIR, the CDER Office of Drug Security, Integrity and Recalls (ODSIR), Division of Import Operations and Recalls notifies the applicant whether the PLAIR has been granted. The notification is sent by e-mail to the applicant, the appropriate CDER review division, and the Office of Regulatory Affairs/Division of Import Operations.[2]

Drug products offered for importation under a granted PLAIR are detained by FDA as unapproved drugs. However, rather than issuing a refusal of admission, the Agency exercises enforcement discretion and keeps the detention in place until the Agency either approves the NDA/ANDA or for 6 months, whichever occurs first. The drug product will be subject to refusal and either destruction or exportation if the Agency does not approve the sponsor's NDA/ANDA or if 6 months have passed since the entry date of the initial shipment under a PLAIR.

FDA's determination to grant a PLAIR is subject to the applicant's meeting the following conditions:

1. The PLAIR submission contains a written certification that neither the applicant nor the applicant's consignee will sell, offer for sale, or further distribute in domestic commerce the drug product without an approved application for the drug product.

2. The responsible foreign facility has a satisfactory inspectional history and is either the subject of an ongoing FDA GMP inspection or is in substantial conformity with applicable good manufacturing practices (21 CFR parts 210 and 211).

[2] If there are any changes made after the original PLAIR submission, an amended PLAIR should be submitted. If it is acceptable, CDER ODSIR will notify ORA of the amendment.

Reference ID: 3051613

3. Bulk unapproved finished dosage form drug products are to be delivered to a facility identified in the pending NDA or ANDA to permit further processing, after which the products should remain at the facility where the processing occurred or be transferred to a single site controlled by or under contract with the applicant. For unapproved finished dosage form drug products in final packaged form that do not require further processing, the applicant should state that the drug products will be delivered to a single site controlled by or under contract with the applicant. In both cases, the products should remain under quarantine pending final approval of the application, and remain subject to the terms and conditions of the U.S. Customs and Border Protection entry bond that covers the importation of the specific shipment. Warehouse/distribution facilities controlled by or under contract with the applicant must comply with applicable cGMPs, including proper storage conditions and appropriate temperature and humidity controls. See 21 CFR 211.42 and 211.46; see also 21 CFR 205.50(c)

Upon receiving notice from FDA that the NDA/ANDA is approved, the applicant should send a copy of the approval letter by e-mail to the district office. FDA will determine whether the product that was imported under a PLAIR meets all the requirements of the approved application. FDA's decision to grant a PLAIR is not binding on the Agency. The granting of a PLAIR is not a promise to approve the full application at any future time period and companies who import in reliance on a PLAIR do so at their own risk. FDA may elect to refuse admission of a drug if, for example, the applicant distributes the unapproved drug product in a manner not specified under the granted PLAIR, or 6 months have passed since the entry date of the initial shipment under a PLAIR and approval of the NDA or ANDA has not been granted. Within 90 days of an Agency decision to refuse admission into the United States, articles must be exported or destroyed, as required by section 801(a) of the Act. The Agency has encountered instances in which drug products that had been warehoused subject to a pending NDA/ANDA approval did not conform with late changes made to the approved drug product labeling, or instances in which the NDA/ANDA did not receive FDA approval.

ATORVASTATIN

The applicants of the four atorvastatin ANDAs to which this memorandum is addressed have each submitted a PLAIR. The PLAIRs of Teva, Sandoz, and Apotex were approved on November 21, 2011. As of the date of this memo, no decision has been made on the PLAIR of Mylan/Matrix.

All four of these ANDAs were submitted after ANDA 076477 was submitted by Ranbaxy. Ranbaxy's ANDA 076477 was the first substantially complete ANDA submitted with paragraph IV certifications to the patents listed in the Orange Book for Pfizer's Lipitor. Because of this, Ranbaxy is eligible for 180-day generic drug exclusivity.

The very complicated situation with atorvastatin is explained in detail elsewhere in the administrative records of the atorvastatin ANDAs (largely in Ranbaxy's ANDA 076477), and will not be repeated here. However, in summary, the status of Ranbaxy's ANDA has been the subject of widespread speculation, and the possibility of certain subsequent applicants being eligible for immediate full approval under various scenarios has also been widely speculated

Reference ID: 3051613

upon. FDA, moreover, does not have full knowledge of all aspects of the situation. In particular, there may (or may not) be contractual arrangements between the various parties, including Ranbaxy, the details of which may (or may not) affect the ability of one or more subsequent applicants to be fully approved before the expiration of Ranbaxy's 180-day exclusivity period.

The ANDAs of the four PLAIR applicants are all at an advanced stage of review.[3] In fact, during the month of November, OGD was anticipating that most, and perhaps all four, might be tentatively approved. To the best of our knowledge on November 21, when three of the PLAIRs were granted, Ranbaxy was eligible for 180-day exclusivity, and Ranbaxy's earliest launch date would be November 30, 2011 (as widely reported for more than three years, based on their 2008 settlement agreement with Pfizer). This would mean that no subsequent applicant could be approved until May 28, 2012, at the earliest, which being more than 6 months from November 21, 2011, is hardly "imminent" (at least one applicant claimed in its PLAIR that approval of its ANDA was imminent.) This, however, is not grounds for denying the PLAIR particularly in circumstances like those present here where applicants are aware of the exclusivity and considering whether to challenge it and/or to strike a deal that permits marketing before the exclusivity runs.

The PLAIRs were voluntarily submitted by the four applicants, and it is fair to assume that these applicants were fully aware of Ranbaxy's status as a first applicant and the significance of November 30. It is also fair to assume that these applicants are aware that the granting of a PLAIR is no guarantee of ANDA approval, imminent or otherwise, and that drug product will be subject to refusal and either destruction or exportation if 6 months have passed since the entry date of the initial shipment under a PLAIR. These are known risks. As noted above, the Agency does not necessarily know what has happened (or perhaps will happen) with respect to Ranbaxy's exclusivity. The possibility exists that Ranbaxy could, perhaps even in the very near future, relinquish or selectively waive its exclusivity, thereby permitting the approval of one or more of the PLAIRs ANDAs, assuming of course the ANDA is otherwise eligible for approval.

[3] According to our records, the CMC portions of ANDA 078773 (Teva), ANDA 077575 (Sandoz), ANDA 090548 (Apotex) all were considered "acceptable" when the PLAIRs were granted on Nov. 21. The record shows that, at that time, FDA was still in the process of finalizing its resolution of certain issues pertaining to these ANDAs and the current USP monograph for atorvastatin calcium. As of Nov 21, however, it appeared that the three ANDAs in question would meet the standards of identity in the current USP monograph. With regard to ANDA 091226 (Mylan/Matrix), there were impurity issues that, as of the date of this memorandum, were not yet fully resolved and therefore have precluded an "acceptable" finding.

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/s/

LEIGH A SEARS
11/30/2011

ROBERT L WEST
11/30/2011
Deputy Director, Office of Generic Drugs

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2011

FROM: Dave Read
Regulatory Counsel, Office of Generic Drugs (HFD-600)

TO: ANDA 090548

SUBJECT: Telecon

At about 6 pm on November 29, 2011, I received a telephone call from Lara FitzSimmons, representing Apotex. She inquired about a memorandum that she understood was under review pertaining to the sameness of the API. She asked if I could share with her where that memorandum was in the agency. I said I could not. She thanked me, and the call ended.

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/s/

ROBERT T GAINES
11/30/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 28, 2011

FROM: Paul Schwartz, Ph.D.
Associate Director of Product Quality Coordination
Office of Generic Drugs

THROUGH: Lawrence X. Yu, PhD
Deputy Director of Science and Chemistry
Office of Generic Drugs

SUBJECT: API sameness

TO: ANDA 090548 Atorvastatin Calcium Tablets, 10, 20, 40, 80 mg by Apotex

The Reference Listed Drug for generic atorvastatin calcium tablet applications is Pfizer's Lipitor, NDA 020702. The drug substance (or active ingredient) used by Pfizer to manufacture Lipitor is atorvastatin calcium. The atorvastatin calcium in Lipitor is the calcium salt (2:1) trihydrate of atorvastatin, a crystalline form of the molecule. The drug substance used by Apotex in ANDA 0090548 is atorvastatin calcium; it is (b) (4) and in a propylene glycol solvate form.

There is a USP monograph for the atorvastatin calcium drug substance. Upon consideration of the USP monograph, FDA has determined that an ANDA applicant for generic atorvastatin calcium tablets can demonstrate active ingredient "sameness" for the purposes of section 505(j) by demonstrating that the active ingredient meets the standards for identity in the atorvastatin calcium drug substance monograph. The question considered in this memorandum is whether the active ingredient in Apotex's ANDA meets the standards for identity in the monograph notwithstanding differences in polymorphic form.[1]

Both the trihydrate and the (b) (4) forms are listed in the USP monograph. The USP is silent, however, on the polymorphic form (including solvate form) of the drug substance. The USP Atorvastatin Calcium Reference Standard is the trihydrate crystalline form as in the Pfizer product. The USP Identification test indicated for use in the atorvastatin calcium drug substance monograph includes infrared absorption as described in USP chapter <197>. To pass the infrared absorption identification test, the test sample must exhibit peaks (maxima) only at the

1 As noted in the agency's guidance for industry entitled ***ANDAs: Pharmaceutical Solid Polymorphism*** (July 2007), polymorphic forms include solvate forms.

same wavelengths as the USP Reference Standard (USPRS). Since the drug substance used by Apotex is in a different polymorphic form from that of the USPRS for atorvastatin calcium, the infrared spectra by the IR method do not match peak to peak.

The USP, noting that "[d]ifferences that may be observed in the spectra so obtained sometimes are attributed to the presence of polymorphs," provides that [u]nless otherwise directed in the individual monograph, therefore continue as follows. …dissolve equal portions of the test specimen and the Reference Standard in equal volumes of a suitable solvent, evaporate the solutions to dryness in similar containers under identical conditions and repeat the test on the residues." USP General Chapter <197>. This method is termed "the modified IR method."

Since the USP drug substance monograph for atorvastatin calcium does not direct otherwise, it is permissible for Apotex to use the modified IR method. When Apotex used this USP modified IR method, the spectra matched those from the RLD. These results were confirmed by the FDA's Division of Pharmaceutical Analysis in St. Louis. The FDA laboratory concluded that the IR peaks matched and therefore the Apotex drug substance passed the USP Identification test.

USP's recognition that differences may be observed due to the presence of polymorphs, and its provision of the modified IR method, are consistent with the agency's position on polymorphs (including solvate forms) in demonstrating active ingredient "sameness" for the purposes of ANDAs that is set forth in the agency's guidance for industry entitled *ANDAs: Pharmaceutical Solid Polymorphism* (July 2007). This guidance states that "differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the [Federal Food, Drug and Cosmetic Act] and FDA regulations." Id. at 5.

Accordingly, it is concluded that while the drug substance used in Apotex's atorvastatin calcium tablets is in a different polymorphic form (including solvate form) from that in the Pfizer Lipitor product, it is considered to be the same active ingredient because the Apotex drug substance meets the standards of identity as prescribed in the current USP monograph for atorvastatin calcium.

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/s/

LEIGH A SEARS
11/30/2011

ROBERT L WEST
11/30/2011
Deputy Director, Office of Generic Drugs

APOTEX
ADVANCING GENERICS

November 22, 2011

Dr. Suhas Patankar
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Dear Dr. Patankar:

Re: TELEPHONE AMENDMENT
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg; ANDA No. 090548

Apotex Inc. is hereby submitting a Telephone Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, ANDA No. 090548 submitted in response to the telephone call received by Kiran Krishnan on November 22, 2011. This amendment provides for an updated drug substance specification. Apotex has complied with request to tighten the limit of impurity [redacted] (b) (4) from "NMT [redacted] (b) (4) %" to "NMT [redacted] (b) (4) %" to be aligned with the limit of USP [redacted] (b) (4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp. at telephone number (954) 384-3986 or fax number (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

APOTEX
ADVANCING GENERICS

November 21, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Re: **REQUEST FOR FINAL APPROVAL**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

In follow up to our earlier correspondence dated July 14, 2011 seeking final action and final approval on Atorvastatin Calcium Tablets ANDA 090548, we hereby request FDA to grant final approval for ANDA 90548 Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg, on the basis that to the best of our knowledge, the review of the application is substantively complete and is therefore approvable. At this time, we are aware that there are no outstanding items required from Apotex.

Apotex is also requesting final approval on the basis of its November 11, 2010 controlled correspondence addressing the issue of generic marketing exclusivity for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg. For the reasons discussed therein, Apotex submits that no ANDA filer remains eligible for 180-day exclusivity for these products. Apotex is thus eligible for immediate final approval at this time.

This correspondence is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

APOTEX
ADVANCING GENERICS

November 16, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Re: GRATUITOUS LABELING AMENDMENT
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg; ANDA No. 090548

Apotex Inc. is hereby submitting a Gratuitous Labeling Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 90-548. This amendment is being submitted to withdraw the Gratuitous Labelling amendment dated August 18, 2011, and revert back to the container and carton labels submitted in the Labeling Amendment dated February 26, 2010.

The container and carton labels have been reverted to indicate Atorvastatin Calcium as the drug substance as per those labels submitted in the labeling amendment dated February 26, 2010. These labels were previously reviewed and were found to be adequate. Updated spl labeling has also been provided to incorporate representative revised container labels. Note there is no change to the prescribing information.

Please refer to Addendum 1 for details.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

for: Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

APOTEX
ADVANCING GENERICS

November 8, 2011

Dr. Vilayat Sayeed
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

Dear Dr. Sayeed:

Re: Gratutious Amendment - Chemistry
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg; ANDA No. 090548

Further to the telephone discussion between yourself and Kiran Krishnan, Apotex Corp. today, please find enclosed additional information for your consideration in regard to the IR spectral identification of the drug substance used in the manufacture of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

We are concerned that the IR spectral identification question remains outstanding given that Apotex has complied with USP <197> and has shown that its IR spectra for its atorvastatin calcium is the same as that of the USP reference standard. To further support our conclusions regarding the IR spectral information provided in Apotex's amendments of September 19, 2011 and October 18, 2011, we are providing a consultant report from (b) (4) (b) (4) who has reviewed the same amendments that were submitted. (b) (4) is a physical analytical chemist specializing in molecular spectroscopy. He served on the USP General Chapters Expert Committee during the years 2005 to 2010 and during that time was instrumental in the revision of the USP General Chapter <197> Spectrophotometric Identification Tests. (His resume is appended to the report).

In the attached report, (b) (4) states that there is no spectral difference between the IR spectra obtained for the Apotex atorvastatin calcium versus the IR spectrum of the USP Atorvastatin Calcium Reference Standard under the conditions of the method utilized. We believe that the report from (b) (4) confirming the similarity of the IR spectra is unequivocal and that it should, in addition to the data Apotex previously provided, enable the Agency to make a positive determination of the conformance of the IR identification of atorvastatin calcium with USP. Should any additional clarification be required, we would be pleased to further discuss with the Agency through a teleconference, which could include participation from (b) (4) to respond to any questions.

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
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MEMBER CGPA

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations

APOTEX
ADVANCING GENERICS

October 28, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 28, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 28, 2011
Date

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APOTEX
ADVANCING GENERICS

October 27, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 27, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 27, 2011
Date

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APOTEX
ADVANCING GENERICS

October 26, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 26, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 26, 2011
Date

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APOTEX
ADVANCING GENERICS

October 25, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 25, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 25, 2011
Date

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APOTEX
ADVANCING GENERICS

October 24, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

October 24, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 24, 2011
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

APOTEX
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October 21, 2011

Office of Generic Drugs
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Bernice Tao
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APOTEX INC.

Oct. 21, 2011
Date

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CANADA'S PHARMACEUTICAL COMPANY
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PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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BT

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 21, 2011
Date

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APOTEX
ADVANCING GENERICS

October 20, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 20, 2011
Date

APOTEX
ADVANCING GENERICS

October 20, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 20, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 20, 2011
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

APOTEX
ADVANCING GENERICS

October 19, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

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APOTEX INC.

Oct. 19, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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Oct. 19, 2011
Date

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APOTEX
ADVANCING GENERICS

October 18, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

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APOTEX INC.

Oct. 18, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

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U.S. Patent No. 8,026,376 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 18, 2011
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

QUALITY TELEPHONE DEFICIENCY

ANDA 090548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Apotex Corp.
U.S. Agent for Apotex Inc.
ATTN: Kiran Krishnan

TEL: (954) 384-3986

FAX: (866) 392-1774

FROM: Suhas Patankar

FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 1, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendments dated September 19, 2011 and September 28 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

The Telephone Deficiencies will be considered Quality Minor Deficiencies after 10 working days.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090548 **APPLICANT:** Apotex Inc
DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiency presented below represents Telephone deficiency.

(b) (4)

B. In addition to responding to the deficiency presented above, please acknowledge the following comment:

Please be aware that there is a monograph proposed in the PF 37(5) In-Process Revision, for Atorvastatin Calcium Tablets.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIVAKUMAR R VAITHIYALINGAM
10/18/2011

APOTEX
ADVANCING GENERICS

October 17, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 17, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 17, 2011
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

APOTEX
ADVANCING GENERICS

October 14, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

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APOTEX INC.

Oct. 14, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

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U.S. Patent No. 8,026,376 B2

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Oct. 14, 2011
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APOTEX
ADVANCING GENERICS

October 13, 2011

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CDER, FDA
Document Control Room
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APOTEX
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October 12, 2011

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CDER, FDA
Document Control Room
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Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Oct. 12, 2011

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

APOTEX
ADVANCING GENERICS

October 11, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 11, 2011
Date

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 11, 2011
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

APOTEX
ADVANCING GENERICS

October 07, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 7, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 7, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

APOTEX
ADVANCING GENERICS

October 06, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 6, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 6, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER
CGPA

APOTEX
ADVANCING GENERICS

October 05, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct 5, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 5, 2011
Date

APOTEX
ADVANCING GENERICS

October 04, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct. 4, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 4, 2011
Date

APOTEX
ADVANCING GENERICS

October 03, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Oct 3, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Oct. 3, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER
CGPA

APOTEX
ADVANCING GENERICS

September 30, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept. 30, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Sept. 30, 2011

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090548

METHODS VALIDATION
MATERIALS RECEIVED

APOTEX Corp.
Attention: Kiran Krishnan
FAX: 866-392-1774
Phone: 954-384-3986

Dear Kiran Krishnan:

Please refer to your Abbreviated New Drug Application (ANDA) submitted to the Food and Drug Administration for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg and to our Sep. 27, 2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 0/30/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES F ALLGIRE
09/30/2011

APOTEX
ADVANCING GENERICS

September 29, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept. 29, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '376 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Sept. 29, 2011

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

APOTEX
ADVANCING GENERICS

September 28, 2011

Robert Gaines
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

Dear Mr. Gaines:

Re: **QUALITY MINOR AMENDMENT/ RESPONSE TO INFORMATION REQUEST**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg;
ANDA No. 090548

Apotex Inc. is hereby submitting a Quality Minor Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted in response to a FDA Minor Quality Telephone Deficiency Letter dated September 27, 2011.

Apotex has responded to the best of our ability to numerous review cycles on ANDA 090548 and have dutifully addressed each of the questions raised by the agency including the USP identification test by IR. We are confirming that our data demonstrates that the Apotex's Atorvastatin Propylene Glycol Solvate meets the USP criteria for identification by IR. We trust that all the technical review issues will now be closed.

Apotex hereby requests that ANDA 090548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg be considered for final approval.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Global Regulatory Operations

APOTEX
ADVANCING GENERICS

September 28, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept. 28, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).



Sept. 28, 2011

f. Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date

APOTEX
ADVANCING GENERICS

September 27, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 8,026,376 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept. 27, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 8,026,376 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 8,026,376 B2 ("the '376 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '376 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '376 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

fr Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Sept. 27, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

QUALITY TELEPHONE DEFICIENCY

ANDA 090548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Apotex Corp.
U.S. Agent for Apotex Inc.
ATTN: Kiran Krishnan

TEL: (954) 384-3986

FAX: (866) 392-1774

FROM: Robert Gaines

FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 1, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendments dated August 30, and September 19, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

The Telephone Deficiencies will be considered Quality Minor Deficiencies after 10 working days.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090548 **APPLICANT:** Apotex Inc
DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent Telephone deficiencies.

(b) (4)

B. In addition to responding to the deficiencies presented above:

Please directly submit 25 mgs each samples of Apotex drug substance Atorvastatin Calcium propylelne glycol solvate and USP reference standard for Atorvastain Calcium, to the address listed below:

Food and Drug Administration
CDER/OPS/OTR
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, MO 63101

Attention: James Allgire, Ph.D.
Team Leader

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIVAKUMAR R VAITHIYALINGAM
09/27/2011

APOTEX
ADVANCING GENERICS

September 19, 2011

Dr. Suhas Patanakar
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: **GRATUITOUS CMC AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Dear Dr. Patanakar,

Apotex Inc. is hereby submitting a Gratuitous CMC Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted to revise the drug substance IR method to comply with the USP Monograph for Atorvastatin Calcium.

In addition, a revised petition to USP on September 16, 2011 replacing our petition dated August 10, 2011 is also included in this amendment. A summary of the changes along with the list of supporting data that is provided is attached as Attachment 1.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept. 19, 2011
Date

APOTEX
ADVANCING GENERICS

September 02, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept 02, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '996 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

for Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Sept. 02, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

September 01, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

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Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Sept. 01, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Sept. 01, 2011

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 31, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 31, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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for Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 31, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 30, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 30, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '996 patent, according to the records of the U.S. Patent and Trademark Office.
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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

for Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 30, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 29, 2011

Dr. Suhas Patankar
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Dear Dr. Patankar:

Re: TELEPHONE AMENDMENT
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Telephone Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, ANDA No. 090548. This amendment is being submitted in response to the telephone call received by Kiran Krishnan on August 26, 2011.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp. at telephone number (954) 384-3986 or fax number (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

for: Bernice Tao
Director, Global Regulatory Operations

APOTEX
ADVANCING GENERICS

August 29, 2011

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CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

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Sincerely,

for Bernice Tao
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Aug. 29, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

for Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 29, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 26, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 26, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 26, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

August 19, 2011
ATORVASTATIN MEETING
9:00-10:30 am

Attendees:
Keith Webber
Dave Gill
Laxma Nagavelli
Haitao Li
Suhas Patankar
Bob West
Tim Ames
Robert Gaines
Leigh Ann Sears
Sivakumar Vaithiyalingam
Gil Kang
Cecilia Parise
Andre Raw
Robert Lionberger
Lawrence Yu

This group meeting was held to discuss the expedited Atorvastatin's current CMC status and their potential Tentative Approval status. The 5 ANDA's discussed were:

076477 (Ranbaxy)
077575 (Sandoz)
078773 (TEVA)
090548 (Apotex)
091226 (Mylan/Matrix)

As an action item, it was decided that since TEVA, Apotex, and Mylan ANDA's do not currently meet the USP Monograph; they will receive a communication next week to have the firm to petition USP for conversion of draft pending USP monograph to authorized USP monograph.

The possibility for in-use studies/simulated studies and comparing other in-use stability studies were discussed for the ANDA's.

At the conclusion of the meeting, it was decided more time to review the ANDA's were needed to have an answer to the ANDA statuses. A meeting will be held in 3 weeks to discuss the ANDA's cmc statuses.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEIGH A SEARS
08/26/2011

LAXMA R NAGAVELLI
08/26/2011

RECORD OF TELEPHONE CONVERSATION

Background Information:

Amendment to DMF (b) (4) dated February 16, 2011 reports USP impurity assignments. Apotex (b) (4) /USP (b) (4); Apotex (b) (4) /USP (b) (4) structures are inconsistent with the earlier submissions. (b) (4) for DMF and (b) (4) in DS section of ANDA are at (b) (4)%. This is a USP specified impurity at a level beyond ICH Q3A qualification threshold which needs a revision.

Vaithyialingam and Patankar called the firm on Friday 8/26/11 at 11:30 am.

FDA:

1. Please evaluate the discrepancy between Apotex (b) (4) /USP (b) (4) structure in the February 16, 2011 AM and structures provided in the earlier submissions for DMF and ANDA. Please include the justification and mechanistic pathway in support of the revision where applicable.

2. Please evaluate the discrepancy between Apotex (b) (4) /USP (b) (4) structure in the February 16, 2011 AM and structures provided in the earlier submissions for DMF and ANDA. USP (b) (4) is an (b) (4) while, the structure in the AM is a (b) (4). Please clarify.

3. Impurities (b) (4) in DMF and (b) (4) in DS section of ANDA are at NMT (b) (4)%. This is a specified impurity in current USP monograph at a level is beyond ICH Q3A qualification threshold. Please revise the DS acceptance criterion in DMF and ANDA.

4. Please revise and submit all pertinent pages.

Firm: The firm will submit the amendment.

FDA:

Please submit electronic AM or fax the information and follow up by an official copy. The Division Fax # is 240-276-8474.

DATE:
August 26, 2011

ANDA NUMBER:
90548

IND NUMBER:
N/A

TELECON

INITIATED BY:
APPLICANT
FDA

MADE:
BY TELEPHONE
IN PERSON

PRODUCT NAME:
Atorvastatin Ca Tab. 10, 20, 40, and 80 mg

FIRM NAME:
Apotex Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Kiran Krishnan, Bernice Tao, Reg. Affairs

TELEPHONE NUMBER:
954-384-3986

SIGNATURES:

Siva Vaithyialingam

Suhas Patankar

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIVAKUMAR R VAITHIYALINGAM
08/26/2011

SUHAS J PATANKAR
08/26/2011

APOTEX
ADVANCING GENERICS

August 25, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 25, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 25, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 24, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

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Aug. 24, 2011
Date

APOTEX
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PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Apotex Inc.

Aug. 24, 2011
Date

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Tel: (416) 749-9300 Fax: (416) 401-3849
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APOTEX
ADVANCING GENERICS

August 23, 2011

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CDER, FDA
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August 23, 2011
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PATENT CERTIFICATION

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Apotex Inc.

Aug - 23, 2011
Date

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Tel: (416) 749-9300 Fax: (416) 401-3849
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APOTEX
ADVANCING GENERICS

August 22, 2011

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CDER, FDA
Document Control Room
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Aug. 22, 2011
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Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '996 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 22, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 19, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 19, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 19, 2011
Date

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MEMBER CGPA

APOTEX
ADVANCING GENERICS

August 18, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 18, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

R/ao

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 18, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
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MEMBER CGPA

APOTEX
ADVANCING GENERICS

August 18, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: **GRATUITOUS LABELING AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Gratuitous Labeling Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted to revise statements on the container and carton labels.

The carton and container labels have been revised to specifically indicate Atorvastatin Calcium Propylene Glycol Solvate as the drug substance. Updated spl labeling has also been provided to incorporate representative revised container labels.

Please note, there is no change to the prescribing information as the prescribing information already states Atorvastatin Calcium Propylene Glycol Solvate as the drug substance. Please refer to Addendum 1 for a description of the label revision and labels provided in this submission.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 18, 2011
Date

APOTEX
ADVANCING GENERICS

August 17, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 17, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 17, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
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MEMBER CGPA

APOTEX
ADVANCING GENERICS

August 16, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 16, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 16, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
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MEMBER CGPA

APOTEX
ADVANCING GENERICS

August 15, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 15, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 15, 2011
Date

APOTEX
ADVANCING GENERICS

August 12, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 12, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 12, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 12, 2011

Dr. Suhas Patankar
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Dear Dr. Patankar:

Re: GRATUTIOUS AMENDMENT – Submission of Petition to USP
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Gratutious Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, ANDA No. 090548 to notify FDA that Apotex has submitted a petition to USP to include a monograph for Atorvastatin Calcium Propylene Glycol solvate in the USP.

Apotex has submitted the petition to USP following the request by FDA in the deficiency letter received on April 25, 2011. At the time and in its response of May 17, 2011, Apotex was unable to submit the petition to USP. We have appended a copy of the petition submitted to USP along with accompanying attachments.

It is pertinent to point out that Apotex maintains product labelling which does not claim USP and specifically claims Atorvastatin Calcium Propylene Glycol Solvate as the drug substance in its Prescribing Information. As such, Apotex is in compliance with the provisions in the FDA Food, Drug and Cosmetic Act, Section 501 [21 USC 351] Adulterated Drugs and Devices (b) which state that "*No drug defined in an official compendium shall be deemed to be adulterated under this paragraph because it differs from the standard of strength, quality, or purity therefor set forth in such compendium, if its difference in strength, quality or purity from such standards is plainly stated on its label*". Therefore, Apotex has correctly complied with the provision by stating the difference in the purity of the drug from an official compendium in declaring the active ingredient as atorvastatin calcium propylene glycol solvate and not atorvastatin calcium.

As such, whilst the petition to USP for a monograph for Atorvastatin Calcium Propylene Glycol solvate is under review by USP, Apotex meets the requirements according to the FDA Food, Drug and Cosmetics Act in relation to a USP compendial claim and therefore believes that in the aspect of the USP product monograph, there is no impediment that prevents the granting of the approval of Apotex's ANDA for Atorvastatin Calcium Tablets.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp. at telephone number (954) 384-3986 or fax number (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations

APOTEX
ADVANCING GENERICS

August 11, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 11, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '996 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 11, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 10, 2011

Dr. Suhas Patankar
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Dear Dr. Patankar:

Re: TELEPHONE AMENDMENT
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Telephone Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, ANDA No. 090548. This amendment is being submitted in response to the telephone call received by Kiran Krishnan August 5, 2011.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp. at telephone number (954) 384-3986 or fax number (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889.

Sincerely,

for Bernice Tao
Director, Global Regulatory Operations

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3809
www.apotex.com

MEMBER CGPA

APOTEX
ADVANCING GENERICS

August 10, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 10, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 10, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 9, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug 9, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 9, 2011
Date

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APOTEX
ADVANCING GENERICS

August 8, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 8, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 8, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 05, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

August 5, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug 5, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

RECORD OF TELEPHONE CONVERSATION

Background Information:

DMF (b) (4) and ANDA drug substance identification tests by IR, are submitted prior to finalization of USP drug substance monograph. The firm will be asked to submit information that they meet the monograph requirements for ID by IR. In addition, the DP stability acceptance criterion for impurity (b) (4) needs to be revised to a more stringent level.

Patankar called the firm on Thursday 8/4/11 at 11:00 am and 2:00 pm and Friday 8/5/11 at 11:00 am and 1:00 pm.

FDA:

1. Please clarify whether the DS meets the USP monograph requirements of Identification by IR <197K>.
2. Please revise the DP stability acceptance criterion for impurity (b) (4) needs to be revised to a more stringent level.

Firm: The firm will submit the amendment.

FDA:

Please submit electronic AM or fax the information and follow up by an official copy. The Division Fax # is 240-276-8474.

DATE:
August 5, 2011

ANDA NUMBER:
90548

IND NUMBER:
N/A

TELECON

INITIATED BY:
- ☐ **APPLICANT**
- ☒ **FDA**

MADE:
- ☒ **BY TELEPHONE**
- ☐ **IN PERSON**

PRODUCT NAME:
Atorvastatin Ca Tab. 10, 20, 40, and 80 mg

FIRM NAME:
Apotex Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Kiran Krishnan, Reg. Affairs

TELEPHONE NUMBER:
954-384-3986

SIGNATURES:

Suhas Patankar

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUHAS J PATANKAR
08/05/2011

APOTEX
ADVANCING GENERICS

August 04, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 4, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 4, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

August 03, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug 3, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug 3, 2011
Date

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APOTEX
ADVANCING GENERICS

August 02, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,988,996 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Aug. 2, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,988,996 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,988,996 B2 ("the '996 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '996 patent, purportedly expiring on or about May 23, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '996 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '996 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Aug. 2, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 22, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4)1

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Yao
Director, Global Regulatory Operations
APOTEX INC.

Date July 22, 2011

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.
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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 22, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
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APOTEX
ADVANCING GENERICS

July 21, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4)1

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 21, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date July 21, 2011

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
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APOTEX
ADVANCING GENERICS

July 20, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 20, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date July 20, 2011

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 19, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Date July 19, 2011

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 19, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 18, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 18, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 18, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
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APOTEX
ADVANCING GENERICS

July 15, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

Date July 15, 2011

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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B Tao

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date July 15, 2011

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 14, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
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APOTEX INC.

July 14, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date July 14, 2011

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 14, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Re: **REQUEST FOR FINAL ACTION**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex hereby requests FDA to take final action on ANDA 90548 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg and grant final approval to the application. On July 12, 2011 Apotex submitted an amendment to withdraw the [redacted] (b) (4) site (manufacturing) from its application and, at this time, we have responded to all Agency requests and we believe that there are no outstanding items required from Apotex. As such there is no reason which prevents the Agency from taking final action on this application.

Apotex also respectfully requests a response to its November 11, 2010 controlled correspondence addressing the issue of generic marketing exclusivity for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg. For the reasons discussed therein, Apotex submits that no ANDA filer remains eligible for 180-day exclusivity for these products. Apotex is thus eligible for immediate final approval at this time. In the alternative, in the event the Agency determines otherwise, Apotex is entitled to an immediate tentative approval.

This correspondence is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

APOTEX
ADVANCING GENERICS

July 13, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 13, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.
As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 13, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 12, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Re: **WITHDRAWAL OF GRATUITOUS CMC AMENDMENT DATED MARCH 17, 2011**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

At this time, we would like to withdraw the Gratuitous CMC Amendment to ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg that was dated March 17, 2011. As a result, we are withdrawing our proposal to include the addition of (b) (4) site as an alternate manufacturing site for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The Manufacturers section, 3.2.P.3.1, has been revised and is included in this submission.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

APOTEX
ADVANCING GENERICS

July 12, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 12, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.
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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

Date July 12, 2011

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 11, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Yao
Director, Global Regulatory Operations
APOTEX INC.

July 11, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 11, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 8, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 8, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 8, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 7, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 7, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 7, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 6, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 6, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 6, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

July 1, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

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Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

July 1, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '614 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.
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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

July 1, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

June 30, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
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June 30, 2011
Date

APOTEX
ADVANCING GENERICS

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Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

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Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

June 30, 2011
Date

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www.apotex.com

APOTEX
ADVANCING GENERICS

June 29, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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APOTEX
ADVANCING GENERICS

June 28, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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June 28, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

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Bernice Tao
Director, Global Regulatory Operations
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June 28, 2011
Date

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APOTEX
ADVANCING GENERICS

June 27, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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APOTEX
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U.S. Patent No. 7,964,614 B2

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B/ao

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

June 27, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
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APOTEX
ADVANCING GENERICS

June 24, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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June 24, 2011
Date

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PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

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June 24, 2011
Date

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Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

June 21, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,964,614 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations
APOTEX INC.

June 21, 2011
Date

APOTEX
ADVANCING GENERICS

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,964,614 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,964,614 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '614 patent, purportedly expiring on or about April 2, 2018, with pediatric exclusivity purportedly expiring on or about October 2, 2018, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '614 patent, according to the records of the U.S. Patent and Trademark Office.

As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '614 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Global Regulatory Operations
Apotex Inc.

June 21, 2011
Date

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

APOTEX
ADVANCING GENERICS

May 17, 2011

Robert Gaines
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Dear Mr. Gaines:

Re: **QUALITY MINOR AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Quality Minor Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted in response to a FDA Minor Quality Deficiency Letter dated April 25, 2011.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (866) 392-1774, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3817.

Sincerely,

Bernice Tao
Director, Global Regulatory Operations

QUALITY DEFICIENCY - MINOR

ANDA 090548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Apotex Corp. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: (866) 392-1774

FROM: Robert Gaines FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 1, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated February 22, and March 17, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090548 **APPLICANT:** Apotex Inc
DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.



Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUHAS J PATANKAR
04/25/2011
for Vilayat Sayeed, Ph.D.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2011

FROM: Robert L. West, Deputy Director
Office of Generic Drugs

THROUGH: Keith O. Webber, Ph.D., Deputy Director
Office of Pharmaceutical Science

SUBJECT: Expedited Review of Certain Atorvastatin ANDAs

TO: ANDA 077575 - Sandoz Inc.; ANDA 078773 - Teva Pharmaceuticals USA; ANDA 090548 - Apotex Inc.; ANDA 091226 - Matrix Laboratories/Mylan Pharmaceuticals

THIS DOCUMENT CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION

Pfizer's Lipitor (atorvastatin calcium) is a cholesterol-lowering agent that has been very widely prescribed for many years. The purpose of this memorandum is to document the agency's basis for expediting the review of certain atorvastatin ANDAs.[1] The actual decision to expedite the review of eligible atorvastatin ANDAs was made in late February 2011; reviewers were notified of this decision at that time.

Ranbaxy submitted its atorvastatin ANDA in 2002. It was the first generic applicant to submit an ANDA for atorvastatin. Ranbaxy challenged all the patents listed by Pfizer as covering Lipitor. By challenging the patents, under the FD&C Act Ranbaxy became eligible for 180 days of generic drug exclusivity. As a pre-MMA ANDA, the Ranbaxy ANDA is not subject to the forfeiture provisions now found in the 180-day exclusivity provisions of the Act.

[1] It is acknowledged that the circumstances here do not fit squarely under OGD's MaPP 5240.3, which among other things describes circumstances under which an ANDA will be given expedited review. However, the circumstances here (e.g., the existence and complexity of the questions related to the Ranbaxy AIP and ANDA reliability, the highly uncertain date upon which ANDAs may be eligible for final approval, the review issues posed by the applications, and the size of the market demand for this drug product) are of such an unusual nature that they could not have been anticipated. Review of these applications on an expedited basis is, however, consistent with OGD's long-term goal of reviewing pending ANDAs in such a manner that, by the time patent and exclusivity barriers to approval have expired, appropriate reviews will have been completed. With first generic ANDAs that have been found scientifically approvable, OGD has a long history of approving these as promptly as permitted under the statutory provisions pertaining to patents, patent litigation, and exclusivity. Prompt review of ANDAs does not, of course, guarantee that any application will be ready for final approval as of a specific date. To be approved, an application must meet the requirements under section 505(j) of the FD&C Act and applicable regulations.

In a letter dated February 25, 2009, CDER informed Ranbaxy that CDER was applying its Application Integrity Policy (AIP) to the applications CDER identified as originating from Ranbaxy's Paonta Sahib site in India. CDER concluded that there was:

> "a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications … developed at the Ranbaxy Laboratories, Paonta Sahib site."

Certain "subsequent applicants" (i.e., those applicants whose ANDAs would not be approved prior to or during Ranbaxy's 180-day exclusivity period) have written the agency and stated that the agency should declare Ranbaxy ineligible for 180-day exclusivity (in short, because of the AIP). Mylan recently brought suit against the agency on this point. No decision has been made, at this time, about the status of Ranbaxy's eligibility for 180-day exclusivity. Issues related to Ranbaxy's eligibility for exclusivity and the review of the Ranbaxy ANDA are not addressed in this memorandum.

November 30, 2011, is the earliest date Ranbaxy could market under its 2008 settlement agreement with Pfizer. If Ranbaxy were to obtain approval of its ANDA and market promptly after that date, approval of subsequent ANDAs could be blocked until the end of May, 2012. [2] However, June 28, 2011, is the expiration date of the pediatric exclusivities attaching to two key Lipitor patents. If Ranbaxy loses its eligibility for 180-day exclusivity, the ANDAs identified in this memorandum could become eligible for approval on June 28, 2011.[3]

In managing the workload in OGD, we must take into account these unusual circumstances and the possibility that Ranbaxy may lose its claim for exclusivity either by relinquishing it or by an agency determination that Ranbaxy is not eligible for exclusivity, e.g., because Ranbaxy's ANDA was not "substantially complete" at the time of its submission. If this were to happen, the agency has concluded that it is in the public interest to have completed its scientific reviews of any atorvastatin ANDA that otherwise could be approved and marketed to the American public as early as June 28, 2011. To date, no atorvastatin ANDA has been tentatively approved.

---

[2] On March 23, 2011, counsel for Ranbaxy notified FDA that if it does not receive final approval by March 1, 2012, Ranbaxy will not object to FDA's approval of any other ANDA for atorvastatin after May 30, 2012 (i.e., the approximate date upon which Ranbaxy's exclusivity would expire if it began commercial marketing promptly after an approval on November 30, 2011). Ranbaxy's representations diminish significantly, but do not completely eliminate, the possibility that its eligibility for exclusivity could result in an indefinite delay in approval of generic Lipitor. Among other things, Ranbaxy could attempt to withdraw the commitment made in the letter.

[3] There is one applicant as to whom there may be no patent barrier to approval as early as May 2011. However, that applicant currently has significant deficiencies in its application, so it is not likely to be technically approvable by that date.

Reference ID: 2930036

OGD has identified[4] those ANDAs that meet the following criteria:

- patent litigation has been settled and there has been a representation by the ANDA applicant that the settlement will permit approval as early as June 28, 2011;
- the applicant was not sued (so there is no 30-month stay of approval to consider); or
- the relevant 30-month stays will have expired before June 28, 2011.

Sandoz's ANDA 077575, Teva's ANDA 078773, Apotex's ANDA 090548, and Matrix/Mylan's ANDA 091226 currently meet one or more of these criteria, and have been designated for expedited review. OGD's process for review is intended to permit the approval of generic atorvastatin as soon as applicable scientific, regulatory, and legal requirements have been met.

[4] Identification was based on documents submitted by ANDA sponsors and available court documents. It should be noted that, of the ANDAs the reviews of which are *not* being expedited, all were sued on the '156 patent and the earliest 30-month stay does not expire until April 27, 2012. In addition, there is one ANDA that was submitted so recently (acknowledged for receipt on March 21, 2011) that litigation information is not yet available.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
04/08/2011

ROBERT L WEST
04/08/2011
Deputy Director
Office of Generic Drugs

KEITH O WEBBER
04/08/2011

APOTEX
ADVANCING GENERICS

March 17, 2011

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Re: **GRATUITOUS CMC AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Gratuitous CMC Amendment to ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The amendment is being submitted as a proposal to include an alternate manufacturing site for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Specifically, the changes involve:

1. Addition of an alternate site, [redacted] (b) (4) site for the manufacturing of Atorvastatin Calcium Tablets,10 mg, 20 mg, 40 mg and 80 mg.

A summary of the changes along with the list of supporting data that is provided is attached as Attachment 1.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Regulatory Affairs New Products

ANDA 090548
Atorvastatin by Apotex
Compliance status update

From: CDER EESQUESTIONS
Sent: Wednesday, March 16, 2011 11:27 AM
To: Gaines, Robert
Cc: CDER EESQUESTIONS
Subject: RE: ANDA 90548

Hi Bob,

Unfortunately, Apotex is a very complicated case. There was a recent inspection in February of the Apotex sites in this application and they are initially OAI again. There are serious compliance issues and review of these EIRs could take months. I do not foresee any changes to the WH status before June because the inspections following the warning letters issued find the firm still unacceptable which raises serious issues. I see that Apotex is the sponsor of this application so it should be of no surprise to them that the application will not be approved because of the outstanding compliance issues.

Hope this helps!
Derek

From: Gaines, Robert
Sent: Wednesday, March 16, 2011 11:08 AM
To: CDER EESQUESTIONS
Subject: ANDA 90548
Importance: High

Hello.

This application was granted expedited review on 3/14/11 in anticipation of a possible 6/28/11 approval (pending legal review). I see that a new withhold recommendation was made on 3/10/11. Is there an upcoming inspection or do you anticipate any changes before June? Please advise.

Thanks.

Bob

Robert Gaines, PharmD
LCDR, United States Public Health Service
Quality Project Manager, Team 33
Office of Generic Drugs
Food and Drug Administration
7500 Standish Place Room E145
Rockville, MD 20855
Phone: 240-276-8495
Fax: 240-276-8474

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/s/

ROBERT T GAINES
03/16/2011

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 090548 APPLICANT: Apotex Inc.
DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg DATE OF SUBMISSION:See below email

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,& MaPP 5240.3). At least one of the criteria must be met to receive Expedited Review Status:

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - ♦ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - ♦ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where l8O-day generic drug exclusivity prevented full approval of all strengths).
   e) MaPP 5240.3 conditions.

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	RG 3/13/11
Chemistry Team Leader (sign as needed)	Grant☒ Deny☐	SP 3/13/11
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☒ Deny☐	VS 3/13/11
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☐ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: Team 33
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE
Paste Email Copy Below:

Reference ID: 2917568

From: West, Robert L
Sent: Friday, March 11, 2011 11:08 AM
To: Sears, Leigh Ann; Vu, Thuyanh (Ann); Gaines, Robert; Chun, Nam
Cc: Sayeed, Vilayat A; Gill, Devinder; Vaithiyalingam, Sivakumar; Patankar, Suhas; Hassall, Rita R; Webber, Keith; Read, David T; Ames, Timothy W; Rickman, William P; Yu, Lawrence; Shimer, Martin; Golson, Lillie D; Grace, John F; Lee, Koung U; Nagavelli, Laxma
Subject: EXPEDITED REVIEW GRANTED FOR ANDA'S 77-575 (SANDOZ) AND 90-548 (APOTEX) FOR ATORVASTATIN CALCIUM TABLETS - CONFIDENTIAL

Atorvastatin Teams:

Please refer to my email dated February 17, 2011, in which I noted that the Office had granted "expedited review" status to Teva's ANDA 78-773 and to Matrix/Mylan's ANDA 91-226 for Atorvastatin Calcium Tablets.

At this time, we are also granting "expedited review" status to the following ANDAs for Atorvastatin Calcium Tablets:

ANDA 90-548 Apotex CMC Team 33 Bio complete and acceptable.

ANDA 77-575 Sandoz CMC Team 34 Bio complete and acceptable.

We, along with CDER's Office of Chief Counsel, have determined that both Apotex and Sandoz could become eligible for final approval about the same time as Teva and Matrix/Mylan, but for different reasons (expiration of 30-month statutory hold period v. settlement agreements with the NDA holder).

Thus, as an issue of fairness to the applicants and out of concern that the office needs to anticipate all options with respect to its review of this drug product, "expedited review" status is granted to Apotex and Sandoz for their Atorvastatin Calcium Tablet ANDA.

Bob/Leigh Ann: Please make certain that the proper entries are made in DARRTS for both the Apotex and Sandoz applications to reflect the "expedited review" status and notify Office of Compliance of their priority status.

Thank you for your cooperation,

Bob

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT T GAINES
03/14/2011

APOTEX
ADVANCING GENERICS

February 22, 2011

Robert Gaines
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Dear Mr. Gaines:

Re: **QUALITY MINOR AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Quality Minor Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted in response to a FDA Minor Quality Deficiency dated January 12, 2011.

At this time, we would also like to provide the following additional information:

- Revised drug substance method validation reports for assay and related compounds.
- An updated Calcium Acetate USP specification

A summary of the changes along with the list of supporting data that is provided in Attachment 4.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs New Products

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

MEMBER CGPA

QUALITY DEFICIENCY - MINOR

ANDA 090548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Apotex Corp. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: (866) 392-1774

FROM: Robert Gaines FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 1, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated November 9, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090548 **APPLICANT:** Apotex Inc

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.



B: Comments:

1. Please update your long term stability data results, if applicable.

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUOPING SUN
01/12/2011

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

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Suite 500
Chicago, IL 60654
www.rmmslegal.com

312-527-2157 main phone
312-527-4205 main fax

Liz Dickinson Rec'd a copy of this document via e-mail

ORIG-1
51-73

3 January 2011

William A. Rakoczy
312.222.6301 telephone
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lfitzsimmons@rmmslegal.com

November 11, 2010

PRIVILEGED AND CONFIDENTIAL
ANDA COMMUNICATION, ANDA NO. 90-548

VIA E-MAIL
AND OVERNIGHT DELIVERY

Ralph S. Tyler
Chief Counsel
Office of Chief Counsel
Food and Drug Administration
10903 New Hampshire Avenue
Building 31, Room 4544
Silver Spring, MD 20993

Keith Webber
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, HFD-600
Rockville, MD 20855

RECEIVED
NOV 12 2010
OGD

Re: Apotex Inc.'s ANDA No. 90-548 for
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Messrs. Tyler and Webber:

On behalf of Apotex Inc., the undersigned hereby respectfully requests that FDA confirm that Ranbaxy Laboratories is not eligible for any 180-day exclusivity for atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg.

INTRODUCTION

Apotex has filed an abbreviated new drug application ("ANDA") for atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg. On information and belief, Ranbaxy purports and claims to hold first-filer status for these drug products, based on its paragraph IV certifications to one or more unexpired patents listed in connection with the reference listed drug, Lipitor® (atorvastatin calcium) Tablets. As explained in more detail below, FDA has invoked its Application Integrity Policy ("AIP") against Ranbaxy's largest manufacturing facility based in Paonta Sahib, India, out of which, Apotex understands and believes, Ranbaxy filed its atorvastatin calcium ANDA. If so (and we believe that it is), under the Agency's own fraud policies, Ranbaxy's ANDA no longer is valid, and certainly cannot be used to secure generic

exclusivity and delay the approval of other applicants like Apotex. In fact, even should Ranbaxy seek to correct the deficiencies leading up to the Agency's invocation of AIP, including the submission of any new or corrected stability data, Ranbaxy would be required to do so through the submission of a *new* application. Ranbaxy's pending atorvastatin ANDA therefore must be deemed invalid and withdrawn, thereby extinguishing any eligibility for exclusivity Ranbaxy might have claimed for atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg.

FACTUAL BACKGROUND

RLD: Lipitor® Tablets

The reference listed drug ("RLD") at issue here is Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg, approved under New Drug Application ("NDA") No. 20-702 as a cholesterol-lowering agent. FDA currently lists six patents in connection with Lipitor® Tablets in the Orange Book:

- **U.S. Patent No. 4,681,893 ("the '893 patent")**, which expired on September 24, 2009, with pediatric exclusivity that expired on March 24, 2010.

- **U.S. Patent No. 5,273,995 ("the '995 patent")**, which purportedly expires on December 28, 2010, with pediatric exclusivity that purportedly expires on June 28, 2011.

- **U.S. Patent No. RE40667 ("the RE667 patent")**, which is a reissue of the '995 patent, and purportedly expires on December 28, 2010, with pediatric exclusivity that purportedly expires on June 28, 2011.

- **U.S. Patent No. 5,686,104 ("the '104 patent")**, which purportedly expires on November 11, 2014, with pediatric exclusivity that purportedly expires on May 11, 2015.

- **U.S. Patent No. 6,126,971 ("the '971 patent")**, which purportedly expires on January 19, 2013, with pediatric exclusivity that purportedly expires on July 19, 2013.

- **U.S. Patent No. 5,969,156 ("the '156 patent")**, which purportedly expires on July 8, 2016, with pediatric exclusivity that purportedly expires on January 8, 2017.

Atorvastatin Calcium Tablet ANDAs

On August 7, 2008, Apotex filed ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, referencing Pfizer's Lipitor® Tablets as the RLD. Apotex's ANDA contains a paragraph III certification to the '893 patent, and paragraph IV certifications to all remaining Orange Book-listed listed patents, namely, the '995, '104, '971, '156 and RE667 patents. On December 17, 2008, Pfizer sued Apotex for infringement over the '995 patent in both the U.S. District Courts for the Northern District of Illinois and the District of Delaware. Apotex counterclaimed for declaratory judgments of noninfringement and invalidity of the '104, '971 and '156 patents. Pfizer subsequently sued Apotex for infringement of the RE667 and '156 patents as well. Apotex's Delaware action was eventually transferred and consolidated with the Illinois action, which is still pending.

On information and belief, there are at least five other publicly-known paragraph IV ANDA-filers for atorvastatin calcium tablets: Ranbaxy, Teva, Matrix (a subsidiary of Mylan), KUDCO and Dr. Reddy's (DRL). Each applicant purportedly has filed paragraph IV certifications to at least the '104, '971 and '156 patents. Pfizer sued each applicant in Delaware. As explained in more detail below, Pfizer eventually settled its litigation with Ranbaxy. Pfizer also settled its litigation with Teva. Pfizer's litigation against Matrix, KUDCO, DRL and Apotex is still pending, and no substantive orders have been entered.

Ranbaxy's Paragraph IV ANDA

Based on public records, Ranbaxy claims to be the first applicant to have filed a paragraph IV ANDA for atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg. According to public records, Ranbaxy initially filed its ANDA (No. 76-477) on or about August 19, 2002, and purports to have amended its ANDA in 2003 to include a paragraph IV certification to both the '893 and '995 patents. As we understand it, Ranbaxy also purports and claims to be the first applicant to have filed paragraph IV certifications to at least the '104, '971, and '156 patents. On information and belief, Ranbaxy filed its Atorvastatin Calcium ANDA, and/or prepared and obtained the supporting data for that application, out of its Paonta Sahib facility. (*See* Ranbaxy Q4 2009 Earnings Conference Call Tr., at 13-14 (Feb. 25, 2010), excerpt attached hereto at Ex. A; *see also* Angel Broking Ranbaxy Laboratories 2QCY2009 Result Update (July 24, 2009) (noting that Ranbaxy "said that it has filed *Valtrex* from the Dewas facility, and *Lipitor* from Paonta Sahib"), excerpt attached hereto at Ex. B; Motilal Oswal Ranbaxy Laboratories 2QCY10 Results Update (Aug. 12, 2010) (stating that "[t]he Lipitor exclusivity is linked to successful clearance of the Poanta [sic] facility"), excerpt attached hereto at Ex. C.)

On February 21, 2003, Pfizer sued Ranbaxy for infringement of claim 1 of the '893 patent in the United States District Court for the District of Delaware. On April 11, 2003, Pfizer sued Ranbaxy again in Delaware, this time for infringement of the '995 patent. These

cases were consolidated in June 2003, and Pfizer later limited its claims relating to the '995 patent to claim 6. After a trial, Pfizer prevailed in the district court on all claims.

On August 2, 2006, the Federal Circuit affirmed the district court's holding of infringement and validity of the '893 patent, but reversed the district court's decision with respect to the '995 patent, and found that claim 6 of the '995 patent was invalid for improper dependency. Ranbaxy petitioned the Federal Circuit for rehearing and rehearing en banc, which the court denied on October 23, 2006. Ranbaxy's petition for writ of certiorari to the Supreme Court was also denied on January 22, 2007.

After the Federal Circuit's decision finding claim 6 of the '995 patent invalid, Pfizer filed a reissue application to correct the improper dependency. The U.S. Patent and Trademark Office ultimately reissued the '995 patent as the RE667 patent on March 17, 2009, which FDA listed in the Orange Book shortly thereafter.

On June 18, 2008, Ranbaxy publicly announced that it had come to an agreement with Pfizer to settle their litigations worldwide. According to public filings, Ranbaxy announced that it has a license to market generic atorvastatin in the United States effective November 30, 2011. (6/18/08 Ranbaxy Press Release, attached hereto at Ex. D.) This, of course, is at least 6 months (or more) *after* Ranbaxy would have been eligible to commercially launch its product based on the patent litigation. In other words, even putting the approval and fraud issues aside (discussed more below), Ranbaxy's patent settlement actually *delayed* Ranbaxy's market entry well beyond when Ranbaxy could have gone to market in view of Ranbaxy's patent victory on the '995 patent. Moreover, to make matters worse, this does not include the additional (and unlawful) delays that will be inflicted upon Apotex and others by any generic atorvastatin exclusivity that Ranbaxy may claim as a result of its fraudulent ANDA filing, as described below.

Ranbaxy's Fraud On The Agency

In the last several years, Ranbaxy has been the subject of numerous Agency investigations, Warning Letters, and Import Alerts. Many of these formal Agency disciplinary actions have been linked to Ranbaxy's largest manufacturing facility based in Paonta Sahib, India, out of which Ranbaxy manufactures and conducts testing on solid oral dosage forms, including, on information and belief, Atorvastatin Calcium Tablets. Most relevant here, on February 25, 2009, FDA issued a memorandum formally determining that Ranbaxy had "***submitted untrue statements of material fact in abbreviated and new drug applications filed with the Agency***" from the Paonta Sahib site, and that these submissions "***were material to FDA's review of these applications***." (2/25/09 Mem. from Dr. Woodcock to Mr. Singh, at 1, 3, attached hereto at Ex. E) (emphasis added). FDA explained that its "findings concern the submission of information, such as from stability test results in support of pending and approved drug applications." (*Id.* at 1.) Specifically, FDA found that Ranbaxy had submitted falsified or

fraudulent information and data to the Agency from its Paonta Sahib facility, including, among other things:

- stability data that contained "untrue statements of material fact" and "failed to include critical information about the storage and testing of the product";
- stability test reports revealing that test dates previously submitted to the Agency were "false";
- "protocols and stability data submitted by Ranbaxy" in connection with certain applications which failed to describe "unusual storage conditions for stability testing," including the refrigeration of over two hundred stability samples;
- stability test reports which had incorrectly estimated the number of days that over 100 stability samples were held and/or had incorrect values for test results;
- stability data for pending ANDAs that included at least "2257 errors in entries for the dates of analysis" and "errors in 1385 entries for stability test results" relating to specification limits; and,
- exhibit batch records which "contained the signatures or initials of Ranbaxy employees who were not present in the facility on the dates documented in the batch records."

(*Id.* at 1-5.)

FDA concluded that "[t]hese and other findings indicate ***a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications (pending and approved) that [Ranbaxy] has filed with the Agency and which contain data developed at the Ranbaxy Laboratories, Paonta Sahib site***." (*Id.* at 5) (emphasis added). FDA further noted that "the Agency does not intend ordinarily to conduct or to continue its normal substantive scientific review (including review of data and labeling) of any such pending application or supplement . . . that contain data developed at the Paonta Sahib site, during a validity assessment of that application." (*Id.*)

To address Ranbaxy's falsified data, FDA invoked its "Application Integrity Policy (AIP)" against the Paonta Sahib facility. As FDA explained in its press release announcing this measure, "[w]hen the AIP is implemented, the FDA stops all substantive scientific review of any new or pending drug approval applications that contain data generated by the Paonta Sahib facility." (FDA News, "FDA Takes New Regulatory Action Against

Ranbaxy's Paonta Sahib Plant in India" (Feb. 25, 2009), attached hereto at Ex. F.) FDA also directed Ranbaxy to the Agency's policy entitled "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities" ("fraud policy"), which, as explained in more detail below, outlines the Agency's policies regarding validity assessments and corrective actions taken when a company submits false or fraudulent data within an application.

LEGAL AND REGULATORY BACKGROUND

Hatch-Waxman And The Generic 180-Day Exclusivity Incentive

Before 1984, a company seeking to market a generic version of an FDA-approved drug had to repeat the expensive and time-consuming safety and efficacy studies that already were conducted for the NDA drug. In 1984, Congress simplified the procedure for obtaining approval of generic drugs with the Hatch-Waxman Amendments to the Federal Food Drug and Cosmetic Act. Hatch-Waxman permits a company to file an Abbreviated New Drug Application ("ANDA") that relies on information from the NDA. An ANDA applicant must establish, *inter alia*, that its drug product is bioequivalent to the NDA drug. 21 U.S.C. § 355(j)(2)(A)(iv). The ANDA must also include a "certification" to any patent information listed in the Orange Book. *Id.* § 355(j)(2)(A)(vii). With certain exceptions not relevant here, if an ANDA applicant seeks FDA approval to market its drug product before expiration of the Orange-Book listed patent, the applicant must submit a so-called "paragraph IV certification" to that patent. *Id.* § 355(j)(2)(A)(vii)(IV). The first company to submit an ANDA for a drug product containing a paragraph IV certification to any patent listed in the Orange Book is entitled to market its generic product free from generic competition for 180 days.[1] *See id.* § 355(j)(5)(B)(iv). This period of generic exclusivity can be triggered either through the ANDA filer's commercial marketing or a final court decision finding the relevant patent invalid, unenforceable, or not infringed. *See* 21 U.S.C. § 355(j)(5)(B)(iv) (2002).

The 180-day exclusivity period is critical to carrying out Congress' goal of "get[ting] generic drugs into the hands of patients at reasonable prices–fast." *In re Barr Labs.*, 930 F.2d 72, 76 (D.C. Cir. 1991). As the courts repeatedly have acknowledged, the 180-day generic exclusivity period is *the sole* incentive that Congress created in order to facilitate its goal of expediting consumer access to lower-priced drug products. *See Teva Pharms. USA, Inc. v. Pfizer, Inc.*, 395 F.3d 1324, 1328 (Fed. Cir. 2005) ("This provision provides an economic incentive for generic manufacturers to challenge the validity of listed patents and to 'design around' patents to find alternative, non-infringing forms of patented drugs."); *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 33 (D.D.C. 2000) (stating that Congress created the 180-day

[1] Because Ranbaxy's paragraph IV ANDA purportedly was filed before December 8, 2003, 180-day exclusivity for all atorvastatin ANDAs is governed by Section 505(j)(5)(B) of the Federal Food, Drug, and Cosmetic Act, as it existed before Congress passed the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"). Under FDA's view of the pre-MMA regime, each listed patent can purportedly give rise to 180 days of generic marketing exclusivity.

exclusivity provision to "encourage generic drug makers to incur the potentially substantial litigation costs associated with challenging pioneer drug makers' patents"); *Apotex, Inc. v. Shalala*, 53 F. Supp. 2d 454, 461 (D.D.C. 1999) (noting that the "purpose of the exclusivity incentive and the entire ANDA regime is to make available more low cost generic drugs." (internal quotation marks and citation omitted)).

Importantly, in enacting Hatch-Waxman, Congress warned applicants against "filing sham ANDAs or ANDAs which are substantially incomplete." H.R. REP. NO. 98-857, pt. I, at 24 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2657. FDA too has recognized that allowing "ANDA applicants to file incomplete or 'sham' ANDAs and to supplement them later to secure a place in the review queue in an attempt to secure the first ANDA approval" is contrary to Hatch-Waxman's legislative history. 59 Fed. Reg. 50338, 50350 (Oct. 3, 1994). FDA, moreover, repeatedly has emphasized that 180-day exclusivity is ***not*** meant to reward applicants who simply race to be first-to-file. Rather, according to the Agency, 180-day exclusivity is reserved for applicants that submit substantially complete applications containing studies and data that meet FDA's standards for approval. 64 Fed. Reg. 42873, 42875 (Aug. 6, 1999).

FDA's Fraud/Application Integrity Policies

As noted above, by invoking its Application Integrity Policy (AIP) against Ranbaxy's Paonta Sahib facility, FDA already has determined that Ranbaxy has submitted studies and data that do ***not*** meet the Agency's standards for approval. According to the Agency, when AIP is invoked, it applies to "all of a firm's applications affected by a wrongful act, that is, whenever the wrongful act raises a significant question regarding the reliability of data in those applications. A wrongful act is any act that may subvert the integrity of the review process." (Application Integrity Policy, Section 1-1-6, "Invoking the AIP," ¶ 2.A.) Additionally, by invoking the AIP, the Agency will "defer[] substantive scientific review pending a validity assessment of data and information in all of the affected applications." (*Id.*, Section 1-1-3 ¶ 10.)

In addition to its AIP, FDA has published a Compliance Policy Guide (CPG 7150.09), entitled "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities" ("fraud policy"), setting forth the Agency's "general approach regarding applicants that seek to subvert the agency's review and approval processes for premarket applications" by committing wrongful acts and submitting fraudulent data. 56 Fed. Reg. 46191 (Sept. 10, 1991). FDA published notice of this policy in the September 10, 1991 Federal Register. FDA explains its fraud policy as follows:

> Actions on the part of an applicant to subvert the integrity of an FDA review process through acts such as submitting fraudulent applications, making untrue statements of material facts, or giving or promising bribes or illegal gratuities may call into question the integrity of some or all of the applicant's submissions to the

> agency. In such cases, FDA will conduct an investigation to identify all instances of wrongful acts and to determine the extent to which the wrongful acts may have affected approved or pending applications. . . . If the wrongful acts have raised a significant question regarding reliability of data in some or all of the applicant's pending applications, FDA ordinarily will conduct validity assessments of those applications.
>
> * * *
>
> If the agency determines that the criteria for approval cannot be met because of unresolved questions regarding reliability of data, the agency will not approve the application.
>
> ***When FDA finds, based on fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application*** (in the case of a pending application) or to proceed to withdraw approval (in the case of an approved application), ***regardless of whether the applicant attempts to replace the unreliable data with a new submission*** in the form of an amendment or supplement. Thus, ***if the applicant wishes to replace the false data with a new submission, the new submission should be in the form of a new application***.

(CPG 7150.09, Sec. 120.100 (emphasis added)); *see also* 56 Fed. Reg. 46191.

Similarly, in its Federal Register Notice, FDA explained that ***"[f]raudulent data in an application ordinarily should be remedied by withdrawing the application and submitting a new application***, even if the data are associated with a 'nonpivotal' study." 56 Fed. Reg. 46191 (emphasis added). In addition, "[u]nder the fraud policy, FDA ordinarily will proceed to withdraw approval of applications found to contain fraudulent data. ***The agency is not prepared to make a general exception to this policy for applicants who cooperate with the agency in its investigations***." (*Id.*) (emphasis added).

ARGUMENT

I. Ranbaxy is Not Eligible For 180-Day Exclusivity for Atorvastatin

As explained above, Ranbaxy claims to be the first applicant to have filed a paragraph IV certification to at least the '893, '995, '104, '971 and '156 patents. Under FDA's view of pre-MMA exclusivity rules, each listed patent purportedly can give rise to a separate

eligibility for exclusivity, which can be triggered only by Ranbaxy's own commercial marketing or by a final court decision finding the relevant patent(s) invalid, unenforceable or not infringed.[2] But where, as here, the purported first-filer has committed fraud on the Agency by submitting false data in connection with its application, such applicant no longer is entitled to *any* exclusivity in connection with that ANDA. Ranbaxy therefore no longer is eligible for 180-day exclusivity based on its paragraph IV ANDA for atorvastatin calcium tablets for at least the following reasons.

First, as explained in more detail below, under FDA's own fraud policies, Ranbaxy cannot correct its tainted ANDA through an amendment or supplement—Ranbaxy must submit a new application, making its original ANDA no longer valid, and certainly no longer entitled to exclusivity. *Second*, FDA regulations contain provisions intended to protect subsequent filers, such as Apotex, in circumstances such as these. Indeed, where, as here, the first-filer has not lawfully and actively pursued approval at all times during the pendency of its application, FDA may immediately approve all subsequent filers as soon as they are otherwise ready for approval. *Finally*, as both Congress and FDA previously have recognized, Hatch-Waxman is furthered only when FDA awards 180-day exclusivity to applicants who have submitted substantially complete applications that meet FDA's approval requirements. Applicants, such as Ranbaxy, who submit sham filings with falsified data do not qualify as lawful first-filers and are not entitled to this valuable incentive.

A. Under FDA's Fraud Policies And Procedures, Ranbaxy Is Not Entitled To 180-Day Exclusivity.

As discussed in detail above, FDA has formally determined that Ranbaxy has submitted false and fraudulent data in connection with numerous pending and approved applications submitted out of Ranbaxy's Paonta Sahib facility. (*See* Ex. E, 2/25/09 Mem. from Dr. Woodcock to Mr. Singh.) In so doing, FDA noted that its findings "***indicate a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in [Ranbaxy's] applications[.]***" (*Id.* at 5) (emphasis added). By invoking the AIP against Ranbaxy's Paonta Sahib facility, FDA in fact already has determined that Ranbaxy's actions have "subvert[ed] the integrity of the review process" and "raise[] a significant question regarding the reliability of data" in all affected applications filed out of that facility.

[2] While not relevant to the issues raised herein related to Ranbaxy's fraud on the Agency, there can be no dispute that any eligibility for exclusivity Ranbaxy may have had with respect to the '893 and '995 patents has long since expired or been extinguished. As discussed above, on August 2, 2006, the Federal Circuit found the '893 patent valid and infringed by Ranbaxy's proposed atorvastatin product. At that time, Ranbaxy's paragraph IV certification to the '893 patent would have been converted (or deemed to be converted) to a paragraph III certification. Moreover, any exclusivity as to the '893 patent was extinguished as soon as that patent expired on September 24, 2009. Similarly, any eligibility for exclusivity as to the '995 patent was triggered by the Federal Circuit's August 2006 decision finding the asserted claim of the '995 patent invalid. That 180-day period has now long expired.

(Application Integrity Policy, Section 1-1-6, "Invoking the AIP," ¶ 2.A.) FDA thus already has grounds to refuse to approve *any* applications for which such fraudulent data was submitted. (CPG 7150.09, Sec. 120.100 (explaining that, "[w]hen FDA finds, based on fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application")).

On information and belief, Ranbaxy's atorvastatin calcium ANDA was filed out of its Paonta Sahib facility and is subject to the Agency's AIP. (*See* Ex. A, Ranbaxy Q4 2009 Earnings Conference Call Tr., at 13-14 (Feb. 25, 2010); *see also* Ex. B, Angel Broking Ranbaxy Laboratories 2QCY2009 Result Update (July 24, 2009) (noting that Ranbaxy "said that it has filed *Valtrex* from the Dewas facility, and *Lipitor* from Paonta Sahib"); Ex. C, Motilal Oswal Ranbaxy Laboratories 2QCY10 Results Update (Aug. 12, 2010) (stating that "[t]he Lipitor exclusivity is linked to successful clearance of the Poanta [sic] facility")). Assuming this is true (and we currently have no information to believe otherwise), FDA should immediately refuse to approve Ranbaxy's ANDA, "regardless of whether [Ranbaxy] attempts to replace the unreliable data with a new submission." (CPG 7150.09, Sec. 120.100.) In that case, with an unapprovable ANDA, the application must either be withdrawn or deemed withdrawn and invalid. Either way, Ranbaxy should no longer be eligible for any exclusivity.

In addition, even if Ranbaxy seeks to replace or otherwise cure the false data with a new submission, FDA must require Ranbaxy to submit such submission in the form of a *new* application. (CPG 7150.09, Sec. 120.100.) Under FDA's long-standing fraud policy, Ranbaxy cannot simply amend its ANDA or submit a supplement in an attempt to correct its falsified data. (*Id.*) This is true even should Ranbaxy seek to change the manufacturing and testing facility for its atorvastatin calcium products. As FDA already has determined, the falsification of stability data and submission of fraudulent reports is material to the Agency's review of Ranbaxy's affected ANDAs. The Agency, moreover, already has stated that it will not "make a general exception to [its] policy for applicants who cooperate with the agency in its investigations." 56 Fed. Reg. 46191 (Sept. 10, 1991). Ranbaxy's fraudulent data and submission therefore can only "be remedied by withdrawing the application and submitting a new application." *Id.* In that event, of course, Ranbaxy would no longer be eligible for any exclusivity.

The bottom line is that Ranbaxy committed fraud on the FDA, and cannot now use any eligibility for exclusivity arising out of that fraud to block the approval of other filers. Regardless of whether Ranbaxy's current ANDA is deemed unapprovable and/or withdrawn because of fraud, or whether Ranbaxy submits a new application to attempt to cure any fraud, it is no longer eligible for any exclusivity. FDA, moreover, need not wait until Ranbaxy's atorvastatin calcium ANDA is withdrawn to determine the issue of Ranbaxy's eligibility for exclusivity. Ranbaxy's entire application is forever tainted and cannot be saved outside of the submission of a brand new application. FDA therefore can and should find that Ranbaxy no longer is entitled to 180-day exclusivity for atorvastatin calcium products. Any other determination would be arbitrary, capricious, and contrary to law.

B. FDA Can And Should Immediately Approve Apotex's ANDA As Soon As It Is Otherwise Approvable Because Ranbaxy Did Not Lawfully Pursue Approval Of Its ANDA.

FDA further cannot delay approval of Apotex's ANDA based on Ranbaxy's application because Ranbaxy has not lawfully pursued approval under 21 C.F.R. § 314.107(c)(3). FDA therefore must award Apotex immediate final approval as soon as all other substantive requirements for approval have been met and any other statutory stays of approval have been lifted.

Under Section 314.107(c)(3), "if FDA concludes that the applicant submitting the first application is not actively pursuing approval of its abbreviated application, FDA will make the approval of subsequent abbreviated applications immediately effective if they are otherwise eligible for an immediately effective approval." 21 C.F.R. § 314.107(c)(3). Here, Ranbaxy cannot be said to have been lawfully "actively pursuing approval" of its atorvastatin calcium ANDA if, at the same time, Ranbaxy was submitting fraudulent data in connection with that application. Any such submissions unquestionably do not constitute a "good faith effort to pursue marketing approval in a timely manner." 59 Fed. Reg. at 50354. "In determining whether a sponsor is actively pursuing marketing approval, FDA will consider all relevant factors, such as the sponsor's compliance with regulations and the timeliness of its responses to FDA's questions or application deficiencies during the review period." *Id.* If FDA thus finds that Ranbaxy has at any point filed false data in connection with its atorvastatin application, Ranbaxy cannot be found to have complied with the governing statutory or regulatory requirements.

As FDA itself acknowledges, generic exclusivity was not intended to reward applicants for racing to the Agency with an incomplete application just to secure first applicant status. Section 314.107(c)(3) affords FDA the opportunity to prevent first-filers, such as Ranbaxy, who do not comply with their legal responsibilities, from delaying the approval of other generic applicants. FDA thus can and should immediately approve Apotex's atorvastatin calcium ANDA as soon as it is otherwise eligible. Any other decision would be arbitrary, capricious, and contrary to law.

C. The Purpose Of Hatch-Waxman Is Furthered Only If FDA Finds That Ranbaxy Is Not Eligible For 180-Day Exclusivity.

As explained above, Congress created 180-day generic exclusivity as a reward for only those applicants that have submitted substantially complete ANDAs that comply with the statutory and regulatory requirements for approval. H.R. REP. NO. 98-857, pt. I, at 24; *see also* 59 Fed. Reg. at 50350 (noting that it would be contrary to Hatch-Waxman's legislative history to allow "ANDA applicants to file incomplete or 'sham' ANDAs and to supplement them later to secure a place in the review queue in an attempt to secure the first ANDA approval"). Congress created the exclusivity incentive, moreover, to enable competitors to bring more affordable

generic drugs to market as quickly as possible. H.R. REP. NO. 98-857, pt. I, at 14; *Barr Labs.*, 930 F.2d at 76.

If Ranbaxy did submit false data in connection with its atorvastatin calcium ANDA, as Apotex suspects, Ranbaxy can not be said to have submitted a substantially complete application. Rather, Ranbaxy's application is nothing but a sham filing intended solely to gain exclusivity, notwithstanding the costs to other lawful generic applicants, not to mention consumers. Here, unfortunately, the costs are severe. Ranbaxy not only has settled its litigation preventing it from being able to market its generic atorvastatin products until November 30, 2011 at the earliest, but FDA's invocation of its AIP and fraud policies against Ranbaxy mean that all of Ranbaxy's affected applications, including arguably atorvastatin, are ineligible for approval until the Agency has completed its validity assessments, if at all. Thus, because Ranbaxy can not open up the generic atorvastatin calcium market, FDA would be acting contrary to legislative intent and the purpose behind Hatch-Waxman if it failed to approve all subsequent filers, such as Apotex, as soon as they were otherwise approvable. For this additional reason, FDA must find that Ranbaxy is not entitled to 180-day exclusivity for atorvastatin calcium tablets. Any other conclusion would be arbitrary, capricious, and contrary to law.

CONCLUSION

As a result of Ranbaxy's fraud on the Agency, a number of Ranbaxy's applications filed from its Paonta Sahib facility are forever tainted and cannot be saved outside of the submission of new ANDAs. On information and belief, Ranbaxy's atorvastatin calcium tablet ANDA is one of the many "affected" applications that are subject to FDA's Application Integrity Policy. If this is true, as discussed above, under FDA's own regulations and policies, and consistent with Congressional intent, FDA must find that Ranbaxy is not eligible for 180-day exclusivity for atorvastatin calcium tablet products. Any other conclusion would be arbitrary, capricious, and contrary to law.

Apotex respectfully requests the courtesy of a response from the Agency by December 15, 2010. Should the Agency fail to respond by that date, Apotex reserves all rights to proceed accordingly, including any and all legal action.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

William A. Rakoczy

Lara E. FitzSimmons

Counsel for Apotex Inc.

cc (via e-mail):
Robert West, *Deputy Director, Office of Generic Drugs*
Elizabeth Dickinson, *Counsel, Office of Chief Counsel*

Exhibit A

FINAL TRANSCRIPT

Thomson StreetEvents℠

RANBAXY - Q4 2009 RANBAXY LABORATORIES LTD Earnings Conference Call

Event Date/Time: Feb. 25. 2010 / 12:45PM GMT

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Kartik Mehta - *Daiwa Securities Markets - Analyst*

Yes. And any probability of a charge back in Q2 when the exclusivity would -- in terms of excess inventory, which would be there by the end of this quarter because -- sorry?

Omesh Sethi - *Ranbaxy Laboratories Limited - CFO*

Surely, this will have an impact on the coming quarter's tax to this extent.

Kartik Mehta - *Daiwa Securities Markets - Analyst*

Okay. And so, just one last one was, could you share the consolidated net debt at the end of the year including the (inaudible)? Thanks.

Omesh Sethi - *Ranbaxy Laboratories Limited - CFO*

Our consolidated net debt is about $500 million.

Kartik Mehta - *Daiwa Securities Markets - Analyst*

Thank you.

Operator

Thank you, Mr. Mehta. Our next question comes from the line of Kesvinder Suri from Span Capital. Please go ahead.

Kesvinder Suri - *Span Capital - Analyst*

Yes. With regards to this Paonta under AIP, what's the status re Lipitor because I believe you're filing for Lipitor at [Paonta] facility?

Atul Sobti - *Ranbaxy Laboratories Limited - CEO and Managing Director*

Well, I think anything to do with Paonta is currently part of the AIP. Obviously, I think --

Kesvinder Suri - *Span Capital - Analyst*

But do you -- what I'm trying to arrive at, is there any risk to our exclusivity on Lipitor?

Atul Sobti - *Ranbaxy Laboratories Limited - CEO and Managing Director*

I think we -- there are various alternatives, options, stuff that is there. It's a little premature for us to be discussing anything there.

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Kesvinder Suri - *Span Capital - Analyst*

Okay. But have you taken -- like you were to take it on an exclusivity by exclusivity with the FDA, so have you taken it up with the FDA (inaudible) Lipitor?

Atul Sobti - *Ranbaxy Laboratories Limited - CEO and Managing Director*

Various discussions have taken place, but there is no specified agreed outcome yet. It's in process.

Kesvinder Suri - *Span Capital - Analyst*

Okay. And with regards to Romania, you mentioned there was pricing pressures and you were contemplating whether to take a hit on goodwill or not. Could you provide us an update on that?

Atul Sobti - *Ranbaxy Laboratories Limited - CEO and Managing Director*

In Romania, like most countries in 2009, had a challenge. And we do hope, as the first quarter has started, that Romania is actually starting to show good results. Russia, for example, started from Q4 itself.

I would think that Romania should be back well in 2010. We still maintain leadership there. We are pretty well invested. So, I don't think there should be major concerns, if it pans out the way it started in 2010.

Kesvinder Suri - *Span Capital - Analyst*

And if you could provide us a break up of the other operating income because it appears it's a negative figure for the fourth quarter if I compare it with your nine months' result.

Omesh Sethi - *Ranbaxy Laboratories Limited - CFO*

Actually, there is a classification and declassification of other operating income. The way we used to report earlier, there is a change. So, the other operating income actually is split in two parts. Part of the other operating income is shown along with the sales table. And then, there is another line, which is interest and other income. So, that is where actually some of the other operating income are included. Especially a divestment of (technical difficulty).

Kesvinder Suri - *Span Capital - Analyst*

Okay. And just a last question on these ForEx things. The gains what we've realized, those are actual realizations, or they're just the entries which would subsequently get reversed upon ForEx movement?

Omesh Sethi - *Ranbaxy Laboratories Limited - CFO*

It's a combination.

Kesvinder Suri - *Span Capital - Analyst*

Okay, fine. Could you provide a break up or something which could give a more indicative kind of thing, any --?

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Exhibit B

2 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Exhibit C

3 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Exhibit D

Print

RANBAXY AND PFIZER SETTLE LIPITOR LITIGATION WORLDWIDE

Ranbaxy will Market Generic Atorvastatin in the U.S. with 180 Days Exclusivity from Nov. 30, 2011

Agreement Also Resolves Caduet, Accupril Litigation in the US

Gurgaon, Harayana, India; Princeton, NJ, USA – June 18 , 2008

Ranbaxy Laboratories Limited (Ranbaxy), announced today that it has entered into an agreement with Pfizer Inc. to settle most of the patent litigation worldwide involving Atorvastatin (Lipitor), the world's most-prescribed cholesterol-lowering medicine. This decision will allow for an earlier introduction of a generic formulation that will benefit patients and many healthcare systems throughout the world. Lipitor is the world's largest selling drug with worldwide sales in 2007 of $12.7 billion .

The agreement pertains solely to Ranbaxy and its affiliates and does not cover legal challenges to the Lipitor patents involving other generic manufacturers. However, as Ranbaxy was the first generic challenger to the listed Lipitor patents, it retains the right to the marketing exclusivity of 180 days in the United States. Under the terms of the agreement, Ranbaxy will have a license to sell generic versions of Atorvastatin and the fixed-dose combination of Atorvastatin-Amlodipine besylate in the United States effective Nov. 30, 2011.

Welcoming the development, Malvinder Mohan Singh, CEO and MD, Ranbaxy Laboratories Ltd., said, "This comprehensively settles outstanding issues between Ranbaxy and Pfizer bringing to closure a number of ongoing patent disputes. It also provides certainty and visibility to the launch of Ranbaxy's Generic Atorvastatin, with180 day market exclusivity in the US and an early entry in other markets. This will make the worlds largest selling drug more accessible to patients who will gain from the timely availability of an affordable quality option."

Ranbaxy will also have a license to sell Atorvastatin on varying dates in an additional 7 countries, including: Canada, Belgium, Netherlands, Germany, Sweden, Italy and Australia. Ranbaxy and Pfizer have also resolved their disputes regarding Atorvastatin in Malaysia, Brunei, Peru and Vietnam.

In addition, the lawsuits between Pfizer and Ranbaxy regarding Atorvastatin will be dismissed in select countries and the lawsuits between Pfizer and Ranbaxy regarding the fixed dose combination product containing Atorvastatin and amlodipine will be dismissed in the U.S. and Ranbaxy will no longer contest the validity of Pfizer's patents in such countries. Such patent challenges by Ranbaxy regarding Lipitor have been underway in numerous markets since 2003.

The Atorvastatin patents involved in this agreement are the basic compound patent, which expires in the United States in 2010; the enantiomer patent, which expires in the United States in 2011; and various process and crystalline form patents, which expire in 2016 and 2017; and the combination patent for fixed-dose combination product which expires in 2018.

The agreement also covers the fixed-dose combination of Atorvastatin-Amlodipine besylate (presently marketed under the brand Caduet, which also contains crystalline Form I Atorvastatin), a fixed-dose combination product indicated for patients suffering from both high blood pressure and high levels of cholesterol. The patent for the fixed-dose combination expires in 2018. The settlement also resolves additional patent litigation between the companies involving the branded drugs Accupril (in the U.S.) and Viagra (in Ecuador) and all patent litigation with Ranbaxy relating to generic formulation of Quinapril hydrochloride in the United States and Sildenafil in Ecuador.

Litigation between Ranbaxy and Pfizer relating to Lipitor will continue in five other European countries -- Finland, Spain, Portugal, Denmark and Romania.

About Ranbaxy Laboratories Limited

Ranbaxy Laboratories Limited, India's largest pharmaceutical company, is an integrated, research based, international pharmaceutical company producing a wide range of quality, affordable generic medicines, trusted by healthcare professionals and patients across geographies. Ranbaxy's continued

focus on R&D has resulted in several approvals in developed markets and significant progress in New Drug Discovery Research. The Company's foray into Novel Drug Delivery Systems has led to proprietary "platform technologies," resulting in a number of products under development. The Company is serving its customers in over 125 countries and has an expanding international portfolio of affiliates, joint ventures and alliances, ground operations in 49 countries and manufacturing operations in 11 countries.

:: Close ::

Exhibit E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

February 25, 2009

Mr. Malvinder Mohan Singh
CEO & Managing Director
Ranbaxy Laboratories Limited
Corporate Office
Plot 90; Sector 32
Gurgaon - 122001 (Haryana)
India

Dear Mr. Singh:

The Center for Drug Evaluation and Research has determined that Ranbaxy Laboratories Limited (Ranbaxy) submitted untrue statements of material fact in abbreviated and new drug applications filed with the Agency. These findings concern the submission of information, such as from stability test results in support of pending and approved drug applications, from the Ranbaxy Laboratories Limited site located at Paonta Sahib, Sirmour District, Himachal Pradesh, India, (herein referred to as the "Paonta Sahib site"). The following are examples of the observations that support our conclusion that Ranbaxy submitted untrue statements of material fact in drug applications filed with the Agency:

1. Ranbaxy submitted stability information in numerous approved and pending applications that contain untrue statements of material fact, because Ranbaxy failed to include critical information about the storage and testing of the product. During a February 2006 inspection of the Paonta Sahib manufacturing facility, FDA found that hundreds of stability samples, many of which were being used for room temperature or accelerated stability studies, were being stored in refrigerators at approximately (b) (4) between the time they were removed from their stability chamber and the time they were tested. Among other things, FDA investigators found that the sample logbooks did not identify the samples that were being held in the refrigerators, their storage duration in the refrigerators, and the justification for this storage. FDA issued a June 15, 2006 warning letter to Ranbaxy based on its findings during this inspection, including the circumstances of these refrigerated stability samples.

2. Ranbaxy submitted an August 26, 2006 warning letter response that included corrections to the stability data previously submitted to the agency in several abbreviated new drug applications (ANDAs). The corrected stability test reports for Fluconazole Tablets, Ciprofloxacin Tablets, and (b) (4) show instances where stability test dates that previously had been submitted to the applications were false. In some cases stability testing was conducted several months later than the dates reported in the applications. Additionally, the firm reported stability test results for a given batch as occurring at the required accelerated or long term (e.g., 3, 6, 9, 12

month) time intervals, but actually conducted all of these tests on the same day, or within a period of days.

For Fluconazole Tablets and Ciprofloxacin Tablets, we found that even after Ranbaxy submitted its August 2006 warning letter response with the corrected stability test dates, the firm continued to submit the false stability test dates in annual report submissions to the respective applications.

These submissions of false information about the stability testing of the products were material to FDA's review of the applications.

3. In July 27, 2007 correspondence with the Division of Manufacturing and Product Quality, Ranbaxy's legal counsel, Kate C. Beardsley, provided the results of Ranbaxy's and (b) (4) stability verification project (hereafter referred to as "the verification report"). This report indicates that on February 22, 2006, Ranbaxy found 239 stability samples in the (b) (4) (b) (4) refrigerators which were being used to generate stability data for US drug applications.

   The verification report also included an August 22, 2006 listing of 67 stability samples for US filings that were held in the (b) (b refrigerators. The listing shows that many of the stability samples were from exhibit batches and that, based on Ranbaxy's estimates, the samples were held in the (b) (b refrigerators between 2 days and 201 days. The report also indicates that the time held in the refrigerator is estimated because documentation was not available which clearly shows the length of time the samples were held in the refrigerators.

   This unusual storage condition for stability testing was not defined in the submitted protocol for U.S. drug applications, and prior to the February 2006 inspection, was not reported to FDA. The stability protocols and stability data submitted in Ranbaxy's filings specify the use of controlled room temperature storage of stability samples at (b and (b) (4) relative humidity (RH) or storage of stability samples for accelerated studies at (b) (4) (b and (b) (4) RH. Thus, these protocols and stability data submitted by Ranbaxy to the applications, which failed to describe the refrigeration of stability samples, were false. These submissions of false information about the stability of the products were material to FDA's review of the applications.

4. The July 27, 2007 correspondence includes the results of Ranbaxy's verification audit of its stability data associated with the samples held in the (b) (4) refrigerator. The verification report indicates that numerous discrepancies were found in the data, as follows:

   - 129 stability samples (comprising 171 stability test reports) which were on stability were verified from a list of 239 samples for U.S. filings in the (b) (4)

refrigerator. (According to the verification report, the remaining stability samples were for discontinued stability studies.)

- All of the 129 samples were analyzed for all stability stations required by the respective protocol and all results were found to be within specifications.

- Dates of analysis for these 129 samples needed correction in all 171 stability test reports.

- In thirteen instances there was an incorrect estimate of the number of days that the stability samples were held at (b) (4) (Apparently, these instances were found in internal stability reports.)

- There were 122 instances of stability reports having incorrect values for test results (i.e., incorrectly transcribed from raw data).

- The package type was incorrectly reported in one stability report.

The verification report includes copies of updated stability test reports with numerous corrections in the stability data. These submissions of false information about the stability testing of the products were material to FDA's review of the applications.

5. The July 27, 2007 correspondence also includes the results of Ranbaxy's verification audit of the stability data filed with the Agency for approval of (b) (4) pending ANDAs; and audits of the stability data filed in 15 approved ANDAs. The audit results included the following findings:

   - Audit of the stability data in (b) (4) pending ANDAs found 2257 errors in entries for the dates of analysis; and errors in 1385 entries for stability test results, and tests for which corrections were made in specification limits.

   - Audit of the stability data filed in 15 approved ANDAs selected for the audit found a combined total of 1676 errors, which include errors in entries for the dates of analyses, packaging and errors in stability test results.

   These submissions of false information about the stability testing of the product were material to FDA's review of these applications.

6. Our review of certain stability reports that were corrected by Ranbaxy based on audits conducted during its verification project, and which were submitted as corrected to the Agency in the July 27, 2007 correspondence from Ms. Beardsley, and in subsequent filings to the affected drug applications, revealed the following:

- The corrected stability test reports show that in numerous instances stability testing actually was conducted several weeks or months later than the dates that originally were reported in the drug applications or annual reports. Additionally, the corrected data shows that in many instances the stability test results reported at different time intervals, (e.g., 3, 6, and 9 months) actually were conducted on the same day or within a few days of each other.

- Simvastatin Tablets are included in Ranbaxy's listing of stability samples for U.S. filings that were held in the (b) (4) refrigerators, and Simvastatin Tablet stability reports that were corrected by Ranbaxy based on its verification audit are included in Ms. Beardsley's July 27, 2007 correspondence with Mr. Campbell.

  We observed several differences between the corrected stability reports included in the July 27, 2007 correspondence, and other corrected stability reports for the same batches that were included with Ranbaxy's November 1, 2007 annual report submission to Ohm Laboratories ANDA 76-285, Simvastatin Tablets. Both sets of corrected stability reports show that they were prepared, checked and approved by three individuals of your firm.

  For the batches that were identified in the listing of stability samples held in the (b) (4) refrigerators, the corresponding corrected stability reports included with the July 27, 2007 correspondence note that controlled room temperature samples were kept at (b) (4) for varying periods up to 116 days before completion of analysis. In contrast, the corrected stability reports that were submitted to the Office of Generic Drugs with the November 1, 2007 annual report lack any reference to the storage of Simvastatin stability samples at (b) (4)b There also are instances where for the same batches, the stability test dates and test results differ between the two submissions of corrected stability reports.

- Corrected stability reports were included in Ranbaxy's June 18, 2007 and September 14, 2007 amendments to pending NDA (b) (4) . The June 18, 2007 amendment states that none of the changes made to correct the originally submitted stability data affect previous conclusions about the product's stability; yet the amendment also states that based on the 18 month stability data, Ranbaxy is withdrawing the (b) (4) package configuration. In fact, the corrected data shows that a specified impurity in one batch exceeded the specification limits at the (b) (4) month test interval. This test result would have affected the conclusion about the product's stability at the (b) (4) month test interval had the firm not withdrawn the (b) (4) package configuration.

  The September 14, 2007 amendment includes both the uncorrected and corrected stability data, and shows that prior to the verification project the original stability data submitted for approval of the (b) (4) package configuration erroneously

reported a passing result for the same specified impurity at the (b) (4) month stability test interval.

All of the above examples of the submission of false information were material to the review of the applications.

7. During a March 2008 preapproval inspection for pending ANDA (b) (4) , at Batamandi (Unit II) in the Paonta Sahib site, it was found that exhibit batch records previously submitted for FDA approval of the pending ANDA contained the signatures or initials of Ranbaxy employees who were not present in the facility on the dates documented in the batch records. The employees' signatures or initials appeared in blocks documenting the performance and verification of certain manufacturing steps. This observation also is the subject of the FDA Warning Letter issued to your firm on September 16, 2008. The submission of this false information was material to the review of the application. Your firm withdrew its pending ANDAs (b) (4) ; and (b) (4) ; both of which listed Batamandi as the manufacturing site.

These and other findings indicate a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications (pending and approved) that your firm has filed with the Agency and which contain data developed at the Ranbaxy Laboratories, Paonta Sahib site.

In accordance with FDA policy, the Agency will assess the validity of the data and information in all of Ranbaxy's affected applications which contain data developed at the Paonta Sahib site. This assessment, which is ongoing, is a part of the review of these applications, and thus will take priority over substantive scientific data review until questions of data integrity are resolved. This means that the Agency does not intend ordinarily to conduct or to continue its normal substantive scientific review (including review of data and labeling) of any such pending application or supplement, or of any new application or supplemental applications filed after the date of this letter, that contain data developed at the Paonta Sahib site, during a validity assessment of that application.

In the case of certain applications, however, the Agency may review and act on an application prior to completion of the validity assessment in special circumstances where such an action is clearly in the interest of public health.

The Agency's policies regarding validity assessments and corrective actions that companies may take are described more fully in the Agency's policy entitled "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities, Final Policy" which was published in the Federal Register of Tuesday, September 10, 1991. This Policy states in part:

> When FDA finds, based on fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application (in the case of a pending application) or to proceed to withdraw approval (in the case of an approved application), regardless of whether the applicant attempts to replace the unreliable data with a new submission in the form of an amendment or supplement. Thus, if the applicant wishes to replace the false data with a new submission, the new submission should be in the form of a new application. The new application should identify the parts of the original application that were found to be false. The truthfulness and accuracy of the new application should be certified by the president, chief executive officer, or other official most responsible for the applicant's operations.

Guidance for firms (regarding audits) and the Agency in conducting validity assessments also is contained in a document entitled "Points to Consider for Internal Reviews and Corrective Action Operating Plans" the availability of which was announced in the same issue of the Federal Register.

These documents can be obtained at the following web addresses:

> http://www.fda.gov/ora/compliance_ref/frn/fraud_ill_grat.html and
> http://www.fda.gov/ora/compliance_ref/aip_points.html

If you intend to cooperate with the Agency to attempt to resolve the questions of data integrity and reliability, and/or you wish to discuss the Agency's finding that a validity assessment is warranted, you should arrange a meeting with Mr. Richard L. Friedman, Director, Division of Manufacturing and Product Quality. He can be reached at the following address and telephone number:

Mr. Richard L. Friedman, Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 4224
Silver Spring, Maryland 20993
Phone: (301) 796-3267

If you do not intend to address the question of validity with regard to a pending or approved application which contains data developed at the Paonta Sahib site, you may withdraw the application pursuant to 21 CFR 314.150(d). Enclosed is a listing of all Ranbaxy's applications that are currently approved, pending, or for which a not-approvable letter has been issued. Please confirm your agreement with this listing and

inform the Agency of the action you intend to take with regard to each of the applications within ten days of the date of issuance of this letter.

Although the Agency's policy, "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities, Final Policy" is being applied only to pending and approved applications which contain data developed at the Paonta Sahib site, we note that it is your firm's responsibility to ensure the accuracy and reliability of all submissions to the Agency.

Sincerely,

Janet Woodcock, M.D.,
Director,
Center for Drug Evaluation and Research

Enclosure

Cc: Ms. Kate C. Beardsley
Buc & Beardsley
Suite 600
919 Eighteenth Street, N.W.
Washington, D.C. 20006-5503

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

March 2, 2009

Mr. Malvinder Mohan Singh
CEO & Managing Director
Ranbaxy Laboratories Limited
Corporate Office
Plot 90; Sector 32
Gurgaon – 12201 (Haryana)
India

RE: February 25, 2009 letter from FDA to Ranbaxy

Dear Mr. Singh:

I am writing concerning the Agency's letter to you of February 25, 2009. That letter noted that Ranbaxy's legal counsel, Kate C. Beardsley, transmitted to FDA, by correspondence dated July 27, 2007, audit reports from the stability verification project that was conducted by Ranbaxy and a hired consultant. We understand that some individuals may have read the agency's February 25, 2009 letter to suggest that Ms. Beardsley and/or her firm were responsible for generating the information that was submitted to FDA. No such suggestion was intended. Our current understanding is that Ms. Beardsley and her firm only transmitted those audit reports to FDA. We hope this clears up any confusion. Thank you.

Sincerely,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Cc: Ms. Kate C. Beardsley, Esq.

Exhibit F

U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
Feb. 25, 2009

Media Inquiries:
Rita Chappelle, 301-796-4672
Consumer Inquiries:
888-INFO-FDA

FDA Takes New Regulatory Action Against Ranbaxy's Paonta Sahib Plant in India

Agency halts review of drug applications from plant due to evidence of falsified data; invokes Application Integrity Policy

The U.S. Food and Drug Administration today announced that a facility owned by India-based Ranbaxy Laboratories falsified data and test results in approved and pending drug applications. The facility, Paonta Sahib, has been under an FDA Import Alert since September 2008.

The FDA is continuing to investigate this matter to ensure the safety and efficacy of marketed drugs associated with Ranbaxy's Paonta Sahib site. To date, the FDA has no evidence that these drugs do not meet their quality specifications and has not identified any health risks associated with currentl marketed Ranbaxy products.

In the meantime, the FDA recommends that patients not disrupt their drug therapy because this could jeopardize their health. Individuals who are concerned about their medications should talk with their health care professional.

The affected applications are for drugs that fall into three categories:

- Approved drugs made at the Paonta Sahib site for the U.S. market;
- Drugs pending approval at the FDA that are not yet marketed; and
- Certain drugs manufactured in the United States that relied on data from the Paonta Sahib facility.

Companies must provide truthful and accurate information in their marketing applications, said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research (CDER). The American public expects and deserves no less.

To address the falsified data, the FDA has invoked its Application Integrity Policy (AIP) against the Paonta Sahib facility. The AIP is invoked when a company's actions raise significant questions about the integrity of data in drug applications. This AIP covers applications that rely on data generated by the Paonta Sahib facility only.

Under the AIP, the FDA has asked Ranbaxy to cooperate with the agency to resolve the questions of data integrity and reliability. This would include implementing a Corrective Action Operating Plan (CAOP) to provide assurance of the integrity and reliability of data from the Paonta Sahib facility. A CAOP includes, but is not limited to, conducting a third-party independent audit of applications associated with Paonta Sahib.

When the AIP is implemented, the FDA stops all substantive scientific review of any new or pending drug approval applications that contain data generated by the Paonta Sahib facility.

The FDA's investigations revealed a pattern of questionable data raising significant questions regarding the reliability of certain applications, and this warrants applying the Application Integrity Policy, said Deborah Autor, director of CDER's Office of Compliance. Today's action reflects the FDA's continued vigilance and its steadfast commitment to safeguarding the public's health.

On Sept. 16, 2008, the FDA issued two warning letters and instituted an Import Alert barring the entry of all finished drug products and active pharmaceutical ingredients from Ranbaxy's Dewas, Paonta Sahib and Batamandi Unit facilities due to violations of U.S. current Good Manufacturing Practices requirements. That action barred the commercial importation of 30 different generic drugs into the United States and remains in effect.

For more information:

- For drug safety information, read: FDA's Drug Safety Initiative[1]
- Read the FDA's 2008 Warning Letters to Ranbaxy and the Import Alert
- Read the redacted AIP letter to Ranbaxy[2]
- Read about the Application Integrity Policy
- See a list of companies that have received an AIP

#

RSS Feed for FDA News Releases[3] [what is RSS?[4]]

Links on this page:

1. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm
2. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm118411.htm
3. http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/PressReleases/rss.xml
4. http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/ucm144575.htm

APOTEX
ADVANCING GENERICS

November 9, 2010

Bob Gaines
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Dear Mr. Gaines:

Re: **QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Quality Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted in response to a FDA Minor Quality Deficiency dated September 20, 2010.

At this time, we would also like to provide the following additional information:

- Correction of the chemical structure for the impurity (b) (4) Please refer to Attachment 1.

- Based on the completion of process validation studies, there are some modifications to the manufacturing parameters that are proposed. Please refer to Attachment 2.

- An update to the Establishment Information in Module 1 and the Manufacturer section, 3.2.P.3.1.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs New Products

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Oct 8, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BTS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

October 8, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Oct 8, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	October 8, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
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☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	October 8, 2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

October 7, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BST

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

October 7, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

October 7, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	October 7, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

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Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

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Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

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☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	Oct 7, 2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

October 6, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

October 6, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

October 6, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

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Apotex Inc.	October 6, 2010
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APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

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Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

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N/A

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☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	10-6-2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Oct 5, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BCS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

October 5, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

October 5, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	October 5, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	10-5-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

October 4, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

10-4-10

Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao ECS — October 4, 2010

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	October 4, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

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Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

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ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
BSS Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	10-4-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Oct 1, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
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Bernice Tao TSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

October 1, 2010
Date

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Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

October 1, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

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(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	10-1-2010
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept 30, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BCT
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 30, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 30, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 30, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

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2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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N/A

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☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
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☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BS	Kiran Krishnan Associate Director, Regulatory Affairs	9-30-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept 29, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BST
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

Sept 29 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao 355

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Sept 29, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 29, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

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Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

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N/A

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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	9-29-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept 28, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BST

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

Sept. 28, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Sept 28, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	Sept 28, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	Sept 28, 2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept 27, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

Sept 27, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Sept 27, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	Sept 27 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-27-2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 24, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 24, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao BST

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 24, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
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See OMB Statement on page 2.

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Apotex Inc.	September 24, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
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☐	16. Debarment certification (FD&C Act 306 (k)(1))
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-24-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 23, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 23, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BCS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 23 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 23 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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N/A

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☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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☐	16. Debarment certification (FD&C Act 306 (k)(1))
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-23-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 22, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 22, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 22, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	Sept. 22, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-22-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 21, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 21, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 21, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 21, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSc	Kiran Krishnan Associate Director, Regulatory Affairs	9-21-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept. 20, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 20, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSc

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 20, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 20, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

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☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
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☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
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☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
BSS Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	9-20-2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

QUALITY DEFICIENCY - MINOR

ANDA 090548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Apotex Inc. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: 1-866-392-1774

FROM: Bob Gaines FDA CONTACT PHONE: (240) 276-8495

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 1, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated June 23, 2009 and March 1, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090548 **APPLICANT:** Apotex Inc

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

[redacted]

(b) (4)

Comments:

1. Please update your long-term stability data results.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALOKA SRINIVASAN
09/20/2010
for Vilayat A. Sayeed, Ph.D.

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept 17, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

Sept. 17, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Sept 17, 2010

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	April 17, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-17-10
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept. 16, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao 355
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 16, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

September 16, 2010
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 16, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

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☐	1. Index
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☐	4. Chemistry section
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
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☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-16-10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

Sept. 15, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 15, 2010
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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Bernice Tao BTS

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

9-15-10

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	September 15, 2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
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☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan 855	Kiran Krishnan Associate Director, Regulatory Affairs	9-15-2010
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 14, 2010 BSS

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

September 14, 2010
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BST

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Sept 14, 2010

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	9-14-2010
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Atorvastatin Calcium Tablets	N/A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Atorvastatin Calcium		N/A
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
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7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	9-14-2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 13 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

9.13.10
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

9.13.10
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	9-13-10
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

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APPLICATION DESCRIPTION

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (for)	Kiran Krishnan Associate Director, Regulatory Affairs	9.13.10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 10, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

9.10.10
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

9.10.10
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	9.10.10
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Atorvastatin Calcium		N/A
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (KK)	Kiran Krishnan Associate Director, Regulatory Affairs	9·10·10

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 9, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

9.9.10
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao ®

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

9.9.10

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	9/9/10
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
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☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
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☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (D)	Kiran Krishnan Associate Director, Regulatory Affairs	9.9.10
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 8, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7620 Standish Place
Rockville, MD 20855

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

9.8.10

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao (BT)

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

9.8.10
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	9/8/10
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
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DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

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REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,790,197 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	9.8.10
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

September 7, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,790,197 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

9/7/2010

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,790,197 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,790,197 B2 ("the '197 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '197 patent, purportedly expiring on or about October 14, 2025, with pediatric exclusivity purportedly expiring on or about April 14, 2026, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the purported holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to the purported owner/assignee of the '197 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '197 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

9/7/2010
Date

APOTEX
ADVANCING GENERICS

May 27, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: PATENT AMENDMENT – NOTICE OF LITIGATION
ANDA No. 90-548
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
US Patent Nos.: RE40667 and RE40667 *PED

Apotex Inc. is hereby submitting a patent amendment to ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

This patent amendment is being filed in accordance with 21 CFR 314.95(b), where Apotex Inc. certifies that Notice of Non-infringement of US Patent numbers RE40667 and RE40667 *PED, has been provided to each person identified under 314.95(a), and that the Notice met the content requirements under 314.95(c). As required by 21 CFR 314.95(e), proof of receipt of the Notice is provided in this submission.

Also an updated notice of litigation incorporating US Patent No.'s RE40667 and RE40667 *PED, was received prior to the expiry of the 45-day period commencing on the patent holder's receipt date of Apotex's notice of patent certification. All pertinent information surrounding the notification of litigation, is provided for in this amendment.

This amendment is submitted in the eCTD format and transmitted via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp, the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at or fax: (866) 392-1774. Alternatively, please do not hesitate to contact me by telephone at (416) 401-7889, by fax: (416) 401-3817, or email btao@apotex.com.

A signed application form (FDA 356h) is also provided.

Sincerely,

Bernice Tao
Director, Regulatory Affairs New Products

APOTEX
ADVANCING GENERICS

March 1, 2010

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

To Whom It May Concern:

Re: **CMC AMENDMENT due to Bioequivalence Letter dated February 1, 2010**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a CMC Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being submitted subsequent to the Bioequivalence Amendment submitted on Feb 22, 2010 in response to the Bioequivalence letter from the Division of Bioequivalence dated February 1, 2010. This amendment provides for revised drug product release and stability specifications and updated dissolution method.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs New Products

APOTEX
ADVANCING GENERICS

February 26, 2010

Ann Vu
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Vu,

Re: **LABELING AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Labeling Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being filed in response to the FDA deficiency letter dated January 20, 2010.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs New Products

APOTEX
ADVANCING GENERICS

February 22, 2010

Nam Chun
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Nam Chun,

Re: **BIOEQUIVALENCE AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 090548

Apotex Inc. is hereby submitting a Bioequivalence Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 090548. This amendment is being filed in response to the FDA deficiency letter dated February 1, 2010.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs New Products

Apotex Inc. 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3849
www.apotex.com

MEMBER CGPA

BIOEQUIVALENCE AMENDMENT

ANDA 090548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Apotex Inc. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: (954) 349-4233

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 6, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendment dated December 24, 2008.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement **Bioequivalence Response to Information Request**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090548

APPLICANT: Apotex Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets,
10 mg, 20 mg, 40 mg and 80 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. For your fasting study (Study No. AQ4221), there was discrepancy between the numbers of sample reassays for code B (29 for the test product and 23 from the reference product per your CTD summary for "Reanalysis of Study Samples") and those for the same code in the reassay individual data submitted (50 for the test product and 40 for the reference product; Appendix 16.5.1.8.6.1 & 2 Summary of Repeat Assays Study AQ4221). You should provide explanation(s) for the discrepancy. Also, you are advised to provide a table listing all the original (if any) and repeat values for samples that were reassayed for the reason of "Analysis incomplete".

2. Your dissolution testing data are acceptable. However, your proposed specification of NLT (b)(4)%(Q) in (b)(4) minutes is not acceptable. Based on the dissolution data submitted, the DBE recommends a more appropriate specification. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

   The dissolution should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37 ± 0.5 ^{0}C, using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) amount of the labeled Atorvastatin Calcium is dissolved in **15** minutes.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90548	ORIG-1		ATORVASTATIN CALCIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DALE P CONNER
02/01/2010

Telephone Fax

ANDA 90548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Apotex Corp.
U.S. Agent for Apotex Inc.

TEL: 954-384-3986

FAX: 954-349-4233

ATTN: Kiran Krishnan

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20mg, 40 mg and 80 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-548 Date of Submission: May 20, 2009

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

---

Labeling Deficiencies:

1. CONTAINER (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
   40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
   80 mg= bottles of 30s, 90s, 500s, and 2500s):

   Acceptable in final print.

2. CARTON (10 x 10)

   Acceptable in final print.

3. BLISTER (Blister card of 10s)

   Acceptable in final print.

4. INSERT

   Due to changes in the insert labeling for the reference listed drug, Lipitor (20702/S-056, approved 6/17/2009), please revise your labeling to be in accord with RLD. The RLD labeling may be accessed at the Drugs@FDA website.

Submit label and labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90548	ORIG-1		ATORVASTATIN CALCIUM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN F GRACE
01/20/2010
for Wm Peter Rickman

CONNOLLY BOVE LODGE & HUTZ LLP
ATTORNEYS AT LAW

WILMINGTON, DE

The Nemours Building
1007 North Orange St.
P.O. Box 2207
Wilmington, DE 19899
TEL: (302) 658 9141
FAX: (302) 658 5614
WEB: www.cblh.com

Jeffrey B. Bove
Partner

TEL (302) 888-6241
FAX (302) 656-9072
EMAIL jbove@cblh.com
REPLY TO Wilmington Office

July 8, 2009

BY CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
HFD-600
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP
N/XP

Re: ANDA No. 90-548
Notice of Filing Legal Action for Patent Infringement

Dear Sir or Madam:

We represent Plaintiffs Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company and Warner-Lambert Company LLC (collectively referred to as "Pfizer") who have brought suit against Apotex Inc. and Apotex Corp. (collectively "Apotex") for infringement of United States Letters Patent No. 5,273,995 ("the '995 patent") by the submission of the Apotex's ANDA No. 90-548 for a generic Lipitor® product. The '995 patent expires on December 28, 2010, and it is subject to a pediatric exclusivity period expiring July 28, 2011. In addition, the '995 patent has also been partially reissued as United States Reissue Patent No. 40,667 pursuant to 35 USC §§ 251-252, and Pfizer has added the Reissue Patent to its original complaint in Delaware.

Pursuant to 21 CFR § 314.107(f)(2), Pfizer provides notification as follows:

(i) The ANDA number is 90-548;

(ii) The name of the abbreviated new drug applicant is Apotex Inc.;

(iii) The notice from Apotex Inc. to Pfizer about the ANDA filing provided an established name for the ANDA drug product as atorvastatin, in the form of tablets, which contain the equivalent of 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin as the active ingredient.

(iv) We certify that the above-referenced patent infringement suits were filed under Civil Action No. 08-948-LDD in the United States District Court for the District of Delaware on

RECEIVED
JUL 16 2009
OGD

December 17, 2008, and Civil Action No. 08-7231 in the United States District Court for the Northern District of Illinois. A copy of the summonses and original complaints are enclosed.

Pfizer received notice dated November 4, 2008, from Apotex pursuant to § 505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA. Accordingly, pursuant to § 505(j)(5)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30-month period beginning from Pfizer's receipt of such notice, i.e., until May 4, 2011, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Jeffrey B. Bove

JBB\
Enclosures

cc: Janet Woodcock, M.D., Director (w/ enclosures)
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-001, Room 6133
White Oak Bldg. 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Jane A. Axelrad (w/ enclosures)
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-005, Room 6140
White Oak Bldg. 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Jeffrey M. Senger, Esquire (w/ enclosures)
Deputy Chief Counsel
Food and Drug Administration
GCF-1, Room 6-57
Parklawn Bldg.
5600 Fishers Lane
Rockville, MD 20857

APOTEX
ADVANCING GENERICS

June 23, 2009

Jeanne Skanchy
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **MINOR AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA 90-548

Dear Ms. Skanchy,

Apotex Inc. is hereby filing a minor amendment to ANDA 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This amendment is being submitted in response to the chemistry, manufacturing and control (CMC) deficiency letter dated March 18, 2009.

In addition, this amendment is being submitted to notify the FDA of our proposal to utilize the atorvastatin calcium propylene glycol solvate drug substance manufactured by both the (b) (4) synthesis processes for the commercial manufacturing of the drug product. Applicable sections of the ANDA have been updated and are provided in this amendment. This differs from our initial proposal to utilize the drug substance manufacturing by (b) (4) synthesis process for commercial manufacturing of the drug product.

Addendum 1 will provide further discussion regarding the updates to our application noted above.

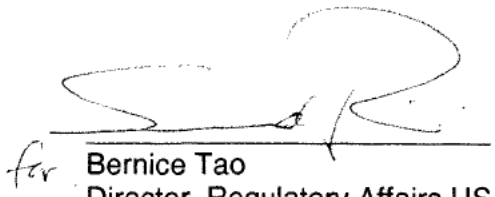
A table of contents of the sections of the eCTD that have been revised as a result of the deficiency responses and the drug substance synthesis processes is attached as Addendum 2.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. A signed application form (FDA 356h) is provided.

APOTEX
ADVANCING GENERICS

I trust that this satisfactorily addresses the concerns raised. If there are any further questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,



for Bernice Tao
Director, Regulatory Affairs US

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 23, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BCS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

June 23, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

June 23, 2009

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	June 23, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
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5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
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7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	6-23-09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 22, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

June 22, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao 355 — June 22, 2009

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

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Kiran Krishnan 355	Kiran Krishnan Associate Director, Regulatory Affairs	6-22-09

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VIA HAND DELIVERY

June 19, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

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Dear Director, Office of Generic Drugs:

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

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PATENT CERTIFICATION

Paragraph IV Certification
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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 18, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

June 18, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao 855

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

June 18, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6-18-09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6-18-09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 17, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6-17-2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6-17-09

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6-17-09
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

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IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

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Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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N/A

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☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
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☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
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☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
BES Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6-17-09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 16, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BST
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

June 16, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BST

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

June 16, 2009

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6-16-09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Atorvastatin Calcium Tablets	N/A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		**CODE NAME** *(If any)*
Atorvastatin Calcium		N/A
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	6-16-09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 15, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6-15-09

Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSE

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

June 15, 2009

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6-15-09
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

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APPLICATION DESCRIPTION

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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N/A

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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6-15-09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 12, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6-12-09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BCS

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6-12-09

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6-12-09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

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2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

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REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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N/A

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6-12-09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 11, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao DSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6-11-09
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6-11-09

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	June 11, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	6-11-09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 10, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao (COM)

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6/10/09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6/10/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/10/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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N/A

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☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/10/07
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 9, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6.9.09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao (BT)

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6.9.09

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6·9·09
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

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☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
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☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (VS)	Kiran Krishnan Associate Director, Regulatory Affairs	6.9.09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 8, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6.8.09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6.8.09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6·8·09
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

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Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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Kiran Krishnan (W)	Kiran Krishnan Associate Director, Regulatory Affairs	6.8.09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 5, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao CDR

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

June 5, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

June 5, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/5/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

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APPLICATION DESCRIPTION

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Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao CDD

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6/9/09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6/9/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/9/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
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☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
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☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
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☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/9/09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 8, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao CDR

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6/8/09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6/8/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/8/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Atorvastatin Calcium		N/A
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
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Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

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Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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CERTIFICATION

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/8/09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 4, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

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Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6/4/2009
Date

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Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

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Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6/4/2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
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See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION **NUMBER**

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/4/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

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Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
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7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/4/2009
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 3, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

June 3, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao (COR) 6/3/2009

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/3/2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Atorvastatin Calcium		N/A
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/3/2009

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

June 2, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao COD

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

6/2/09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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Bernice Tao (on)
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6/2/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/2/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

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Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/2/09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
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Document Control Room
Metro Park North II
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APOTEX INC.

6/1/2009
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

6/1/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	6/1/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	6/1/2009

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 29, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao (CDD)

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

5/29/09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

3/29/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	5/29/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
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Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	5/29/09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 28, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao (COD)
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

5/28/09
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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Bernice Tao (copy) 3/28/09

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
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See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

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Apotex Inc.	5/28/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
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☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
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☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
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7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (COO)	Kiran Krishnan Associate Director, Regulatory Affairs	5/28/09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 27, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

5/27/09
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao (COR) 3/27/09

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	5/27/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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N/A

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☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	3/27/09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 26, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

5/26/2009
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao (cop) 5/26/09

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	5/26/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

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I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	5/26/09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2400 N. Commerce Parkway, Suite 400 Weston, FL 33326	(954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 22, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao (encl.)

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

May 22, 2009
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and the owner/assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to the holder of NDA No. 20-702 and the owner/assignee of the '810 patent meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

5/22/09
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	5/22/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
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☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	5/22/09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 21, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

5/21/09
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

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Bernice Tao

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

May 21, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

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Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

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ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

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CERTIFICATION

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan	Kiran Krishnan Associate Director, Regulatory Affairs	5/21/09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 20, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao (COO)

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

5/20/2009
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

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Bernice Tao CDD — 5/20/07

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

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Apotex Inc.	5/20/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
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DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (COO)	Kiran Krishnan Associate Director, Regulatory Affairs	5/20/09
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

May 20, 2009

Ann Vu
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

Re: Labeling Amendment to Telephone Fax Deficiency
ANDA 90-548; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Ms. Vu:

In response to your Telephone Fax Labeling Deficiency dated March 12, 2009, please find enclosed an amendment to ANDA 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

This amendment is submitted in the eCTD format and transmitted via the Electronic Submission Gateway.

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986 or fax (866) 392-1774. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US

May 20, 2009
Date

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

May 19, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. 7,534,810 B2 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao (CDO)
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

May 19, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. 7,534,810 B2

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. 7,534,810 B2 ("the '810 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '810 patent, expiring on or about April 25, 2025, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to Pfizer Ireland Pharmaceuticals, the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"), and to Pfizer Inc., the purported U.S. agent for Pfizer Ireland Pharmaceuticals, according to the records of the FDA, and the purported assignee of the '810 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to Pfizer Ireland Pharmaceuticals and Pfizer Inc. meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao (COD) — May 19, 2009

Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	May 19, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent 7,534,810 B2

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
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I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan (CRD)	Kiran Krishnan Associate Director, Regulatory Affairs	May 19, 2009
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

Signed off in DFS on 4/27/09

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 90-548
Date of submission: 2/19/09 (electronic submission). OGD is requesting the pharmacology /toxicity consult on the inactive ingredient calcium acetate in the ANDA 90-548 (atorvastatin calcium drug product).

Review Number: 1

Drug Names: Atorvastatin Calcium, 10, 20, 40, 80 mg tablets.

Consult #: 20009-0305 for atorvastatin calcium tablets.

Consult from: Johnny, Young, and Theresa Liu. Request date: 2/24/09 (desired completion date is 4/25/09)

Generic drug name: Atorvastatin calcium tablets from Apotex Inc., Toronto, Canada. Apotex's reference listed drug (RLD) is Lipitor tablets from Pfizer. This is an abbreviated NDA (ANDA).

Drug class: Statins (generic atorvastatin). Lipid altering, hypolipidemic .

Indication: To lower cholesterol.

Type of document: Electronic submission form Apotex Inc., Toronto, Canada. In the current submission, sponsor (Apotex Inc.) is responding to FDA-OGD's deficiency dated 2/7/2005.

Subject of Consult: OGD is requesting a pharmacology/toxicology consult for the inactive ingredient calcium acetate, which is present at doses of (b) (4) in the Apotex's 80 mg dosage form atorvastatin calcium tablets. Since calcium acetate is an approved drug as PhosLo tablets by FDA, the Apotex Inc., Canada was asked to justify or qualify the amounts of calcium acetate in their drug product (in ANDA 90-548).

The sponsor in the current submission (2/19/09) has responded to OGD, and has provided additional information on the calcium acetate. The OGD has asked us to evaluate if the level of calcium acetate in the proposed Apotex tablets in the 80 mg dosage form is acceptable. The consult comments are stated below:

OGD is requesting an inactive ingredient consult for Calcium Acetate, which, for this drug product is being used in their 80 mg dosage form ((b) (4) (b) (4) dosage form)at a level that exceeds the IID max. Apotex originally posited that the proposed level is safe based upon the use of Calcium Acetate as an ACTIVE ingredient in Phoslo Tablets and Gelcapsules. In these NDAs Calcium Acetate appears at a (b) (4) level and is used to bind excessive Phosphate in patients who are undergoing renal dialysis. Apotex was informed by RSB that this rationale is not in-and-of-itself sufficient as justification for their level of use of this ingredient.

Subsequently, Apotex provided several documents which detail the level of Calcium Acetate in food products at higher levels. Additionally, an argument is presented therein the basis for which is the fact that Calcium Acetate will dissociate once it enters the acidic pH of the gut (resulting in both Calcium and acetate ions). RSB has resultantly determined that the ANDA is acceptable for filing based on the fact that both Calcium Acetate and Calcium Carbonate function as Phosphate binders. From published literature it seems clear that Calcium Acetate is the more effective binder of Phosphate. Because the RLD (Lipitor) has a (b) (4) level of Calcium Carbonate present in its formulation Apotex has been asked to provide literature that addresses the comparative effectiveness of Calcium Acetate versus Calcium Carbonate, since the RLD contains Calcium Carbonate at a level approximately (b) (4) as the level of Calcium Acetate used by Apotex. This information is currently in EDR linked as the the 20-FEB-09 entry (letter date: Feb.19, 2009). Please evaluate if the levels of Calcium Acetate proposed by Apotex for use in their drug product is acceptable, specifically for the 80 mg strength.

Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.

Division: Division of Metabolic and Endocrinology products.

Review completion date: 4/14/2009.

Introduction and drug history: Apotex Inc. has submitted an ANDA for atorvastatin calcium as a generic drug. Presently, the reference listed drug (RLD) is marketed in USA with a physician's prescription as Lipitor for oral administration, to reduce both normal and elevated LDL-cholesterol.

As stated earlier, in the current consult, OGD has requested a pharmacology/toxicology review of the amounts of calcium acetate in the Apotex's drug formulation. The highest amount of calcium acetate in the 80 mg tablet (a high dose tablet) is (b) (4), and OGD wants to know if it is safe. Originally calcium acetate was approved as a drug as phosLo tablets and later it was approved as PhosLo capsules, containing 667 mg of calcium acetate per tablet/capsule.

FDA-OGD has raised the concern that although calcium acetate is being used as an excipient in atorvastatin calcium tablets, it also has a pharmacologic effect of binding to dietary phosphate and may cause fecal excretion of dietary phosphate. Currently PhosLo tablets and gel-capsules (containing 667 mg of calcium acetate) are approved for phosphate binding, the drug is indicated for the control of hyper-phosphatemia in the end stage renal disease. The recommended initial dose of PhosLo for the adult dialysis patient is 2 tablets with each meal. The dosage may be increased gradually to bring serum phosphate values below 6 mg/dl, as long as hyper-calcemia does not develop. Most patients require 3-4 tablets with each meal. The therapeutic action of PhosLo is to bind phosphate within the lumen of the gastrointestinal tract to form insoluble calcium phosphate.

As stated earlier, PhosLo was initially approved in a tablet form and later as gelatin capsules (NDA 21-160).

The Apotex Inc. Canada in response has submitted following studies:

1. Justification of Calcium Acetate as an excipient in the Apotex Atorvastatin tablet formulation.
2. Our NDA 19-976 reviews on approved PhosLo (calcium acetate) tablets, including completed pharmacology/toxicology review signed by Dr. Alex Jordan.
3. Four references including effectiveness of calcium acetate as a phosphate binder in patients on peritoneal dialysis.

Apotex Inc., states that currently, calcium acetate in the approved PhosLo tablets contain 667 mg of calcium acetate per tablet. In the clinical study under the NDA 19-976 (PhosLo tablets), patients took 3 to 4 PhosLo tablets per meal (containing active ingredient calcium acetate), and needed to take the total 9 - 12 tablets/day to produce the clinical effect of reducing phosphate levels. This dose of 9-12 tablets represents approximately 6000-8000 mg of calcium acetate ingested/day. In contrast the Apotex's 80 mg atorvastatin tablets (a high dose), contains only (b) (4) of calcium acetate, and patient will therefore ingest maximum calcium acetate of (b) (4) (b) (4). This represents (b) (4) % of the daily dose of calcium acetate in the tablet (compared to PhosLo tablets) and therefore is unlikely that the calcium acetate contained in Apotex's Atorvastatin tablets would produce a pharmacological phosphate-binding effect.

Sponsor states that Lipitor (the RLD or approved atorvastatin tablets) contains calcium carbonate which also has a pharmacological effect on binding phosphate. However, the amount of calcium ions released from Apotex's 80 mg tablets was (b) (4), while from RLD (i.e marketed atorvastatin or Lipitor) was (b) (4) Thus, the amount of calcium ions in Apotex's Atorvastatin Tablets as calcium acetate is about (b) (4) of the amount of calcium ions in Lipitor tablets as calcium carbonate.

Published studies have compared the effectiveness of calcium acetate vs. calcium carbonate as a phosphate binder (Choy BY. et al. HKMJ Vol 4: No 1, March 1998, Moriniere, Ph. et al.

Nephron 1992; 60: 6-11, Hamida F et al. Nephron 1993; 63, 258-262.). In these studies, it has been concluded that the equivalent doses of calcium acetate bound twice as much phosphorus as calcium carbonate in haemo-dialysis patients. In another study, it was found that the dose of elemental calcium in the form of calcium acetate that was needed to achieve similar phosphate levels at 3 months was 66% of that in calcium carbonate (i.e. the mean dose of elemental calcium was 802 mg/day in the form of calcium acetate in the above study vs 1222 mg/day from calcium carbonate). The higher solubility of calcium acetate at an alkaline pH of the intestine means that more free calcium is available for absorption from calcium acetate than from calcium carbonate. Note that calcium ions dissociated from a single 80 mg tablet of Atorvastatin tablet containing calcium acetate is about (b) (4) of that of a single 80 mg Lipitor tablet containing calcium carbonate, therefore only (b) (4) of the elemental calcium in calcium acetate is needed to achieve the same phosphate binding of that in calcium carbonate.

OVERALL SUMMARY AND EVALUATION:

In humans, the phosphate binding activity of calcium acetate takes place within the lumen of the intestine. The superiority of calcium acetate as a phosphate binder is probably due to the greater solubility and hence greater availability of phosphate binding in the lumen of intestine, and thus the drug does not require absorption or metabolism, in order to be effective. Any calcium or acetate absorbed, is metabolized by well established pathways. Less calcium is absorbed after the ingestion of calcium acetate, than other calcium compounds, because of its high solubility in the intestinal contents and hence availability for binding with phosphate to form insoluble salts which are excreted in the stool.

Calcium carbonate has also been widely used as a phosphate binder (Slatopolsky E et al N. Eng. J med. 315: 157-61, 1986 and Fourinier A et al Kidney Int. 29: 114S, 1986). In vitro studies have shown that above pH 5.5, the phosphate binding by calcium acetate and calcium carbonate is 100%. The major important differences between calcium acetate and calcium carbonate are that calcium acetate has a greater solubility at neutral pH. Calcium acetate is highly active in binding phosphate at the pH levels found in the upper intestine.

Note, that orally administered calcium ion per se has no significant toxicity. LD_{50} of calcium acetate is 4.28 grams/kg in rats; the LD_{50} of calcium carbonate is >15 grams/kg in rats. Long term oral administration of calcium acetate in rats at 1.5 g/kg/day for 18 months in a carcinogenicity study caused slight decreases in body weight gains, no increased incidences of tumors were observed, and no other significant toxicity was noted. Thus, dose of 1500 mg/kg/day in the above rat study, will provide 100-fold safety margin in rats to humans for calcium acetate, based on body surface area in both rats and humans. This is based on (b) (4) amount of calcium acetate in the 80 mg Apotex tablet in humans.

Orally administered calcium does not generally lead to hyper-calcemia, as it is quite non-toxic. Calcium not bound to dietary phosphate is added to the pool of dietary calcium within the lumen of the gastrointestinal tract and together with acetate is available for absorption along the small bowel, for more details see NDA 19-976 pharmacology/toxicity review on PhosLo tablets.

Therefore, based on the justification provided by the sponsor, and pharmacology/toxicity review on PhosLo tablets (NDA 19-976/NDA 21-160), it is unlikely that the amount of calcium acetate in Apotex's atorvastatin tablets will have a pharmacological phosphate binding effect. Note that Lipitor tablets containing calcium carbonate could also have a phosphate binding effect.

Safety evaluation:
From the pharmacology/toxicity point of view, the sponsor has qualified the excipient calcium acetate in their atorvastatin calcium drug product.

Internal Recommendations:

Sponsor by providing justification, and available literature references have qualified the amounts of calcium acetate in atorvastatin calcium in ANDA 90-548. Based on the review of previous Pharmacology/toxicity data on PhosLo tablets (i.e. calcium acetate as API in NDA19-976 and NDA 21-160), this reviewer agrees that it is unlikely that the calcium acetate contained in Apotex Atorvastatin tablets would produce a pharmacological phosphate-binding effect.

Thus, from the pharmacology/toxicity point of view, the proposed levels of calcium acetate in ANDA 90-548 are qualified.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/aljuburi/Johnny young/Teresa Liu/Ripper, L
File name: ANDA 90548-OGD consult (atorvastatin consult)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Indra Antonipillai
4/28/2009 10:29:51 AM
PHARMACOLOGIST
The pharm/tox concludes that the proposed levels of calcium acetate are qualified in this ANDA application.
From the pharm/tox point of view, the proposed levels of calcium acetate in the current ANDA application are qualified.

Karen Davis-Bruno
4/28/2009 10:31:21 AM
PHARMACOLOGIST

APOTEX
ADVANCING GENERICS

March 20, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Re: ANDA No. 90-548
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
US Patent No.: RE40667

Please find attached the electronic copy of the Patent Amendment for RE40667 previously submitted in paper format and date stamped received on March 18, 2009 at FDA.

This copy of the amendment is submitted in the eCTD format via the Electronic Submission Gateway.

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986 or fax (866) 392-1774. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US.
Apotex Inc.

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. RE40667

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. RE40667 ("the '667 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '667 patent, expiring on or about December 28, 2010, with pediatric exclusivity expiring on or about June 28, 2011, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to Pfizer Ireland Pharmaceuticals, the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"); to Pfizer Inc., the purported U.S. agent for Pfizer Ireland Pharmaceuticals, according to the records of the FDA; and to Warner-Lambert Company, Warner-Lambert Company LLC, and/or Pfizer Inc., as the purported owner(s) of the '667 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to Pfizer Ireland Pharmaceuticals, Pfizer Inc., Warner-Lambert Company, and Warner-Lambert Company LLC meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

March 18, 2009
Date

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

March 20, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. RE40667 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao PSS
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

March 20, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. RE40667

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. RE40667 ("the '667 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '667 patent, expiring on or about December 28, 2010, with pediatric exclusivity expiring on or about June 28, 2011, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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This notice to Pfizer Ireland Pharmaceuticals, Pfizer Inc., Warner-Lambert Company, and Warner-Lambert Company LLC meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao 855
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

March 20, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	March 20, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor ® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent RE40667

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan DSS	Kiran Krishnan Associate Director, Regulatory Affairs	March 20, 2009
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

March 19, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. RE40667 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BSS

Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

March 19 2009
Date

Apotex Inc. 150 Signet Drive, Toronto, ON M9L 1T9
Tel: (416) 749-9300 Fax: (416) 401-3817
www.apotex.com

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. RE40667

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. RE40667 ("the '667 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '667 patent, expiring on or about December 28, 2010, with pediatric exclusivity expiring on or about June 28, 2011, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

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As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to Pfizer Ireland Pharmaceuticals, the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"); to Pfizer Inc., the purported U.S. agent for Pfizer Ireland Pharmaceuticals, according to the records of the FDA; and to Warner-Lambert Company, Warner-Lambert Company LLC, and/or Pfizer Inc., as the purported owner(s) of the '667 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to Pfizer Ireland Pharmaceuticals, Pfizer Inc., Warner-Lambert Company, and Warner-Lambert Company LLC meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

March 19, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	March 19, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent RE40667

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NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

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☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
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☐	16. Debarment certification (FD&C Act 306 (k)(1))
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☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

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1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
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3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	March 19, 2009
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

March 18, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao BCC
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

March 18, 2009
Date

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Paragraph IV Certification
U.S. Patent No. RE40667

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Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

March 18, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	March 18, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	10 mg, 20 mg, 40 mg and 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Prevention of Cardiovascular Disease
2. Treatment of Hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent RE40667

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan BSS	Kiran Krishnan Associate Director, Regulatory Affairs	March 18, 2009
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

COMPLETE RESPONSE -- MINOR

ANDA 90-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

TO: Apotex Corp.,
U.S. Agent for Apotex Inc.

TEL: 954-384-3986

FAX: 954-349-4233

ATTN: Kiran Krishnan

FDA CONTACT PHONE: (240) 276-8467

FROM: Jeanne Skanchy

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 1, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendments dated August 6, 2008 and February 11, 2009.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (**4** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-548 **APPLICANT:** Apotex Inc

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)





B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A consult has been sent out by the Office of Generic Drugs to evaluate the suitability of calcium acetate as an excipient at the level of (b) (4) mg per day in the drug product. You will be further updated regarding the outcome as applicable.

2. The labeling and bioequivalence portions of your application are pending. Deficiencies, if any, will be conveyed to you under separate covers.

3. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

4. Please provide updated stability data for the drug products.

5. Please be informed that if any changes in dissolution method and criteria are recommended by the Division of Bioequivalence, the revised specifications and certificates of analysis should be provided reflecting the recommendations; and stability data may need to be provided to justify the proposed expiry date based on any changes in dissolution parameters or criteria.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Iser
3/18/2009 01:19:23 PM
signed for V. Sayeed

APOTEX
ADVANCING GENERICS

VIA HAND DELIVERY

March 17, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: Patent Amendment for Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Dear Director, Office of Generic Drugs:

Apotex Inc. is hereby submitting in duplicate an amendment to its Abbreviated New Drug Application No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, to provide a paragraph IV certification for U.S. Patent No. RE40667 pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

Please do not hesitate to contact me if you have any questions at tel: (416) 401-7889 or fax: (416) 401-3817.

Sincerely,

Bernice Tao 855
Bernice Tao
Director, Regulatory Affairs US
APOTEX INC.

March 17, 2009
Date

PATENT CERTIFICATION

Paragraph IV Certification
U.S. Patent No. RE40667

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984 and December 8, 2003, a Patent Certification as to U.S. Patent No. RE40667 ("the '667 patent") is hereby provided for our Abbreviated New Drug Application ("ANDA") No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Apotex Inc. ("Apotex") hereby certifies that, in its opinion and to the best of its knowledge, the '667 patent, expiring on or about December 28, 2010, with pediatric exclusivity expiring on or about June 28, 2011, is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, for which Apotex's ANDA No. 90-548 has been submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the FFDCA, 21 C.F.R. § 314.94(a)(12)(i)(A)(4), and 21 C.F.R. § 314.95(a), Apotex is providing the notice required by Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c) to Pfizer Ireland Pharmaceuticals, the holder of approved New Drug Application ("NDA") No. 20-702 for Lipitor® (Atorvastatin Calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets, according to the records of the U.S. Food and Drug Administration ("FDA"); to Pfizer Inc., the purported U.S. agent for Pfizer Ireland Pharmaceuticals, according to the records of the FDA; and to Warner-Lambert Company, Warner-Lambert Company LLC, and/or Pfizer Inc., as the purported owner(s) of the '667 patent, according to the records of the U.S. Patent and Trademark Office. As required under Section 505(j)(2)(B)(ii)(II) of the FFDCA and 21 C.F.R. § 314.95(d), this notice is being sent at the same time that Apotex's amendment to its ANDA No. 90-548 is being submitted to FDA.

This notice to Pfizer Ireland Pharmaceuticals, Pfizer Inc., Warner-Lambert Company, and Warner-Lambert Company LLC meets the requirements of Section 505(j)(2)(B)(iv) of the FFDCA and 21 C.F.R. § 314.95(c).

Bernice Tao BSS
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.

March 17, 2009
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Apotex Inc.	March 17, 2009
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(416) 749-9300	(416) 401-3809
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Apotex Inc. 150 Signet Drive Toronto, Ontario M9L 1T9 CANADA	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326 USA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* ANDA 090-548

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Atorvastatin Calcium	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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(PROPOSED) INDICATION(S) FOR USE:

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Name of Drug Lipitor® Tablets Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Patent Amendment – Paragraph IV certification for US Patent RE40667

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NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

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☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
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4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kiran Krishnan 355	Kiran Krishnan Associate Director, Regulatory Affairs	March 17, 2009
ADDRESS *(Street, City, State, and ZIP Code)* 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326		Telephone Number (954) 384-3986

Telephone Fax

ANDA 90-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Apotex Corp.
U.S. Agent for Apotex Inc.

TEL: 954-384-3986

FAX: 954-349-4233

ATTN: Kiran Krishnan

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20mg, 40 mg and 80 mg.

Pages (including cover): _4__

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-548 Date of Submission: May 1 and August 6, 2008

Applicant's Name: Apotex Inc.

Established Name: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

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Labeling Deficiencies:

1. CONTAINER (10 mg, 20 mg = bottles of 30s, 90s, 1000s, and 5000s
   40 mg= bottles of 30s, 90s, 500s, 1000s, and 4000s
   80 mg= bottles of 30s, 90s, 500s, and 2500s):

   Please revise to read "Each tablet contains atorvastatin calcium equivalent to YY mg atorvastatin".

2. CARTON (10 x 10)
   a. Please see container comment.

   b. Please add "This unit-dose package is not-child-resistant. If dispensed for outpatient use, a child-resistant container should be used. [Note: the second sentence is optional]"

3. BLISTER (Blister card of 10s)

   a. Please see CONTAINER comment.

   b. We encourage you to differentiate the strengths by shading, boxing or other means.

4. INSERT

   a. GENERAL COMMENTS

      i. Please revise "-" to "to" when denoting a range (e.g. 40 to 80 years of age vs. 40-80 years of age).

      ii. Please do not cite the RLD "Lipitor" in your insert.

      iii. Please capitalize the "c" in "Cytochrome"

      iv. Revise "atorvastatin calcium tablet" to "atorvastatin calcium" throughout the text with the exception of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections.

   b. CLINICAL PHARMACOLOGY, Clinical Studies, Prevention of Cardiovascular Disease

      Add "Trials" to the title of the Table 3.

c. INDICATIONS AND USAGE

Table 7, footnote b, revise to read "...category if an LDL-C [an vs. and]".

d. PRECAUTIONS

Revise the subsection to read:

Pregnancy

Teratogenic Effects

Pregnancy Category X

5. PATIENT INFORMATION SHEET:

a. Please state the number of sheets you intend on providing in order for each patient to receive one.

b. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name is part of a question in the patient package insert.

6. SPL

Please submit your labeling in SPL format.

Submit label and labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA. In addition, please review the guidance for industry titled Providing Regulatory Submissions in Electronic Format-Content of Labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Grace
3/12/2009 06:43:42 PM
for Wm Peter Rickman

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2009-0305**	
TO *(Division/Office)* DMEP - HFD-510 Thru: Leah Ripper, ODEII - HFD 102			**FROM:** Johnny Young	
DATE: 2/24/2009	**IND NO.**	**ANDA NO.** 090548	**TYPE OF DOCUMENT** Original	**DATE OF DOCUMENT** 2/19/2009,
NAME OF DRUG Atorvastatin Calcium		**PRIORITY CONSIDERATION** 60 days	**CLASSIFICATION OF DRUG** Cholesterol Lowering agent	**DESIRED COMPLETION DATE** 4/25/2009

NAME OF FIRM Apotex Inc.

REASON FOR REQUEST

I. GENERAL

- Γ NEW PROTOCOL
- Γ PROGRESS REPORT
- Γ NEW CORRESPONDENCE
- Γ DRUG ADVERTISING
- Γ ADVERSE REACTION REPORT
- Γ MANUFACTURING CHANGE/ADDITION
- Γ MEETING PLANNED BY _____
- Γ PRE NDA MEETING
- Γ END OF PHASE II MEETING
- Γ RESUBMISSION
- Γ SAFETY/EFFICACY
- Γ PAPER NDA
- Γ CONTROL SUPPLEMENT
- Γ RESPONSE TO DEFICPENCY LETTER
- Γ FINAL PRINTED LABELING
- Γ LABELING REVISION
- Γ ORIGINAL NEW CORRESPONDENCE
- Γ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

- □ DISSOLUTION
- □ PROTOCOL-- BIOPHARMACEUTICS
- □ IN--VIVO WAIVER REQUEST
- □ DEFICIENCY LETTER RESPONSE
- □ BIOAVAILABILITY STUDIES
- □ PHASE IV STUDIES

IV.DRUG EXPERIENCE

- □ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- □ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- □ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- □ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- □ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- □ SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS:

OGD is requesting an inactive ingredient consult for Calcium Acetate, which, for this drug product is being used in their 80 mg dosage form (b) (4) (b) (4) /dosage form)at a level that exceeds the IID max. Apotex originally posited that the proposed level is safe based upon the use of Calcium A an ACTIVE ingredient in Phoslo Tablets and Gelcapsules. In these NDAs Calcium Acetate appears at a (b) (4) level and is used to bind excessive Phosphate in patients who are undergoing renal dialysis. Apotex was informed by RSB that this rationale is not in-and-of-itself sufficient as justification for their level of use of this ingredient.

Subsequently, Apotex provided several documents which detail the level of Calcium Acetate in food products at higher levels. Additionally, an argument is presented therein the basis for which is the fact that Calcium Acetate will dissociate once it enters the acidic pH of the gut (resulting in both Calcium and acetate ions). RSB has resultantly determined that the ANDA is acceptable for filing based on the fact that both Calcium Acetate and Calcium Carbonate function as Phosphate binders. From published literature it seems clear that Calcium Acetate is the more effective binder of Phosphate. Because the RLD (Lipitor) has a (b) (4) level of Calcium Carbonate present in its formulation Apotex has been asked to provide literature that addresses the comparative effectiveness of Calcium Acetate versus Calcium Carbonate, since the RLD contains Calcium Carbonate at a level approximately (b) (4) as the level of Calcium Acetate used by Apotex. This information is currently in EDR linked as the the 20-FEB-09 entry (letter date: Feb.19, 2009). Please evaluate if the levels of Calcium Acetate proposed by Apotex for use in their drug product is acceptable, specifically for the 80 mg strength.

Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Theresa Liu

2/24/2009 01:32:45 PM

APOTEX

February 19, 2009

Martin Shimer
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: New Correspondence
ANDA No. 90-548; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Shimer

Further to the acknowledgement letter dated November 3, 2008 for the above-mentioned ANDA and our subsequent discussion regarding the ingredient, calcium acetate, that is included in the Atorvastatin Calcium Tablets as an excipient, please find enclosed additional information to assist in the safety review of calcium acetate in Apotex's formulation.

This correspondence is submitted in the eCTD format and transmitted via the Electronic Submission Gateway.

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. An updated application form, FDA356h is provided in section 1.1.2.

Should you have any questions, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US

Feb 19, 2009
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • **www.apotex.com**

MEMBER CGPA

APOTEX

February 11, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Gratuitous CMC Amendment
ANDA No. 90-548; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Apotex Inc. is hereby submitting a Gratuitous CMC Amendment to ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The amendment is being submitted to present the revised specification limit for the identified degradation products (b) (4) (b) (4) and (b) (4)

A summary of the changes along with the list of supporting data that is provided is attached in Addendum 1.

This amendment is submitted in the eCTD format and transmitted via the Electronic Submission Gateway. A table of contents of those sections of the eCTD that are provided in this amendment is attached as Addendum 2.

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted. An updated application form, FDA356h is provided in section 1.1.2.

Please direct any communications regarding this to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., by telephone at (954) 384-3986 or fax (866) 392-1774. Alternatively, please do not hesitate to contact me by phone at (416) 401-7889, or by fax at (416) 401-3817.

Sincerely,

for Bernice Tao
Director, Regulatory Affairs US

Feb. 11, 2009
Date

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • **www.apotex.com**

MEMBER CGPA

APOTEX

January 16, 2009

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: PATENT AMENDMENT – NOTICE OF LITIGATION
ANDA No. 90-548
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
US Patent Nos.: 5273995 and 5273995*PED

Apotex Inc. is hereby submitting an amendment to ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This amendment is being filed as a notice of litigation for US Patent No.'s 5273995 and 5273995*PED, received prior to the expiry of the 45-day period commencing on the patent holder's receipt date of Apotex's notice of patent certification.

All pertinent information surrounding the notification of litigation is provided for in this amendment.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway.

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp, the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at (954) 349-4223. For any other concerns, please do not hesitate to contact me by phone at (416) 749-9026 or by fax at (416) 401-3817.

Sincerely,

for

Bernice Tao
Director, Regulatory Affairs US.
Apotex Inc.

APOTEX

December 24, 2008

Nam Chun
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Nam Chun,

Re: **BIOEQUIVALENCY AMENDMENT**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 90-548

Apotex Inc. is hereby submitting a Bioequivalency Amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, ANDA No. 90-548. This amendment is being filed in response to the FDA deficiency letter dated December 1, 2008.

A signed application form (FDA 356h) is provided.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp, the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at (954) 349-4223. Alternatively, please do not hesitate to contact me by phone at (416) 749-9026 or by fax at (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US

1. **Your dissolution testing data are acceptable for the 20 mg, 40 mg and 80 mg strengths. Your dissolution testing data for the 10 mg strength are incomplete. One tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. To confirm your data, please repeat the dissolution testing using the FDA-recommended method on the 10 mg strength test and reference products only. The DBE will set the specification for the test product after reviewing the additional dissolution data. The dissolution testing should be conducted in 900 mL of 0.05M Phosphate buffer at pH 6.8 using a Paddle (USP apparatus II) at 75 rpm.**

   Please include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested and resubmit the dissolution testing data summary table containing the newly obtained data.

Response:

We acknowledge your comments. In response to the agency request, dissolution testing of Apotex Atorvastatin Calcium 10 mg tablets, Lot FD051-323 and the 10 mg reference product, Lot 00927V was repeated using the dissolution method ATOR-IMTB-41-SG (USP apparatus #2, 900ml of 0.05M phosphate buffer, pH 6.8) on 12/02/08. The summary tables include the individual data as well as the mean, range and CV for the Apotex and reference products. For the Apotex product, the results are consistent and range from (b) (4)% to (b) (4)% and from (b) (4)% to (b) (4)% dissolved at 5 minutes and 10 minutes respectively (% RSD (b) (4) respectively). The summary and individual unit data for the10 mg strength for both the Apotex and reference products are provided in the dissolution report in section 5.3.1.3.

From: Shimer, Martin
Sent: Monday, November 03, 2008 10:42 AM
To: 'Bernice Tao'
Cc: Shimer, Martin
Subject: RE: Apotex ANDA 90-548 Atorvastatin Calcium Tablets Fedex Courier of Notice

Bernice,

It is permissible to use FedEx in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 90-548.

Regards,

Martin Shimer

From: Bernice Tao [mailto:btao@apotex.com]
Sent: Monday, November 03, 2008 10:39 AM
To: Shimer, Martin
Subject: Apotex ANDA 90-548 Atorvastatin Calcium Tablets Fedex Courier of Notice

Hi Martin
Further to the Acceptable for Filing letter for the Atorvastatin Calcium Tablets ANDA # 90-548 dated November 3, 2008, we would like to request authorisation to utilise Fedex courier in lieu of US Postal Service for the purpose of providing notice to the NDA holders and patent owners associated with the Paragraph IV certifications provided in the ANDA . Could you please confirm accepability?

Regards
Bernice Tao
Director, Regulatory Affairs US
Apotex Inc.
Tel: (416) 401-7889
Fax: (416) 401-3817
www.apotex.com

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Shimer

12/1/2008 08:58:59 AM

CSO

BIOEQUIVALENCE AMENDMENT

ANDA 90-548

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Apotex Inc. TEL: (954) 384-3986

ATTN: Kiran Krishnan FAX: (954) 349-4233

FROM: Nam Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 6, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCY

ANDA: 90-548

APPLICANT: Apotex Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets,
EQ. 10 mg, 20 mg, 40 mg and 80 mg Base

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and the waiver request will be conducted at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable for the 20 mg, 40 mg and 80 mg strengths. Your dissolution testing data for the 10 mg strength are incomplete. One tablet had unusually low dissolution at 5, 10 and 15 min which resulted in very high CV% at these sampling time points. To confirm your data, please repeat the dissolution testing using the FDA-recommended method on the 10 mg strength test and reference products only. The DBE will set the specification for the test product after reviewing the additional dissolution data. The dissolution testing should be conducted in 900 mL of 0.05M Phosphate buffer at pH 6.8 using a Paddle (USP apparatus II) at 75 rpm.

Please include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested. Also, please provide the date(s) of the dissolution testing and resubmit the dissolution testing data summary table containing the newly obtained data.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dale Conner

12/1/2008 05:07:17 PM

APOTEX

November 6, 2008

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Re: ANDA No. 90-548
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
US Patent Nos.: 5273995, 5273995*PED, 5686104, 5686104*PED, 5969156, 5969156*PED, 6126971 and 6126971*PED

In accordance with 21 CFR 314.95(b), Apotex Inc. hereby certifies that Notice of Non-infringement of US Patent numbers 5273995, 5273995*PED, 5686104, 5686104*PED, 5969156, 5969156*PED, 6126971 and 6126971*PED has been provided to each person identified under 314.95(a), and that the Notice met the content requirements under 314.95(c).

As required by 21 CFR 314.95(e), proof of receipt of the Notice is submitted herein.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway.

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc. at telephone (954) 384-3986 or fax: (954) 349-4233, or for any other concerns, please do not hesitate to contact me by telephone at (416) 401-7889 or by fax: (416) 401-3817.

Sincerely,

Bernice Tao
Director, Regulatory Affairs US.
Apotex Inc.

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 90-548 **FIRM NAME**: APOTEX INC.

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM

DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	☐
☐ **BST**	☒ **BDI**	

Random Queue: 12

Chem Team Leader: Iser, Robert Chem PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Beth Fabian-Fritsch

Letter Date: MAY 1, 2008 **Received Date**: MAY 2, 2008

Comments: EC - 4 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Johnny Young	**Recommendation:**
Date 7/9/08 ; 9/19/08; 10/31/08	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date: ____**

ADDITIONAL COMMENTS REGARDING THE ANDA:

The firm has submitted a response to the RTR letter dated 7/23/08. However, the firm's response lacks any data from studies performed to attest the safety of their proposed level of use for calcium acetate. Only literature has been submitted in order to establish justification. After consulting with the clinical team, RSB's decision is to issue the firm a second RTR. (See e-mail thread at the end of this checklist).

Bernice Tao 416.401.7889; (f) 416.401.3809

Neither API nor DP are USP
Has 3674 (b)

(b) (4)

This ANDA has been held up in the filing review due to concerns surrounding the use of Calcium Acetate at a level which exceeds that found in the IID. Apotex originally posited that the proposed level is safe based upon the use of Calcium Acetate used as an active ingredient in Phoslo Tablets and Capsules. In these NDAs Calcium Acetate appears at (b) (4) (b) (4) levels and is used to bind excessive Phosphate levels in patients that are undergoing renal dialysis. Apotex was informed that this rationale is not in and of itself permissible to justify the use of an active ingredient. Apotex provided several documents which relied upon the use of Calcium Acetate in food products at higher levels and they also relied upon a argument based upon the fact that Calcium and Acetate will dissociate once they enter the acidic pH of the gut (resulting in Calcium ions and acetate ions) . RSB has finally determined that this ANDA is acceptable for filing based On the fact that both Calcium Acetate and Calcium Carbonate function as Phosphate binders. From published literature Its seems clear that Calcium Acetate is the more effective binder of Phosphate. Because the RLD Lipitor has a (b) (4) (b) (4) level of Calcium Carbonate present in it's formulation Apotex has been asked to provide literature which addresses The comparative effectiveness of Calcium Acetate and Calcium Carbonate. Since the RLD contains Calcium Carbonate at a level that is approximately (b) (4) as the level of Calcium Acetate used by Apotex. Once submitted by Apotex this information will be sent on consult to the review division. –Martin Shimer 11/3/2008

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES x	☒
1.2	**Cover Letter** Dated: MAY 1, 2008 x	☒
*	**Table of Contents (paper submission only)** YES	☒

1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES x 2. List of Convictions statement (original signature) x	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES or Disclosure Statement (Form FDA 3455) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) '893, '995, '104, '156, '971 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 1/8/2017 a. Pediatric exclusivity submitted? yes b. Expiration of Pediatric Exclusivity?1/8/2017 4. Exclusivity Statement: YES x	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient x b. Type III DMF authorization letter(s) for container closure x 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) x	☒
1.12.11	**Basis for Submission** NDA# : 20-702 x Ref Listed Drug: LIPITOR x Firm: PFIZER x ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use x 2. Active ingredients x 3. Inactive ingredients x 4. Route of administration x 5. Dosage Form x 6. Strength x	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒

1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 10 MG, 20 MG, AND 40 MG	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) x **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained x **1.14.1.3** 1 package insert (content of labeling) submitted electronically x ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained x **1.14.3.3** 1 RLD label and 1 RLD container label x	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** x **Word Processed e.g., MS Word** x A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** x **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** x **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** x **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** x **Word Processed e.g., MS Word** x **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary x Table 4. Bioanalytical Method Validation x Table 6. Formulation Data x **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution x **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies x Table 3. Statistical Summary of the Comparative BA Data x **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study x **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies x	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) x 2. Function or Responsibility x 3. Type II DMF number for API 21574 (4/30/08) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) x **3.2.S.4.2 Analytical Procedures** x **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples x 2. Samples-Statement of Availability and Identification of: a. Drug Substance x b. Same lot number(s) x **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) x 2. Applicant certificate of analysis x **3.2.S.4.5 Justification of Specification** x	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems DMF**	☒
3.2.S.7	**Stability DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition x 2. Inactive ingredients and amounts are appropriate per IIG x	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES 3. Function or Responsibility x 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** x **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization n/a 4. Reprocessing Statement x **3.2.P.3.4 Controls of Critical Steps and Intermediates x** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation n/a 2. Filter validation (if aseptic fill) n/a	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified x **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) x 2. Suppliers' COA (specifications and test results) x **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA x	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** x **3.2.P.5.2 Analytical Procedures** x **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form x 2. Same lot numbers **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form x **3.2.P.5.5 Characterization of Impurities** x **3.2.P.5.6 Justification of Specifications** x	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data x 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing x 5. Source of supply and suppliers address x	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted x 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments x **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data x 2. Batch numbers on stability records the same as the test batch **x**	☒

Please note that the stability studies conducted bracket the proposed marketed package bottles of 90s for all strengths and 5000s for the 10 mg and 20 mg strengths. The respective container closure systems for the 90s pack size are the same as those used to package the 30s, 500s (for 80 mg), 1000s (for 10 mg, 20 mg and 40 mg) that were placed on stability. In addition, bottles containing greater than 1000 tablets to be marketed have the same respective container closure system as those used to package bottles of (b) (4) for the10 mg strength) and (b) (4) (for the 20 mg strength).

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation x Theoretical Yield Actual Yield Packaged Yield	☒

	10 mg	20 mg	40 mg	80 mg
TY	(b) (4)			
AY				
PY				

3.2.R.1.P.2 Information on Components x
3.2.R.2.P Comparability Protocols n/a
3.2.R.3.P Methods Validation Package YES
Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)
(Required for Non-USP drugs)

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) x b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) n/a **2. Lot Numbers of Products used in BE Study(ies):** 80 mg: FD051-317 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) x 2. Summary Bioequivalence tables: Table 10. Study Information x Table 12. Dropout Information x Table 13. Protocol Deviations x **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information x Table 16. Composition of Meal Used in Fed Bioequivalence Study x **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples x Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses x Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples x **5.3.7** **Case Report Forms and Individual Patient Listing** x	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 80 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)x 2. EDR Email: Data Files Submitted: YES SENT TO EDR x 3. In-Vitro Dissolution: YES has 12 unit	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 5/28/08

Component	Ref to Quality Standard	Function	%w/w of total tablet weight	10 mg tablet	20 mg tablet	40 mg tablet	80 mg tablet
				mg/tablet	mg/tablet	mg/tablet	mg/tablet
(b) (4)							
Atorvastatin Calcium Propylene Glycol Solvate	(b) (4)						
Calcium Acetate							
Croscarmellose Sodium							
Sodium Carbonate, (b) (4)							
Microcrystalline Cellulose (b) (4)							
Magnesium Stearate, Vegetable Source							
Colloidal Silicon Dioxide							
(b) (4)							
(b) (4)							
(b) (4)							
Hydroxypropyl Cellulose (b) (4)							

Component	Ref to Quality Standard	Function	%w/w of total tablet weight	10 mg tablet	20 mg tablet	40 mg tablet	80 mg tablet
				mg/tablet	mg/tablet	mg/tablet	mg/tablet
Polyethylene Glycol (b) (4)							(b) (4)
Titanium Dioxide (b) (4)							
Total Tablet Weight:							(b) (4)

(b) (4)

Do any excipients exceed the IIG limit for this route of administration?

As illustrated in the table below, all the excipients used in the formulation of Atorvastatin Calcium Tablets fall below the Inactive Ingredients Guide (IIG) or other applicable limits for this route of administration, except for Calcium Acetate*.

The level of calcium acetate in the IIG is lower than that used in Apotex's Atorvastatin Calcium Tablets. Calcium acetate is known to be used in calcium supplements. Based on a search of available drug products that contain calcium acetate, we refer to the drug Phoslo® (Calcium Acetate) Capsules manufactured by Fresenius Medical Care which is an oral gel capsule which contains 667 mg of calcium acetate per gel capsule. The recommended dosage for this drug is 3-4 capsules per meal. The maximum daily dose of Atorvastatin Calcium Tablets is 80 mg. As such, the amount of calcium acetate ingested from the maximum daily dose of Atorvastatin Calcium Tablets (b) (4) is less than the amount contained in 1 Phoslo® Capsule (667 mg).

In addition, calcium acetate is a naturally occurring calcium salt, found in fruits, and it is widely used in food as stabilizer with no limit on daily intake. Calcium acetate is a natural product. It is categorized by FDA as GRAS (Generally Recognized as Safe). Substances in this category are by definition, under Sec. 201(s) of the FD&C Act, not food additives. Please

The above explanation is not sufficient evidence for acceptance of the firm's proposed level of use for this excipient. Therefore, RTR.

INGREDIENT	ROUTE:DOSAGE FORM	CAS NUMBER	NDA COUNT	LAST NDA	APPROVAL DATE	DIV	MAXIMUM POTENCY/UNIT
CROSCARMELLOSE SODIUM	(b) (4)						(b) (4)
SODIUM CARBONATE							
CELLULOSE, MICROCRYSTALLINE							
MAGNESIUM STEARATE							
SILICON DIOXIDE, COLLOIDAL							
(b) (4)							
HYDROXYPROPYL CELLULOSE							
POLYETHYLENE GLYCOL (b) (4)	ORAL; TABLET	(b) (4)		N021892 3/16/2006	(b) (4)		(b) (4)
TITANIUM DIOXIDE							
CALCIUM ACETATE							(b) (4)

Atorvastatin Calcium Tablets 10 mg (FD051-323)		(b) (4)
Atorvastatin Core Tablets 20 mg (FD051-311)		
Atorvastatin Calcium Tablets 20 mg (FD051-326)		
Atorvastatin Core Tablets 40 mg (FD051-314)		
Atorvastatin Calcium Tablets 40 mg (FD051-329)		
Atorvastatin Calcium Tablets 80 mg (FD051-317)		

Packaging reconciliations

10 mg:

Batch No.: FD051-323

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		
(b) (4)							

Blisters:

	THEORETICAL PACKAGED				ACTUAL PACKAGED & YIELD		
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity
(b) (4)							

20 mg:

Batch No.: FP051-326

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		

(b) (4)

[redacted]

Blisters:

PACKAGING YIELD							
THEORETICAL PACKAGED					ACTUAL PACKAGED & YIELD		
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity

(b) (4)

[redacted]

40 mg:

Batch No.: F0051-024

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		

(b) (4)

[redacted]

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		

(b) (4)

[redacted]

Blisters:

PACKAGING YIELD							
THEORETICAL PACKAGED				ACTUAL PACKAGED & YIELD			
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity

(b) (4)

[redacted]

80 mg:

(b) (4)

Batch No.: ~~FD051-3AB~~ FD051-317

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		
(b) (4)							
			Number	No.			

(b) (4)

(b) (4)

Blisters:

PACKAGING YIELD							
THEORETICAL PACKAGED				ACTUAL PACKAGED & YIELD			
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity
(b) (4)							

Table 3a Statistical Summary of the Comparative Bioavailability Data for Atorvastatin

ATORVASTATIN CALCIUM TABLETS Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study [Study No. ATOR-IMTB-05EB03-2FE (AQ3681)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	146.498	146.562	100.0	95.7 – 104.4
AUCinf (ng*h/ml)	149.248	149.634	99.7	95.5 – 104.2
Cmax (ng/ml)	30.709	29.242	105.0	93.7 – 117.7
Fasted Bioequivalence Study [Study No. ATOR-IMTB-05EB05-2FA (AQ4221)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	166.770	158.556	105.2	101.0 – 109.5
AUCinf (ng*h/ml)	169.856	161.683	105.1	101.2 – 109.1
Cmax (ng/ml)	36.054	35.814	100.7	92.7 – 109.3

Table 3b Statistical Summary of the Comparative Bioavailability Data for 2-Hydroxy-Atorvastatin

ATORVASTATIN CALCIUM TABLETS Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study [Study No. ATOR-IMTB-05EB03-2FE (AQ3681)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	140.379	134.085	104.7	101.0 – 108.5
AUCinf (ng*h/ml)	146.134	141.854	103.0	99.0 – 107.2
Cmax (ng/ml)	18.956	17.100	110.9	101.4 – 121.2
Fasted Bioequivalence Study [Study No. ATOR-IMTB-05EB05-2FA (AQ4221)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	178.294	173.302	102.9	97.2 – 108.9
AUCinf (ng*h/ml)	183.703	179.579	102.3	97.2 – 107.7
Cmax (ng/ml)	29.105	28.500	102.1	92.9 – 112.2

Table 3c Statistical Summary of the Comparative Bioavailability Data for 4-Hydroxy-Atorvastatin

ATORVASTATIN CALCIUM TABLETS Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study [Study No. ATOR-IMTB-05EB03-2FE (AQ3681)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	16.577	15.759	105.2	100.6 – 110.0
AUCinf (ng*h/ml)	21.765	21.031	103.5	99.2 – 107.9
Cmax (ng/ml)	1.149	1.042	110.3	101.7 – 119.5
Fasted Bioequivalence Study [Study No. ATOR-IMTB-05EB05-2FA (AQ4221)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	17.954	16.664	107.7	100.3 – 115.7
AUCinf (ng*h/ml)	24.410	22.905	106.6	100.5 – 113.0
Cmax (ng/ml)	1.046	0.976	107.1	97.4 – 117.9

From: Chang, Nancy
Sent: Monday, September 15, 2008 3:04 PM
To: Hixon, Dena R; Shimer, Martin
Cc: Catterson, Debra M; Young, Johnny
Subject: RE: Pharm/Tox for Calcium Acetate

I agree with Dena. When sponsors point to the "safe" use of a proposed excipient when used as an active, they ignore the fact that there is by definition a pharmacological effect of the active, not to mention associated side effects, which may not necessarily be desirable in a different patient population. That being said, in this particular case, since the maximum proposed amount (b) (4) (b) (4) is lower than the recommended therapeutic dose, it is possible that this dose may be free of desired effects, even in sensitive populations. However, this determination would require review of what data are available regarding dose response for calcium acetate, and also the adequacy of existing pharm/tox data for the PhosLo NDA (assuming that we are allowed to use the data from that NDA, from a regulatory perspective?). I'm also guessing that there is not going to be much, if any, data available to tell us what happens at doses much lower than the recommended therapeutic dose.

From: Hixon, Dena R
Sent: Monday, September 15, 2008 2:50 PM
To: Shimer, Martin; Chang, Nancy
Cc: Catterson, Debra M; Young, Johnny; Hixon, Dena R
Subject: RE: Pharm/Tox for Calcium Acetate

Marty,
I think that we need to avoid the approach of believing that something is OK unless we have clinical data to suggest that it is not OK. That is the approach that FDA took in general prior to the sulfanilamide disaster way back in the 30s when FDA started requiring sponsors to demonstrate the safety of their products before bringing them to the market. I agree with your usual approach of not allowing the use of an entity as an active ingredient to justify the use of that same entity as an inactive ingredient in a generic product. Certainly the very presence of different ingredients in the RLD tells us that it is not necessary for the generic to use something that is so far outside of the IIG range. Why do some generic sponsors insist on being so far "out there"? It seems like a very far stretch to think that the use of this ingredient as a phosphate binder in dialysis patients would justify its use as an excipient in a drug for chronic use in relatively healthy patients with high lipid levels. I believe that if we are to adequately address the growing skepticism of generics we are going to have to push harder for generics to be more like the RLDs that they are referencing and not encourage them to keep trying to be innovative.

That is my two cents without discussing with Nancy.

Nancy,
I welcome your thoughts.

Dena

From: Shimer, Martin
Sent: Monday, September 15, 2008 1:40 PM
To: Chang, Nancy; Hixon, Dena R
Cc: Catterson, Debra M; Young, Johnny
Subject: Pharm/Tox for Calcium Acetate

Nancy and Dena,

RSB refused ANDA 90-548 on 7/23/2008 due to the applicant's proposed level of Calcium Acetate. The maximum level of Calcium Acetate that appears in the online IID is 10 mg for an orally administered drug product. Apotex's proposed formulation for Atorvastatin Calcium tablets uses anywhere between (b) (4) of Calcium Acetate for the 10 mg strength to (b) (4) in the 80 mg strength of Atorvastatin Calcium Tablets. Apotex responded to our RTR on August 6, 2008. On it's face the 8/6/2008 response does not meet our expectations as the firm has not provided any Pharm/Tox studies. The majority of their argument addresses the innocuous nature of the Ca and Acetate ions and any biological reactions to these ions. That said Apotex did include reference to FDA's review of NDA 19976 for Phoslo. A portion of the FDA review indicates that Calcium Acetate is GRAS when used as a sequestrant and that the amounts of Ca and Acetate which would be absorbed from the use of Phoslo could result in hypercalcemia but that in a clinical setting this was unlikely. Phoslo was approved for use as

a phophate binder in dialysis patients with the Tablet dosage form containing 667 mg of Calcium Acetate.

Now the questions....Since Apotex asserts and FDA's review from 19976 seem to indicate that Calcium Acetate is not toxic can we use the review from 19976 to justify the proposed level in this ANDA? In general we have not permitted this approach in the past. That is, we have not allowed the use of an entity that is an active ingredient to justify the use of that same entity as an inactive ingredient. Also would the presence of calcium acetate at levels of use to (b) (4) pose any problem in non-dialysis patients? Would the proposed level of Calcium Acetate potential bind enough phosphate in a healthy individual to represent a clinical problem when the exposure is chronic(Atorvastatin dosed daily for years)? I ask these questions as if we RTR Apotex a second time I'd like to be able to tell them that even though the review of 19976 indicates that Calcium Acetate is relatively non-toxic, OGD has concerns for clinical reasons.

The information provided by Apotex can be located in the EDR in the August 6, 2008 amendment under Module 1 Reference 6.

Thanks,

Marty

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Shimer

11/3/2008 08:44:58 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-548

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Kiran Krishnan
2400 N. Commerce Parkway
Suite 400
Weston, FL. 33326

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to Receive" letter dated July 23, 2008 and your amendment dated August 6, 2008.

NAME OF DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

DATE OF APPLICATION: May 1, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 7, 2008

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeanne Skanchy
Project Manager
240-276-8467

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Shimer
11/3/2008 08:44:33 AM
Signing for Wm Peter Rickman

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 6, 2008

Johnny Young
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Young,

Re: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA No. 90-548
Response to Refusal To File Letter Dated July 23, 2008

Apotex Inc. is hereby amending its ANDA No. 90-548 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg to address the refusal to file letter dated July 23, 2008 from the Office of Generic Drugs, Division of Labeling and Program Support.

A signed application form (FDA 356h) is provided.

This amendment is submitted in the eCTD format via the Electronic Submission Gateway. Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp, the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at (954) 349-4223. For any other concerns, please do not hesitate to contact me by phone at (416) 401-7889 or by fax at (416) 401-3809.

Sincerely,

for Cdn.

Bernice Tao
Director, Regulatory Affairs US

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
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1. *The concentration of the inactive ingredient calcium acetate in your proposed formulation cannot be justified by the Agency in an orally administrated drug product. Therefore the proposed product cannot be approved as an ANDA [21 CFR 314.127 (a) (8) (ii)]. Please provide justification to demonstrate safety, such as pharmacology/toxicology data or examples of approved drug products administered by the same route of administration, which contain this inactive ingredient at the same or a higher concentration. Your reference to another drug product in which is excipient is the active ingredient is insufficient justification for your proposed level of use. Hence, the agency is unable to substantiate the levels of calcium acetate indicated for all your strengths.*

   Response:

   We acknowledge your comment and have provided the justification with regards to the safety of calcium acetate in our proposed formulation.

Furthermore, please address the following:

2. *Resubmit the Letter of Authorization for DMF no.* (b) (4)*, the completed Certificate of Analysis (COA) for Colloidal Silicon Dioxide and page 2 of your completed COA for the* (b) (4) *bottles, for none of these files display any information when opened.*

   Response:

   As requested, we are resubmitting the Letter of Authorization for DMF no. (b) (4), the completed COA for Colloidal Silicon Dioxide and page 2 of the completed COA for the (b) (4) bottles.

3. Provide a commitment to submit final labeling in spl format.

   Response:

   As requested, we commit to submit final labeling in SPL format.

4. Pertaining to 3.2.P.3.2 ("Batch Formulation"): For each tablet strength, express the theoretical yields for both exhibit (ANDA) and commercial batches in terms of numbers of tablets. This is necessary in order to clearly assess the validity of your proposed scale-up, if any. Also, explicitly indicate these theoretical yields, in such terms, on your executed and commercial batch records and reconciliation statements.

   Response:

   We acknowledge your comment. Generally, it is our convention to express the theoretical yield in terms of "kg"; however we have revised our Batch Formulation in 3.2.P.3.2 and the

reconciliation table in section 3.2.R.1.P.1 to express the theoretical yields for both the exhibit (ANDA) and commercial batches in terms of numbers of tablets.

5. Provide a Reprocessing Statement referencing 21 CFR 211.115.

   Response:

   As requested, we have provided a Reprocessing Statement referencing 21 CFR 211.115 in section 3.2.P.3.3.

6. Your stability summary presently indicates that for bracketing purposes (b) (4) ct 10 mg tablets were sampled in (b) (4) packaging containers. However, your actual stability reports list this quantity as (b) (4) tablets. Please either correct or explain this discrepancy. In addition, your bracketing statement, appearing at the end of 3.2.P.8.1, omits the 40 mg dosage units packaged in 500 ct (b) (4) container systems. Please revise it to include this omission.

   Response:

   Please note there was a typographical error made on the stability summary table with respect to the 10 mg tablets that were placed on stability. The actual amount was (b) (4) tablets, consistent with the stability summary report. The amount of (b) (4) has been corrected to (b) (4) tablets. We have also revised the bracketing statement appearing at the end of 3.2.P.8.1 to include the 40 mg dosage units packaged in 500s.

   Please refer to the revised document in 3.2.P.8.1.

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 90-548 **FIRM NAME**: APOTEX INC.

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM

DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Random Queue: 12

Chem Team Leader: Iser, Robert Chem PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Beth Fabian-Fritsch

Letter Date: MAY 1, 2008 **Received Date**: MAY 2, 2008

Comments: EC - 4 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Johnny Young Date 7/9/08	**Recommendation:** ☐ **FILE** ☒ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Bernice Tao 416.401.7889; (f) 416.401.3809

Neither API nor DP are USP
Has 3674 (b)

Calcium Acetate exceeds the IID max (10 mg)

1. resubmit (b) (4) DMF (b) (4) (blank page)
2. commit to spl
3. express ANDA and Commercial batches in terms of no. of tablets (scale-up)
4. reprocessing statement has not been included
5. resubmit CSD completed COA (blank page)
6. missing p.2 of (b) (4) COA
7. stability summary states that 10 mg (b) (4) were tested instead of the actual (b) (4). Also, bracketing statement should include the 40 mg 500s

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES x	☒
1.2	**Cover Letter** Dated: MAY 1, 2008 x	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES x 2. List of Convictions statement (original signature) x	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES or Disclosure Statement (Form FDA 3455) NA	☒

1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) '893, '995, '104, '156, '971 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 1/8/2017 a. Pediatric exclusivity submitted? yes b. Expiration of Pediatric Exclusivity?1/8/2017 4. Exclusivity Statement: YES x	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient x b. Type III DMF authorization letter(s) for container closure no.1 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) x	☐
1.12.11	**Basis for Submission** NDA# : 20-702 x Ref Listed Drug: LIPITOR x Firm: PFIZER x ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use x 2. Active ingredients x 3. Inactive ingredients x 4. Route of administration x 5. Dosage Form x 6. Strength x	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 10 MG, 20 MG, AND 40 MG	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) x **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained x **1.14.1.3** 1 package insert (content of labeling) submitted electronically x ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒

1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained x **1.14.3.3** 1 RLD label and 1 RLD container label x	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** x **Word Processed e.g., MS Word** x A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** x **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** x **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** x **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** x **Word Processed e.g., MS Word** x **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary x Table 4. Bioanalytical Method Validation x Table 6. Formulation Data x **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution x **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies x Table 3. Statistical Summary of the Comparative BA Data x **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study x **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies x	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) x 2. Function or Responsibility x 3. Type II DMF number for API 21574 (4/30/08) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) x **3.2.S.4.2 Analytical Procedures** x **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples x 2. Samples-Statement of Availability and Identification of: a. Drug Substance x b. Same lot number(s) x **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) x 2. Applicant certificate of analysis x **3.2.S.4.5 Justification of Specification** x	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems DMF**	☒
3.2.S.7	**Stability DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition x 2. Inactive ingredients and amounts are appropriate per IIG no, calcium acetate level is excessive	☐
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES 3. Function or Responsibility x 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** no.3 **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization n/a 4. Reprocessing Statement no.4 **3.2.P.3.4 Controls of Critical Steps and Intermediates x** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation n/a 2. Filter validation (if aseptic fill) n/a	☐
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified x **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) x 2. Suppliers' COA (specifications and test results) x **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA x	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** x **3.2.P.5.2 Analytical Procedures** x **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form x 2. Same lot numbers **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form x **3.2.P.5.5 Characterization of Impurities** x **3.2.P.5.6 Justification of Specifications** x	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data x 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing x 5. Source of supply and suppliers address x	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted x 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments x **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data x 2. Batch numbers on stability records the same as the test batch **x**	☒

Please note that the stability studies conducted bracket the proposed marketed package bottles of 90s for all strengths and 5000s for the 10 mg and 20 mg strengths. The respective container closure systems for the 90s pack size are the same as those used to package the 30s, 500s (for 80 mg), 1000s (for 10 mg, 20 mg and 40 mg) that were placed on stability. In addition, bottles containing greater than 1000 tablets to be marketed have the same respective container closure system as those used to package bottles of (b) (4) (for the10 mg strength) and (b) (4) (for the 20 mg strength).

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation x Theoretical Yield Actual Yield Packaged Yield	☒

	10 mg	20 mg	40 mg	80 mg
TY	(b) (4)			
AY				
PY				

3.2.R.1.P.2 Information on Components x
3.2.R.2.P Comparability Protocols n/a
3.2.R.3.P Methods Validation Package YES
Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)
(Required for Non-USP drugs)

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) x b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) n/a **2. Lot Numbers of Products used in BE Study(ies):** 80 mg: FD051-317 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) x 2. Summary Bioequivalence tables: Table 10. Study Information x Table 12. Dropout Information x Table 13. Protocol Deviations x **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information x Table 16. Composition of Meal Used in Fed Bioequivalence Study x **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples x Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses x Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples x **5.3.7** **Case Report Forms and Individual Patient Listing** x	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 80 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)x 2. EDR Email: Data Files Submitted: YES SENT TO EDR x 3. In-Vitro Dissolution: YES has 12 unit	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 5/28/08

Component	Ref to Quality Standard	Function	%w/w of total tablet weight	10 mg tablet	20 mg tablet	40 mg tablet	80 mg tablet
				mg/tablet	mg/tablet	mg/tablet	mg/tablet
(b) (4)							
Atorvastatin Calcium Propylene Glycol Solvate							
Calcium Acetate							
Croscarmellose Sodium							
Sodium Carbonate, (b) (4)							
Microcrystalline Celullose (b) (4)							
Magnesium Stearate, Vegetable Source							
Colloidal Silicon Dioxide							
(b) (4)							
Hydroxypropyl Cellulose (b) (4)							

Component	Ref to Quality Standard	Function	%w/w of total tablet weight	10 mg tablet	20 mg tablet	40 mg tablet	80 mg tablet
				mg/tablet	mg/tablet	mg/tablet	mg/tablet
Polyethylene Glycol (b) (4)							(b) (4)
Titanium Dioxide (b) (4)							
Total Tablet Weight:							(b) (4)

(b) (4)

Do any excipients exceed the IIG limit for this route of administration?

As illustrated in the table below, all the excipients used in the formulation of Atorvastatin Calcium Tablets fall below the Inactive Ingredients Guide (IIG) or other applicable limits for this route of administration, except for Calcium Acetate*.

The level of calcium acetate in the IIG is lower than that used in Apotex's Atorvastatin Calcium Tablets. Calcium acetate is known to be used in calcium supplements. Based on a search of available drug products that contain calcium acetate, we refer to the drug Phoslo® (Calcium Acetate) Capsules manufactured by Fresenius Medical Care which is an oral gel capsule which contains 667 mg of calcium acetate per gel capsule. The recommended dosage for this drug is 3-4 capsules per meal. The maximum daily dose of Atorvastatin Calcium Tablets is 80 mg. As such, the amount of calcium acetate ingested from the maximum daily dose of Atorvastatin Calcium Tablets (b) (4) is less than the amount contained in 1 Phoslo® Capsule (667 mg).

In addition, calcium acetate is a naturally occurring calcium salt, found in fruits, and it is widely used in food as stabilizer with no limit on daily intake. Calcium acetate is a natural product. It is categorized by FDA as GRAS (Generally Recognized as Safe). Substances in this category are by definition, under Sec. 201(s) of the FD&C Act, not food additives. Please

The above explanation is not sufficient evidence for acceptance of the firm's proposed level of use for this excipient. Therefore, RTR.

INGREDIENT	ROUTE:DOSAGE FORM	CAS NUMBER	NDA COUNT	LAST NDA	APPROVAL DATE	DIV	MAXIMUM POTENCY/UNIT
CROSCARMELLOSE SODIUM SODIUM CARBONATE CELLULOSE, MICROCRYSTALLINE MAGNESIUM STEARATE SILICON DIOXIDE, COLLOIDAL (b) (4) HYDROXYPROPYL CELLULOSE POLYETHYLENE GLYCOL (b) (4) TITANIUM DIOXIDE	(b) (4)						(b) (4)
CALCIUM ACETATE	ORAL; TABLET	(b) (4)	N021892	3/16/2006	(b) (4)		(b) (4)

(b) (4)

Atorvastatin Calcium Tablets 10 mg (FD051-323)	
Atorvastatin Core Tablets 20 mg (FD051-311)	
Atorvastatin Calcium Tablets 20 mg (FD051-326)	
Atorvastatin Core Tablets 40 mg (FD051-314)	
Atorvastatin Calcium Tablets 40 mg (FD051-329)	
Atorvastatin Calcium Tablets 80 mg (FD051-317)	

Packaging reconciliations

10 mg:

Batch No.: ED051-323

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		
(b) (4)							

Blisters:

	THEORETICAL PACKAGED				ACTUAL PACKAGED & YIELD		
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity
(b) (4)							

20 mg:

Batch No.: FP051-326

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		
(b) (4)							

Blisters:

PACKAGING YIELD							
THEORETICAL PACKAGED					ACTUAL PACKAGED & YIELD		
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity
(b) (4)							

40 mg:

Batch No.: F1051-024

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		
							(b) (4)

(b) (4)

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		
							(b) (4)

Blisters:

PACKAGING YIELD							
THEORETICAL PACKAGED					ACTUAL PACKAGED & YIELD		
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity
							(b) (4)

80 mg:

(b) (4)

Batch No.: ~~FD051-378~~ FD051-317

Theoretical Packaged				Actual Packaged			
Wt. (kg) issued	Average. Wt. (mg)	Quantity to be Packaged	Less Reject: Weight (kg) and/or Number	Number of Packaged Product Produced		Average Package Fill	Actual Quantity Packaged (Including Part Bottle)
				Batch No.	Quantity		

(b) (4)

(b) (4)

(b) (4)

Blisters:

PACKAGING YIELD						
THEORETICAL PACKAGED				ACTUAL PACKAGED & YIELD		
	TOTE #	Wt (kg)	Avg Wt (mg)	Quantity	Avg. Fill	Number of Units	Quantity

(b) (4)

Table 3a Statistical Summary of the Comparative Bioavailability Data for Atorvastatin

ATORVASTATIN CALCIUM TABLETS Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study [Study No. ATOR-IMTB-05EB03-2FE (AQ3681)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	146.498	146.562	100.0	95.7 – 104.4
AUCinf (ng*h/ml)	149.248	149.634	99.7	95.5 – 104.2
Cmax (ng/ml)	30.709	29.242	105.0	93.7 – 117.7
Fasted Bioequivalence Study [Study No. ATOR-IMTB-05EB05-2FA (AQ4221)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	166.770	158.556	105.2	101.0 – 109.5
AUCinf (ng*h/ml)	169.856	161.683	105.1	101.2 – 109.1
Cmax (ng/ml)	36.054	35.814	100.7	92.7 – 109.3

Table 3b Statistical Summary of the Comparative Bioavailability Data for 2-Hydroxy-Atorvastatin

ATORVASTATIN CALCIUM TABLETS Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study [Study No. ATOR-IMTB-05EB03-2FE (AQ3681)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	140.379	134.085	104.7	101.0 – 108.5
AUCinf (ng*h/ml)	146.134	141.854	103.0	99.0 – 107.2
Cmax (ng/ml)	18.956	17.100	110.9	101.4 – 121.2
Fasted Bioequivalence Study [Study No. ATOR-IMTB-05EB05-2FA (AQ4221)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	178.294	173.302	102.9	97.2 – 108.9
AUCinf (ng*h/ml)	183.703	179.579	102.3	97.2 – 107.7
Cmax (ng/ml)	29.105	28.500	102.1	92.9 – 112.2

Table 3c Statistical Summary of the Comparative Bioavailability Data for 4-Hydroxy-Atorvastatin

ATORVASTATIN CALCIUM TABLETS Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study [Study No. ATOR-IMTB-05EB03-2FE (AQ3681)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	16.577	15.759	105.2	100.6 – 110.0
AUCinf (ng*h/ml)	21.765	21.031	103.5	99.2 – 107.9
Cmax (ng/ml)	1.149	1.042	110.3	101.7 – 119.5
Fasted Bioequivalence Study [Study No. ATOR-IMTB-05EB05-2FA (AQ4221)]				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUCt (ng*h/ml)	17.954	16.664	107.7	100.3 – 115.7
AUCinf (ng*h/ml)	24.410	22.905	106.6	100.5 – 113.0
Cmax (ng/ml)	1.046	0.976	107.1	97.4 – 117.9

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/s/

Martin Shimer

7/23/2008 02:43:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-548

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Kiran Krishnan
2400 N. Commerce Parkway
Suite 400
Weston, FL 33326

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated May 1, 2008, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The concentration of the inactive ingredient calcium acetate in your proposed formulation cannot be justified by the Agency in an orally administered drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127(a)(8)(ii)]. Please provide justification to demonstrate safety, such as pharmacology/toxicology data or examples of approved drug products administered by the same route of administration, which contain this inactive ingredient at the same or a higher concentration. Your reference to another drug product in which this excipient is the **active** ingredient is insufficient justification for your proposed level of use. Hence, the agency is unable to substantiate the levels of calcium acetate indicated for all your strengths.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Furthermore, please address the following:

Resubmit the Letter of Authorization for DMF no. (b) (4), the completed Certificate of Analysis (COA) for Colloidal Silicon Dioxide and page 2 of your completed COA for the (b) (4) bottles, for none of these files display any information when opened.

Provide a commitment to submit final labeling in spl format.

Pertaining to 3.2.P.3.2 ("Batch Formulation"): For each tablet strength, express the theoretical yields for both exhibit (ANDA) and commercial batches in terms of numbers of tablets. This is necessary in order to clearly assess the validity of your proposed scale-up, if any. Also, explicitly indicate these theoretical yields, in such terms, on your executed and commercial batch records and reconciliation statements.

Provide a Reprocessing Statement referencing 21 CFR 211.115.

Your stability summary presently indicates that for bracketing purposes (b) (4)ct 10 mg tablets were sampled in (b) (4) packaging containers. However, your actual stability reports list this quantity as (b) (4) tablets. Please either correct or explain this discrepancy. In addition, your bracketing statement, appearing at the end of 3.2.P.8.1, omits the 40 mg dosage units packaged in 500 ct (b) (4) container systems. Please revise it to include this omission.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Johnny Young
Project Manager
(240) 276-8424

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Martin Shimer
7/23/2008 02:43:29 PM
Signing for Wm Peter Rickman

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

To Whom It May Concern,

Re: Abbreviated New Drug Application
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg
Pre-Assigned ANDA Original Application No. 090-548

Apotex Inc. is hereby submitting an Abbreviated New Drug Application seeking approval to market Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg on the basis of demonstrating comparable bioavailability to the Reference Listed Drug Lipitor ® Tablets manufactured by Pfizer Inc. pursuant to NDA No. 020702.

Comparative, randomized, 2-way crossover bioavailability studies of Apotex Inc's Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg and Pfizer's Lipitor ® Tablets under fasting and fed conditions are included in this application.

The ANDA is submitted in the eCTD format and transmitted via FDA electronic submission gateway. Please note the following:

- In Module 2, the Quality Overall Summary (QOS) is provided in accordance with the Question-based Review (QbR) format. The QOS is provided in both pdf and MS-Word format.

- In Module 2, the Clinical Summary section includes the tables for the bioavailability study (Tables 1 through 8). The remaining tables for the bioavailability study (Tables 9 through 16) are located in Module 5. Table 1 (FDA Form 356h) is included in Module 1.

- In Module 3, Section 3.2.R.2.P, a [redacted] (b) (4) has been submitted.

- In Module 5, comparative dissolution testing between the test and reference products has been provided. The OGD's recommended dissolution method was used for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg. The conditions utilized are: USP Apparatus 2; 75 rpm; 900 mL; 0.05 M Phosphate Buffer, pH 6.8; with sampling times every 5 minutes for 60 minutes. The proposed specification is NLT [redacted] (b) (4)% (Q) in [redacted] (b) (4) minutes for atorvastatin.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

Please note that a Letter of Non-Repudiation Agreement dated December 17, 2007 has been submitted.

Furthermore, Apotex Inc. commits to resolve any issues identified in the methods validation process after approval.

A signed Form 356h is provided.

Please direct any communications regarding this application to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone (954) 384-3986 or fax (954) 349-4233, or alternatively, please do not hesitate to contact myself at telephone (416) 401-7889 or fax (416) 401-3809.

Sincerely,

for Bernice Tao
Director, Regulatory Affairs US

May 1, 2008
Date