CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 078773

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

Sponsor: TEVA Pharmaceuticals USA

Approval Date: May 29, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078773

TEVA Pharmaceuticals USA
Attention: Jean W. Zwicker
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 29, 2006, 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 the tentative approval issued by this office on December 1, 2011, and to your amendments dated April 10, and May 7, 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), respectively, 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 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 notified the agency that TEVA Pharmaceuticals Inc. (TEVA) 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 TEVA 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 078773

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078773

TEVA Pharmaceuticals USA
Attention: Philip Erickson
Senior Director, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 29, 2006, 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 May 15, and September 14, 2007; March 12, 2008; February 15, August 18, August 24, October 28, and November 24, 2010; and February 18, February 23, March 1, April 22, May 5, June 20, August 4 (2 submissions), September 28, September 29, October 10, October 18, October 21, November 17, and November 23, 2011.

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 practices (cGMPs) 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 unexpired 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") 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 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, under this ANDA. You have notified the agency that TEVA Pharmaceuticals Inc. (TEVA) 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 TEVA.

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.

[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).

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. 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 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 Leigh Ann Sears, Project Manager, at (240) 276-8453.

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

12/01/2011

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

LABELING

ATORVASTATIN CALCIUM TABLETS

7310
7311
7312
7313

℞ only

Rev. D 2/2012
322K405760312

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 use

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, 8.5).

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme 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 80 mg group vs. placebo (5.5).

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

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin calcium 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 TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872, X6351 or drug.safety@tevapharm.com; 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 calcium (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 coadministered with atorvastatin calcium (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 and FDA-Approved Patient Labeling

Revised: 02/2012

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PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS

*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). 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 calcium tablets; 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 calcium tablets should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets 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 calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed. In patients with HIV taking nelfinavir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed [*see Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White to off-white, capsule-shaped, film-coated tablets containing atorvastatin calcium equivalent to 10, 20, 40, and 80 mg atorvastatin.

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 calcium tablets 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 calcium tablet 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 CALCIUM TABLETS 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 calcium tablets 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 calcium tablet 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 calcium 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 calcium 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 calcium 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[a], 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

[a] Use with caution and with the lowest dose necessary (12.3)

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

Atorvastatin calcium 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 calcium 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 calcium.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin calcium 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 calcium, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium.

Atorvastatin calcium 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 calcium [*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 calcium.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin calcium 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, 0-24 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 (0-24) 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 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 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)*]

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[a]	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	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

[a] 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 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 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 10 mg daily (n = 5006) or atorvastatin 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 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 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 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 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 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 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 10 to 20 mg daily was generally similar to that of placebo [*see Clinical Studies (14.6) and Use in Specific 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 calcium is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin calcium 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 calcium 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 calcium with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin calcium 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 calcium should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium 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 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 calcium alone [*see Clinical Pharmacology (12.3)*]. The coadministration of atorvastatin calcium 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 coadministered with gemfibrozil, concomitant administration of atorvastatin calcium 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 calcium 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 calcium is used in combination with niacin; a reduction in atorvastatin calcium 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 calcium 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 coadministration of atorvastatin calcium with rifampin is recommended, as delayed administration of atorvastatin calcium after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

When multiple doses of atorvastatin calcium and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.9 Oral Contraceptives

Coadministration of atorvastatin calcium 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 calcium.

7.10 Warfarin

Atorvastatin calcium 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 coadministered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

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 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 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 calcium 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**. 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 calcium therapy [*see Contraindications, Pregnancy (4.3) and Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium 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.

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)*].

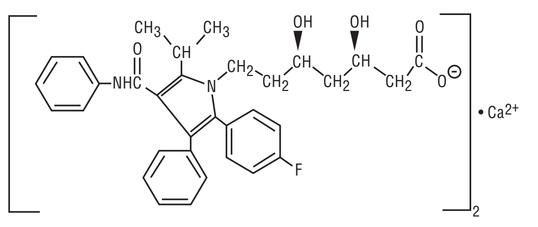
10 OVERDOSAGE

There is no specific treatment for atorvastatin calcium 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 calcium 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.

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). Its structural formula is:



$(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very 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: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium carbonate, magnesium stearate, polydextrose, polyethylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium 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 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 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 calcium, 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 calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium 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 calcium is given with or without food. Plasma atorvastatin calcium 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 calcium is approximately 381 liters. Atorvastatin calcium 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 calcium 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 calcium 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 calcium. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin calcium metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin calcium in humans following coadministration with erythromycin, a known inhibitor of this isozyme [*see Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin calcium 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 calcium 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 calcium is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium 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 calcium 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 calcium between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin calcium; 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 calcium since the drug is extensively bound to plasma proteins.

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

Table 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin

Coadministered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[a]	Change in C_{max}[a]
[b]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[b]Tipranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
[b]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
[b,f]Saquinavir 400 mg BID/ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[b]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[b]Darunavir 300 mg BID/ ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[b]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[b]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[b]Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
[b]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
[b]Grapefruit Juice, 240 mL QD[c]	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%[d]
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%
[b]Rifampin 600 mg QD, 7 days (coadministered)[e]	40 mg SD	↑ 30%	↑ 2.7 fold
[b]Rifampin 600 mg QD, 5 days (doses separated)[e]	40 mg SD	↓ 80%	↓ 40%
[b]Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less than 1%
[b]Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%

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

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

[c] 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).

[d] Single sample taken 8 to 16 h post dose.

[e] Due to the dual interaction mechanism of rifampin, simultaneous coadministration 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.

[f] 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 Coadministered Drugs

Atorvastatin	Coadministered 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	[a]Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20%
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1 mg - ethinyl estradiol 35 mcg	 ↑ 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

[a] 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 represents a plasma AUC (0-24) 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 (0-24) 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.

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 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 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 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.

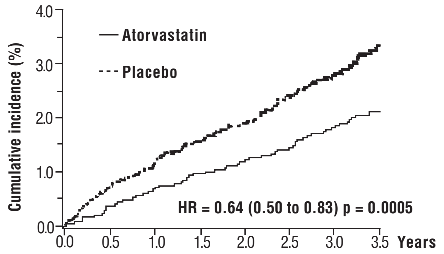


Figure 1: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)

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), 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 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 HbA_{1c} 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 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).

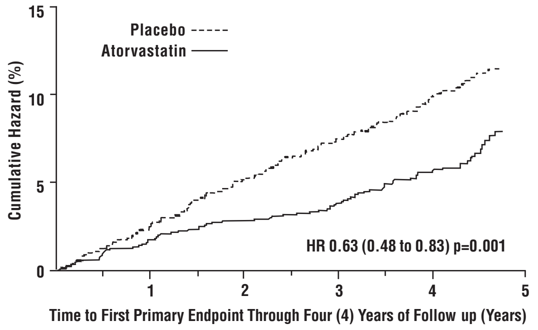


Figure 2: Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Event (Myocardial Infarction, Acute CHD Death, Unstable Angina, Coronary Revascularization, or Stroke) in CARDS

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 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 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin 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 and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 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.

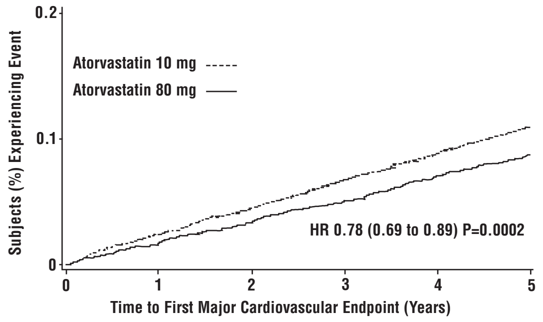


Figure 3: Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

Table 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N = 5006)		Atorvastatin 80 mg (N = 4995)		HR[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)
SECONDARY ENDPOINTS[c]					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
SECONDARY ENDPOINTS[c] (continued)					
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)
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

[c] 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

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 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 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 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 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 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 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 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 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 80 mg group and the simvastatin 20 to 40 mg group.

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.**)

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 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 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 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
95% CI for Diff[b]		-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[c]	-35[c]	-27[c]	-17[c]	+6	-36[c]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[b]		-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[d]	-37[d]	-34[d]	-23[d]	+7	-39[d]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[b]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[a] Significantly different from lovastatin, ANCOVA, p ≤ 0.05

[b] A negative value for the 95% CI for the difference between treatments favors atorvastatin calcium for all except HDL-C, for which a positive value favors atorvastatin calcium. If the range does not include 0, this indicates a statistically significant difference.

[c] Significantly different from pravastatin, ANCOVA, p ≤ 0.05

[d] Significantly different from simvastatin, ANCOVA, p ≤ 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).

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)

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 (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		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)
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. 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 hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to 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 (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-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).

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	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 calcium therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

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

Atorvastatin calcium is supplied as follows:

10 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with “93” on one side and “7310” on the other side of the tablet in bottles of 30.

20 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with “93” on one side and “7311” on the other side of the tablet in bottles of 30.

40 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with “93” on one side and “7312” on the other side of the tablet in bottles of 30.

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with “93” on one side and “7313” on the other side of the tablet in bottles of 30.

Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

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.

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 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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Jerusalem, 91010, Israel

Manufactured For:
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Sellersville, PA 18960

Rev. D 2/2012

PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking them 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 are a prescription medicine that lowers cholesterol in your blood. They lower the LDL-C (“bad” cholesterol) and triglycerides in your blood. They 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 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 can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of their ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

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 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 many 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 nonprescription 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.
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- 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, 20° to 25°C (68° to 77°F).
- 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 they were not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. They may harm them.

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What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium carbonate, magnesium stearate, polydextrose, polyethylene glycol, and titanium dioxide.

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Active Ingredient: atorvastatin calcium

Inactive Ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium carbonate, magnesium stearate, polydextrose, polyethylene glycol, and titanium dioxide.

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Iss. 2/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

LABELING REVIEWS

****APPROVAL SUMMARY#4****
(Supercedes AP SUM #3 dated 5/10/11)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 078773

Dates of Submission: May 7, 2012 and April 10, 2012

Applicant's Name: TEVA Pharmaceuticals USA

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

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REMS required?

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, 40 mg and, 80 mg: bottles of 30s):
Final print acceptable in 5/7/2012 e-submission

Professional Package Insert Labeling: Final print labeling acceptable in 4/10/2012 e-submission

Patient Information Sheet: Final print labeling acceptable in 4/10/2012 e-submission

SPL: DLDE acceptable in 4/10/2012 e-submission

Revisions needed before full approval: No

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 02/28/2012.

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

Email from Haitao on 12/6/10:

Ann,

Based on my review note, 80 mg is only supplied in 30 ct (b) (4) and (b) (4) container. If they have (b) (4), they had better submit to me and I will have to look at the stability data in that container.

The firm called their API (b) (4). It's a mixture of (b) (4) form. Teva's API indeed does not have hydrate form. From chemistry point view, if it is pure and stable, it is fine. I am not sure about legal's aspect.

I hope I have answered your questions. I cc this email to Laxma in case he wants to chime in. We all have to agree, this is a rather complicated ANDA.

Haitao

On 12/6/10: I sent an email to Phil Erickson at TEVA to request the stability data for the 80 mg (b) (4) size:

Good afternoon,

In the labeling amendment submitted 10/28/10, you submitted container label for the 80 mg, (b) (4) size. This packaging size is also noted in the HOW SUPPLIED section. Please submit the stability data and all pertinent chemistry data for this packaging size to chemistry.

Thanks
Ann

Ann,

(b) (4) Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)
Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

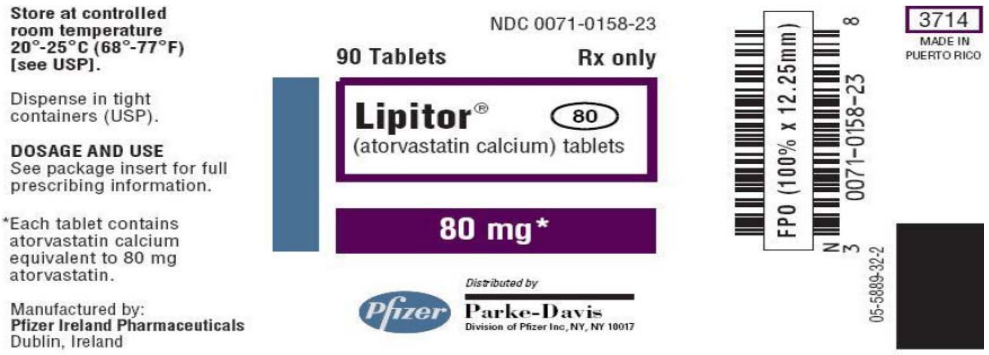
Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks
Ann

FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 8/16/11 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:

   Supplement 056 was approved June 17, 2009, and provided for labeling in PLR format.



   In the amendment dated 5/7/2012, TEVA revised the "Each tablet contains…" statement to read "Each film-coated tablet contains…"

   In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 mg.

   In AF dated 3/1/11: TEVA removed the (b) (4) for the 80 mg strength.

   In AF dated 5/5/11: TEVA revised labeling to reflect the removal of the (b) (4) configurations of the 10 mg, 20 mg and 40 mg strengths, which were withdrawn in the chemistry t-amendment dated 4/22/2011.

In AF 8/4/2011: TEVA revised labeling to reflect the Teva's package insert has been updated to reflect removal of the [redacted] configurations for the 10 mg, 20 mg and 40 mg strengths, and the [redacted] configurations for the 80 mg strength. These package configurations were withdrawn via a minor amendment submitted by Teva on August 4, 2011. As a result, the "How Supplied" section of Teva's insert now reflects only a 30-count configuration for each strength.

In AM 8/4/2011: Teva withdrawn the other count configurations.
A 30-day in-use study was conducted for all strengths of Teva's drug product packaged in the proposed 30-count configurations and reports were provided in Teva's minor amendment dated August 18, 2010. However, due to a change of response factor for [redacted] as discussed in Teva's telephone amendment dated April 22, 2011, results reported for [redacted] have since been recalculated using the RRf value of [redacted] Revised reports containing the recalculated results are provided in **Attachment 8**, and support the stability of the drug product under conditions which simulate anticipated consumer use for this configuration. In addition, the stability protocol which details how the in-use study was conducted is provided in **Attachment 9**. It is important to note that bottle seals were broken on Day 1 of the study and thus bottles remained unsealed for the duration of the 30-day study. Additionally, the study was conducted in our 30 count bottles as they are intended to be provided directly to consumers as unit of use container.
In the interest of expeditiously answering the current review letter and to enable the Agency to complete their review of the CMC portion of this application, we hereby request approval for only the 30-count configuration for each strength. While the [redacted] configurations for the 10 mg, 20 mg and 40 mg strengths, and the [redacted] configurations for the 80 mg strength, meet specifications through the [redacted]-month CRT stability study, we hereby withdraw them from this application. Teva will commercially launch this product in only the 30-count unit of use configurations. [redacted]
Please refer to the revised package component summary in **Attachment 10** that reflects only the 30-count configurations. Revised labeling which reflects the removal of said configurations will be submitted to the Labeling Support Branch under separate cover

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL: NDA 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	PIV	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	PIV	Same As
	Jul 8, 2016 ped			PIV	Same As

5969156	Jan 8, 2017				
6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	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

There is no unexpired exclusivity for this product in the Orange Book (checked 4/27/2012)

In the Patent Amendment dated 1/26/12- Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

See email below from Mary Ann regarding the Patent Listing:

From: Holovac, Mary Ann
Sent: Friday, April 27, 2012 1:57 PM
To: Turner, Betty
Subject: RE: Patent Listing

Hi Betty, If the patent is not listed in the OB then it was not submitted. I checked darrts and don't see anything recent. Pfizer's attorney always sends me a heads up. Any cert by Teva to this patent is invalid. Mary Ann

---

From: Turner, Betty
Sent: Friday, April 27, 2012 11:34 AM
To: Holovac, Mary Ann
Subject: Patent Listing

Hi Mary Ann,

Can you verify whether Pfizer listed Patent No. 8,084,488 for Lipitor Tablets NDA 020702? Its not listed in the OB and Teva submitted a patent amendment to provide certification with regards to this patent.

Thanks,

Betty

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period. TEVA filed 24 separate patent amendments addressing the same patent 7,790,197 which is NOT listed in the OB yet. TEVA wishes to provide certification with regard to this patent. The '197 patent was issued on 9/7/10. Thus, TEVA anticipates that Pfizer of Warner-Lambert would take steps to list the patent within 30 days of issue so as not to be considered late listed.

According to M. Holovac's email dated 12/6/10: Pfizer did NOT list the '197 patent yet.

Note that Ranbaxy has a "Settlement" with Pfizer to sell generic atorvastatin effective from November 30, 2011. Read the FTR for ANDA 76477 for more information about the "Settlement". In effect, Ranbaxy was the first to file a patent cert IV and will have 6 months generic exclusivity when Ranbaxy launches the generic atorvastatin on November 30, 2011.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	

Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration

80 mg Count Container: 30 Bottle: (b) (4) bottle (b) (4) (HDPE) (b) (4) (b) (4) of desiccant and (b) (4)

In 8/18/10 AM: TEVA submitted (b) (4) information

However, TEVA will not market the (b) (4) at the time of approval.

8/4/2011 AF: Note that TEVA will ONLY MARKET the 30s count size on all strengths to clear up "sticky" issues with chemistry to expediate the approval of this ANDA. If necessary, TEVA wil (b) (4) (b) (4)

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg. 208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Only DS is compendial
PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature

RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
All strengths: 30s

See AF and AM dated 8/4/2011 that states TEVA will only market the 30s in ALL strengths.

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7312” on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7313” on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

12. MEDWATCH**:** (checked 4/27/12)
No report of safety labeling changes since last labeling was approved February 2012.

13. REMS:
REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Date of Review: May 9, 2012 Date of Submission: May 7, 2012 and April 10, 2012

Primary Reviewer: Betty Turner

Team Leader: Ruby (Chi-Ann) Wu

N 3 0093-7310-56 3

*Each film-coated tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301850512

Iss. 5/2012

Reference ID: 3129193

NDC 0093-7310-56

ATORVASTATIN CALCIUM Tablets

10 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

NDC 0093-7311-56

ATORVASTATIN CALCIUM Tablets 20 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each film-coated tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301870512

Iss. 5/2012

N 3 0093-7311-56 0

Reference ID: 3129193

NDC 0093-7312-56

ATORVASTATIN CALCIUM Tablets 40 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each film-coated tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301890512

Iss. 5/2012

N 3 0093-7312-56 7

Reference ID: 3129193

NDC 0093-7313-56

ATORVASTATIN CALCIUM Tablets 80 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

* Each film-coated tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301910512

Iss. 5/2012

N 0093-7313-56

Reference ID: 3129193

ATORVASTATIN CALCIUM TABLETS

R 2 3 5 6 7 3

℞ only

7310
7311
7312
7313

Rev. D 2/2012
322K405760312

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 use

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, 8.5).

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme 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 80 mg group vs. placebo (5.5).

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

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin calcium 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 TEVA USA, PHARMACOVIGILANCE at 1-888-838-2872, X6351 or drug.safety@tevapharm.com; 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 calcium (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 coadministered with atorvastatin calcium (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 and FDA-Approved Patient Labeling

Revised: 02/2012

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PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS

*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). 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 calcium tablets; 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 calcium tablets should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets 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 calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed. In patients with HIV taking nelfinavir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed [*see Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White to off-white, capsule-shaped, film-coated tablets containing atorvastatin calcium equivalent to 10, 20, 40, and 80 mg atorvastatin.

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 calcium tablets 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 calcium tablet 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 CALCIUM TABLETS 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 calcium tablets 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 calcium tablet 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 calcium 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 calcium 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 calcium 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[a], 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

[a] Use with caution and with the lowest dose necessary (12.3)

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

Atorvastatin calcium 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 calcium 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 calcium.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin calcium 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 calcium, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium.

Atorvastatin calcium 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 calcium [*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 calcium.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin calcium 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, 0-24 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 (0-24) 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 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 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)*]

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[a]	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	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

[a] 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 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 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 10 mg daily (n = 5006) or atorvastatin 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 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 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 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 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 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 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 10 to 20 mg daily was generally similar to that of placebo [*see Clinical Studies (14.6) and Use in Specific 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 calcium is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin calcium 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 calcium 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 calcium with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin calcium 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 calcium should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium 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 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 calcium alone [*see Clinical Pharmacology (12.3)*]. The coadministration of atorvastatin calcium 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 coadministered with gemfibrozil, concomitant administration of atorvastatin calcium 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 calcium 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 calcium is used in combination with niacin; a reduction in atorvastatin calcium 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 calcium 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 coadministration of atorvastatin calcium with rifampin is recommended, as delayed administration of atorvastatin calcium after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

When multiple doses of atorvastatin calcium and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.9 Oral Contraceptives

Coadministration of atorvastatin calcium 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 calcium.

7.10 Warfarin

Atorvastatin calcium 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 coadministered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

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 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 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 calcium 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**. 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 calcium therapy [*see Contraindications, Pregnancy (4.3) and Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium 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.

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)*].

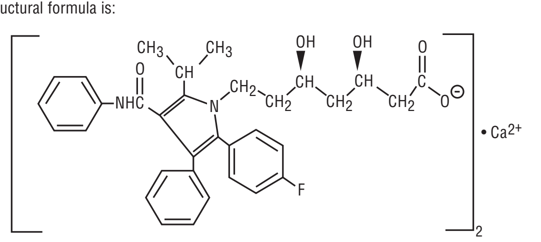
10 OVERDOSAGE

There is no specific treatment for atorvastatin calcium 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 calcium 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.

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). Its structural formula is:



$(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very 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: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium carbonate, magnesium stearate, polydextrose, polyethylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium 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 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 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 calcium, 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 calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium 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 calcium is given with or without food. Plasma atorvastatin calcium 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 calcium is approximately 381 liters. Atorvastatin calcium 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 calcium 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 calcium 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 calcium. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin calcium metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin calcium in humans following coadministration with erythromycin, a known inhibitor of this isozyme [*see Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin calcium 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 calcium 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 calcium is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium 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 calcium 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 calcium between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin calcium; 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 calcium since the drug is extensively bound to plasma proteins.

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

Table 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin

Coadministered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[a]	Change in C_{max}[a]
[b]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[b]Tipranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
[b]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
[b,f]Saquinavir 400 mg BID/ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[b]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[b]Darunavir 300 mg BID/ ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[b]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[b]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[b]Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
[b]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
[b]Grapefruit Juice, 240 mL QD[c]	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%[d]
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%
[b]Rifampin 600 mg QD, 7 days (coadministered)[e]	40 mg SD	↑ 30%	↑ 2.7 fold
[b]Rifampin 600 mg QD, 5 days (doses separated)[e]	40 mg SD	↓ 80%	↓ 40%
[b]Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less than 1%
[b]Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%

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

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

[c] 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).

[d] Single sample taken 8 to 16 h post dose.

[e] Due to the dual interaction mechanism of rifampin, simultaneous coadministration 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.

[f] 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 Coadministered Drugs

Atorvastatin	Coadministered 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	[a]Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20%
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1 mg - ethinyl estradiol 35 mcg	 ↑ 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

[a] 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 represents a plasma AUC (0-24) 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 (0-24) 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.

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 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 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 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.

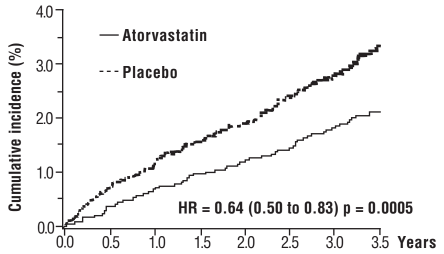


Figure 1: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)

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), 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 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 HbA_{1c} 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 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).

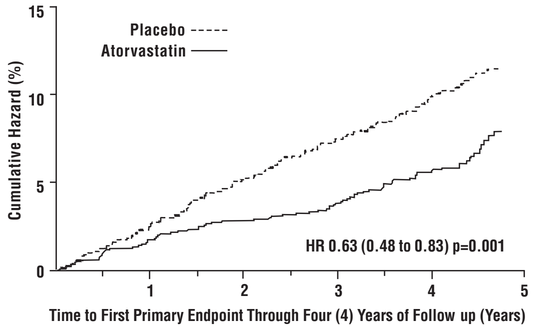


Figure 2: Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Event (Myocardial Infarction, Acute CHD Death, Unstable Angina, Coronary Revascularization, or Stroke) in CARDS

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 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 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin 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 and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 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.

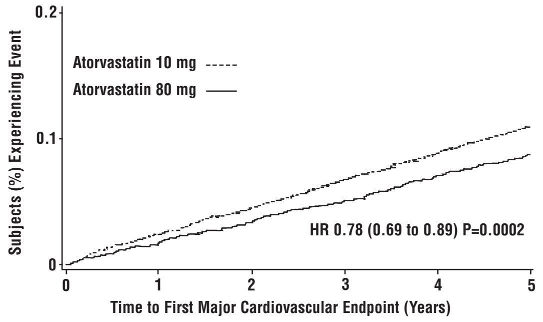


Figure 3: Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

Table 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N = 5006)		Atorvastatin 80 mg (N = 4995)		HR[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)
SECONDARY ENDPOINTS[c]					
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)
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

[c] 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

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 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 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 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 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 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 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 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 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 80 mg group and the simvastatin 20 to 40 mg group.

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.**)

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 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 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 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
95% CI for Diff[b]		-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[c]	-35[c]	-27[c]	-17[c]	+6	-36[c]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[b]		-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[d]	-37[d]	-34[d]	-23[d]	+7	-39[d]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[b]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[a] Significantly different from lovastatin, ANCOVA, p ≤ 0.05

[b] A negative value for the 95% CI for the difference between treatments favors atorvastatin calcium for all except HDL-C, for which a positive value favors atorvastatin calcium. If the range does not include 0, this indicates a statistically significant difference.

[c] Significantly different from pravastatin, ANCOVA, p ≤ 0.05

[d] Significantly different from simvastatin, ANCOVA, p ≤ 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).

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)

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 (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		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)
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. 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 hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to 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 (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-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).

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	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 calcium therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

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

Atorvastatin calcium is supplied as follows:

10 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7310" on the other side of the tablet in bottles of 30.

20 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7311" on the other side of the tablet in bottles of 30.

40 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7312" on the other side of the tablet in bottles of 30.

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet in bottles of 30.

Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

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.

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 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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Rev. D 2/2012

PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking them 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 are a prescription medicine that lowers cholesterol in your blood. They lower the LDL-C ("bad" cholesterol) and triglycerides in your blood. They 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 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 can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of their ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

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 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 many 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 nonprescription 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, 20° to 25°C (68° to 77°F).
- 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 they were not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. They may harm them.

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What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium carbonate, magnesium stearate, polydextrose, polyethylene glycol, and titanium dioxide.

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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
05/10/2012

CHI-ANN Y WU
05/10/2012
For Wm. Peter Rickman

(This review Supersedes AP SUM #3 dated 8/16/11)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 078773 Dates of Submission: April 10, 2012

Applicant's Name: TEVA Pharmaceuticals USA

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

---

LABELING DEFICIENCIES:

A. CONTAINER:

Revise "*Each tablet contains…" statement to read "*Each film-coated tablet contains…"

B. INSERT:

1. HIGHLIGHTS:
   Delete "and FDA Approved Patient Labeling" that appears at the end of the HIGHLIGHTS section

2. FULL PRESCRIBING INFORMATION: CONTENTS*:

   i. Revise subtitle 2.1 and 2.2 to read as follows:

      2.1 Hyperlipidemia
      2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

   ii. Under subtitle 4.1 revise "Elevations in" to read "Elevations of"

   iii. Revise subtitle "6.2 Postmarketing Experience" to read "Postintroduction Reports".

   iv. Revise subtitle 7.1 to read as follows:

      7.1 Strong Inhibitors of Cytochrome P450 3A4:
      Clarithromycin
      Combination of Protease Inhibitors
      Itraconazole

   v. Revise subtitles 14.2, 14.3, and 14.4 to read as follows:

      14.2 Hyperlipidemia and Mixed Dyslipidemia
      14.3 Hypertriglyceridemia
      14.4 Dysbetalipoproteinemia

   vi. Delete "PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS" that appears after subtitle 17.4 Breastfeeding

3. FULL PRESCRIBING INFORMATION:

   i. GENERAL COMMENT:
   Relocate the title for Figure 1; Figure 2, and Figure 3 that appears at the bottom of each

figure, to appear at the top of the figure (Refer to the reference listed drug for guidance).

ii. 4 CONTRAINDICATIONS

a. Revise 4.1 to read as follows.

4.1 Active Liver Disease, which may include unexplained persistent elevations in hepatic transaminase levels

b. Revise 4.2 to read as follows.

4.2 Hypersensitivity to any component of this medication

BASIS OF APPROVAL:

Container Labels (10 mg, 20 mg, 40 mg and, 80 mg: bottles of 30s):
Refer to labeling comments.

Professional Package Insert Labeling: Refer to labeling comments.

Patient Information Sheet: Final print labeling acceptable in 4/10/2012 e-submission

SPL: DLDE acceptable in 8/4/2011 e-submission

Revisions needed before full approval: see comments

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 02/28/2012.
Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

Email from Haitao on 12/6/10:

Ann,

Based on my review note, 80 mg is only supplied in 30 ct, (b) (4) container. If they have (b) (4), they had better submit to me and I will have to look at the stability data in that container.

The firm called their API (b) (4). It's a mixture of (b) (4) and (b) (4) form. Teva's API indeed does not have hydrate form. From

chemistry point view, if it is pure and stable, it is fine. I am not sure about legal's aspect.

I hope I have answered your questions. I cc this email to Laxma in case he wants to chime in. We all have to agree, this is a rather complicated ANDA.

Haitao

On 12/6/10: I sent an email to Phil Erickson at TEVA to request the stability data for the 80 mg (b) (4) size:

Good afternoon,

In the labeling amendment submitted 10/28/10, you submitted container label for the 80 mg, (b) (4) size. This packaging size is also noted in the HOW SUPPLIED section. Please submit the stability data and all pertinent chemistry data for this packaging size to chemistry.

Thanks
Ann

Ann,

(b) (4) Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)
Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

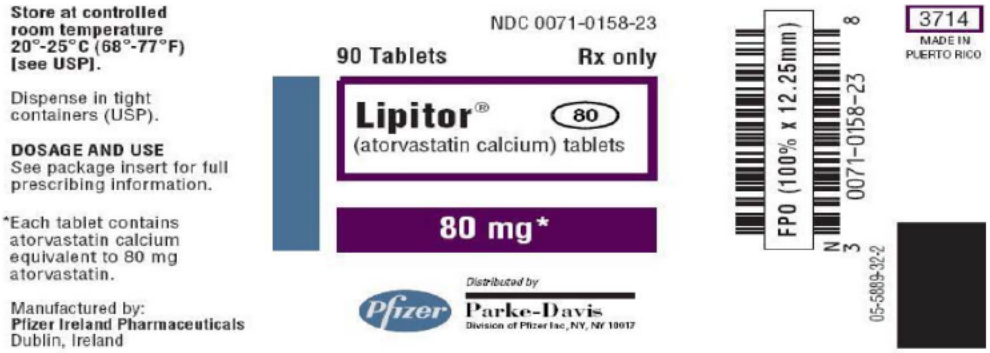
Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks
Ann

FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 8/16/11 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:

Supplement 056 was approved June 17, 2009, and provided for labeling in PLR format.



In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 mg.

In AF dated 3/1/11: TEVA removed the [redacted] (b) (4) for the 80 mg strength.

In AF dated 5/5/11: TEVA revised labeling to reflect the removal of the [redacted] (b) (4) configurations of the 10 mg, 20 mg and 40 mg strengths, which were withdrawn in the chemistry t-amendment dated 4/22/2011.

In AF 8/4/2011: TEVA revised labeling to reflect the Teva's package insert has been updated to reflect removal of the [redacted] (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, and the [redacted] (b) (4) configurations for the 80 mg strength. These package configurations were withdrawn via a minor amendment submitted by Teva on August 4, 2011. As a result, the "How Supplied" section of Teva's insert now reflects only a 30-count configuration for each strength.

In AM 8/4/2011: Teva withdrawn the other count configurations.
A 30-day in-use study was conducted for all strengths of Teva's drug product packaged in the proposed 30-count configurations and reports were provided in Teva's minor amendment dated August 18, 2010. However, due to a change of response factor for [redacted] (b) (4) as discussed in Teva's telephone amendment dated April 22, 2011, results reported for [redacted] (b) (4) have since been recalculated using the RRf value of [redacted] (b) (4) Revised reports containing the recalculated results are provided in **Attachment 8**, and support the stability of the drug product under conditions which simulate anticipated consumer use for this configuration. In addition, the stability protocol which details how the in-use study was conducted is provided in **Attachment 9**. It is important to note that bottle seals were broken on Day 1 of the study and thus bottles remained unsealed for the duration of the 30-day study. Additionally, the study was conducted in our 30 count bottles as they are intended to be provided directly to consumers as unit of use container.
In the interest of expeditiously answering the current review letter and to enable the Agency to complete their review of the CMC portion of this application, we hereby request approval for only the 30-count configuration for each strength. While the [redacted] (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, and the [redacted] (b) (4) configurations for the 80 mg strength, meet specifications through the [redacted] (b) (4)-month CRT stability study, we hereby withdraw them from this application. Teva will commercially

launch this product in only the 30-count unit of use configurations, but wil [redacted] (b) (4)

Please refer to the revised package component summary in **Attachment 10** that reflects only the 30-count configurations. Revised labeling which reflects the removal of said configurations will be submitted to the Labeling Support Branch under separate cover

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL: NDA 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	PIV	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	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		PIV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	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

There is no unexpired exclusivity for this product in the Orange Book (checked 4/27/2012)

In the Patent Amendment dated 1/26/12- Teva Pharmaceuticals USA submits herewith an amendment

to the above-referenced tentatively approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor□ Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor□ Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

See email below from Mary Ann regarding the Patent Listing:

From: Holovac, Mary Ann
Sent: Friday, April 27, 2012 1:57 PM
To: Turner, Betty
Subject: RE: Patent Listing

Hi Betty, If the patent is not listed in the OB then it was not submitted. I checked darrts and don't see anything recent. Pfizer's attorney always sends me a heads up. Any cert by Teva to this patent is invalid. Mary Ann

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From: Turner, Betty
Sent: Friday, April 27, 2012 11:34 AM
To: Holovac, Mary Ann
Subject: Patent Listing

Hi Mary Ann,

Can you verify whether Pfizer listed Patent No. 8,084,488 for Lipitor Tablets NDA 020702? Its not listed in the OB and Teva submitted a patent amendment to provide certification with regards to this patent.

Thanks,

Betty

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period. TEVA filed 24 separate patent amendments addressing the same patent 7,790,197 which is NOT listed in the OB yet. TEVA wishes to provide certification with regard to this patent. The '197 patent was issued on 9/7/10. Thus, TEVA anticipates that Pfizer of Warner-Lambert would take steps to list the patent within 30 days of issue so as not to be considered late listed.

According to M. Holovac's email dated 12/6/10: Pfizer did NOT list the '197 patent yet.

Note that Ranbaxy has a "Settlement" with Pfizer to sell generic atorvastatin effective from November 30, 2011. Read the FTR for ANDA 76477 for more information about the "Settlement". In effect, Ranbaxy was the first to file a patent cert IV and will have 6 months generic exclusivity when Ranbaxy launches the generic atorvastatin on November 30, 2011.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	

80 mg Count Container: 30 Bottle: (b) (4) bottle (b) (4) (HDPE) (b) (4)
(b) (4) of desiccant and (b) (4)
(b) (4)
(b) (4)

In 8/18/10 AM: TEVA submitted (b) (4)

information



However, TEVA will not market the (b) (4) at the time of approval.

8/4/2011 AF: Note that TEVA will ONLY MARKET the 30s count size on all strengths to clear up "sticky" issues with chemistry to expediate the approval of this ANDA. If necessary, TEVA will submit supplements after approval to add additional packaging size.

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg. 208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Only DS is compendial
PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature

RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
All strengths: 30s

See AF and AM dated 8/4/2011 that states TEVA will only market the 30s in ALL strengths.

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7310” on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7311” on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7312” on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7313” on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

12. MEDWATCH**:** (checked 4/27/12)
No report of safety labeling changes since last labeling was approved February 2012.

13. **REMS:**

REMS required?

☐ Yes ☒ No

REMS acceptable?

☐ Yes ☐ No ☒ n/a

Date of Review: April 27, 2012 Date of Submission: April 10, 2012

Primary Reviewer: Betty Turner Team Leader: Ruby (Chi-Ann) Wu

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ANDA 078773 DR

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
04/27/2012

CHI-ANN Y WU
04/28/2012
For Wm. Peter Rickman

****APPROVAL SUMMARY#3****
(Supercedes AP SUM #2 dated 5/10/11)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78773 Date of Submission: August 4, 2011

Applicant's Name: TEVA Pharmaceuticals USA

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

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REMS required?

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 and 40 mg: 30s, (b) (4); 80 mg: 30s, (b) (4)):
Final print acceptable in February 23, 2011 e-submission

Professional Package Insert Labeling: Final print labeling acceptable in 8/4/2011 e-submission

Patient Information Sheet: Final print labeling acceptable in 8/4/2011 e-submission

SPL: DLDE acceptable in 8/4/2011 e-submission

Revisions needed before full approval: No

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:

Email from Haitao on 12/6/10:

Ann,

Based on my review note, 80 mg is only supplied in 30 ct, (b) (4) container. If they have (b) (4), they had better submit to me and I will have to look at the stability data in that container.

The firm called their API (b) (4). It's a mixture of (b) (4) and (b) (4) form. Teva's API indeed does not have hydrate form. From chemistry point view, if it is pure and stable, it is fine. I am not sure about legal's aspect.

I hope I have answered your questions. I cc this email to Laxma in case he wants to chime in. We all have to agree, this is a rather complicated ANDA.

Haitao

On 12/6/10: I sent an email to Phil Erickson at TEVA to request the stability data for the 80 mg (b) (4) size:

Good afternoon,

In the labeling amendment submitted 10/28/10, you submitted container label for the 80 mg, (b) (4) size. This packaging size is also noted in the HOW SUPPLIED section. Please submit the stability data and all pertinent chemistry data for this packaging size to chemistry.

Thanks
Ann

Ann,

(b) (4) Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)
Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks
Ann

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-056; approved 6/17/09: The PI is now in PLR format.

   In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 mg.

   In AF dated 3/1/11: TEVA removed the (b) (4) for the 80 mg strength.

   In AF dated 5/5/11: TEVA revised labeling to reflect the removal of the (b) (4) configurations of the 10 mg, 20 mg and 40 mg strengths, which were withdrawn in the chemistry t-amendment dated 4/22/2011.

   In AF 8/4/2011: TEVA revised labeling to reflect the Teva's package insert has been updated to reflect removal of the (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, and the (b) (4)-count configurations for the 80 mg strength. These package configurations were withdrawn via a minor amendment submitted by Teva on August 4, 2011. As a result, the "How Supplied" section of Teva's insert now reflects only a 30-count configuration for each strength.

   In AM 8/4/2011: Teva withdrawn the other count configurations.
   A 30-day in-use study was conducted for all strengths of Teva's drug product packaged in the proposed 30-count configurations and reports were provided in Teva's minor amendment dated August 18, 2010. However, due to a change of response factor for (b) (4) as discussed in Teva's telephone amendment dated April 22, 2011, results reported for (b) (4) have since been recalculated using the RRf value of (b) (4) Revised reports containing the recalculated results are provided in **Attachment 8**, and support the stability of the drug product under conditions which simulate anticipated consumer use for this configuration. In addition, the stability protocol which details how the in-use study was conducted is provided in **Attachment 9**. It is important to note that bottle seals were broken on Day 1 of the study and thus bottles remained unsealed for the duration of the 30-day study. Additionally, the study was conducted in our 30 count bottles as they are intended to be provided directly to consumers as unit of use container.

In the interest of expeditiously answering the current review letter and to enable the Agency to complete their review of the CMC portion of this application, we hereby request approval for only the 30-count configuration for each strength. While the (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, and the (b) (4) configurations for the 80 mg strength, meet specifications through the (b) (4) month CRT stability study, we hereby withdraw them from this application. Teva will commercially launch this product in only the 30-count unit of use configurations, but will (b) (4)

Please refer to the revised package component summary in **Attachment 10** that reflects only the 30-count configurations. Revised labeling which reflects the removal of said configurations will be submitted to the Labeling Support Branch under separate cover

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, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIV	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	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		PIV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	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

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period. TEVA filed 24 separate patent amendments addressing the same patent 7,790,197 which is NOT listed in the OB yet. TEVA wishes to provide certification with regard to this patent. The '197 patent was issued on 9/7/10. Thus, TEVA anticipates that Pfizer of Warner-Lambert would take steps to list the patent within 30 days of issue so as not to be considered late listed.

According to M. Holovac's email dated 12/6/10: Pfizer did NOT list the '197 patent yet.

Note that Ranbaxy has a "Settlement" with Pfizer to sell generic atorvastatin effective from November 30, 2011. Read the FTR for ANDA 76477 for more information about the "Settlement". In effect, Ranbaxy was the first to file a patent cert IV and will have 6 months generic exclusivity when Ranbaxy launches the generic atorvastatin on November 30, 2011.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration

	(b) (4)		
Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4)		30's Configuration
	(b) (4)		

80 mg Count Container: 30 Bottle: (b) (4) bottle (b) (4) (HDPE) (b) (4)
(b) (4) of desiccant and (b) (4)

(b) (4)

(b) (4)

In 8/18/10 AM: TEVA submitted (b) (4) information

(b) (4)

However, TEVA will not market the (b) (4) at the time of approval.

8/4/2011 AF: Note that TEVA will ONLY MARKET the 30s count size on all strengths to clear up "sticky" issues with chemistry to expediate the approval of this ANDA. If necessary, TEVA will submit supplements after approval to add additional packaging size.

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg. 208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Only DS is compendial
PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature

RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
All strengths: 30s

See AF and AM dated 8/4/2011 that states TEVA will only market the 30s in ALL strengths.

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and

"7310" on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7313" on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

Date of Review: August 10, 2011 Date of Submission: August 4, 2011

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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

NDC 0093-7310-56

ATORVASTATIN CALCIUM Tablets 10 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

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

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301850111 Iss. 9/2010

N 3 0093-7310-56 3

Reference ID: 2998720

NDC 0093-7311-56

ATORVASTATIN CALCIUM Tablets 20 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301870111 Iss. 9/2010

N 3 0093-7311-56 0

Reference ID: 2998720

*Each tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7312-56 7

323K301890111 Iss. 9/2010

Reference ID: 2998720

NDC 0093-7312-56

ATORVASTATIN CALCIUM Tablets 40 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

NDC 0093-7313-56

ATORVASTATIN CALCIUM Tablets

80 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

* Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured in Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301910111

Iss. 9/2010

N 0093-7313-56 3

Reference ID: 2998720

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
08/10/2011

JOHN F GRACE
08/16/2011

****APPROVAL SUMMARY#2****
(Supercedes AP SUM dated 3/8/11)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78773 Date of Submission: May 5, 2011

Applicant's Name: TEVA Pharmaceuticals USA

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

---

REMS required?

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 and 40 mg: 30s, (b) (4); 80 mg: 30s, (b) (4)):
Final print acceptable in February 23, 2011 e-submission

Professional Package Insert Labeling: Final print labeling acceptable in 5/5/2011 e-submission

Patient Information Sheet: Final print labeling acceptable in 3/1/2011 e-submission

SPL: DLDE acceptable in 3/1/2011 e-submission

Revisions needed before full approval: No

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:

Email from Haitao on 12/6/10:

Ann,

Based on my review note, 80 mg is only supplied in 30 ct, [redacted] container. If they have [redacted] they had better submit to me and I will have to look at the stability data in that container.

The firm called their API [redacted]. It's a mixture of [redacted] and [redacted] form. Teva's API indeed does not have hydrate form. From chemistry point view, if it is pure and stable, it is fine. I am not sure about legal's aspect.

I hope I have answered your questions. I cc this email to Laxma in case he wants to chime in. We all have to agree, this is a rather complicated ANDA.

Haitao

On 12/6/10: I sent an email to Phil Erickson at TEVA to request the stability data for the 80 mg [redacted] size:

Good afternoon,

In the labeling amendment submitted 10/28/10, you submitted container label for the 80 mg, [redacted] size. This packaging size is also noted in the HOW SUPPLIED section. Please submit the stability data and all pertinent chemistry data for this packaging size to chemistry.

Thanks
Ann

Ann,

[redacted] Teva used [redacted] form. Another firm used [redacted] form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)
Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks
Ann

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-056; approved 6/17/09: The PI is now in PLR format.

   In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 mg.

   In AF dated 3/1/11: TEVA removed the (b) (4) for the 80 mg strength.

   In AF dated 5/5/11: TEVA revised labeling to reflect the removal of the (b) (4) configurations of the 10 mg, 20 mg and 40 mg strengths, which were withdrawn in the chemistry t-amendment dated 4/22/2011.

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, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIV	Same As
5686104	Nov 11, 2014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING	PIV	Same As

			HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA		
5969156	Jul 8, 2016 ped Jan 8, 2017	—		PIV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	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

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period. TEVA filed 24 separate patent amendments addressing the same patent 7,790,197 which is NOT listed in the OB yet. TEVA wishes to provide certification with regard to this patent. The '197 patent was issued on 9/7/10. Thus, TEVA anticipates that Pfizer of Warner-Lambert would take steps to list the patent within 30 days of issue so as not to be considered late listed.

According to M. Holovac's email dated 12/6/10: Pfizer did NOT list the '197 patent yet.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration

	(b) (4)
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4) 30's Configuration
	(b) (4)
Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4) 30's Configuration
	(b) (4)

80 mg Count Container: 30 Bottle: (b) (4) bottle (b) (4) (HDPE) (b) (4)
(b) (4) of desiccant and (b) (4)

(b) (4)

(b) (4)

In 8/18/10 AM: TEVA submitted (b) (4) information



However, TEVA will not market the (b) (4) at the time of approval.

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg. 208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Only DS is compendial
PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature

RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the [redacted] form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
10 mg: 30s, [redacted]
20 mg: 30s, [redacted]
40 mg: 30s, [redacted]
80 mg: 30s, [redacted]

[Vol B1.2, pg. 574] and 2.3.P.8 of AC dated 3/12/08

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7313" on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

Date of Review: May 8, 2011 Date of Submission: May 5, 2011

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

(b) (4)

NDC 0093-7310-56

ATORVASTATIN CALCIUM Tablets 10 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

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

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301850111 Iss. 9/2010

N 3 0093-7310-56 3

Reference ID: 2943618

(b) (4)

(b) (4)

NDC 0093-7311-56

ATORVASTATIN CALCIUM Tablets 20 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301870111 Iss. 9/2010

N 3 0093-7311-56 0

Reference ID: 2943618

(b) (4)

(b) (4)

NDC 0093-7312-56

ATORVASTATIN CALCIUM Tablets 40 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301890111 Iss. 9/2010

N 3 0093-7312-56 7

Reference ID: 2943618

(b) (4)

(b) (4)

NDC 0093-7313-56

ATORVASTATIN CALCIUM Tablets 80 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

* Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured in Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K301910111

Iss. 9/2010

N 0093-7313-56

Reference ID: 2943618

(b) (4)

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
05/08/2011

JOHN F GRACE
05/10/2011

****APPROVAL SUMMARY****
(Supercedes TA SUM #2 dated 12/8/2010)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78773 Dates of Submission: February 23, and March 1, 2011

Applicant's Name: TEVA Pharmaceuticals USA

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

---

REMS required?

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 and 40 mg: 30s, [redacted (b) (4)]; 80 mg: [redacted (b) (4)]):
Final print acceptable in February 23, 2011 e-submission

Professional Package Insert Labeling: Final print labeling acceptable in 3/1/2011 e-submission

Patient Information Sheet: Final print labeling acceptable in 3/1/2011 e-submission

SPL: DLDE acceptable in 3/1/2011 e-submission

Revisions needed before full approval: No

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:

Email from Haitao on 12/6/10:

Ann,

Based on my review note, 80 mg is only supplied in 30 ct, (b) (4) container. If they have (b) (4) they had better submit to me and I will have to look at the stability data in that container.

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Thanks
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(b) (4) Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

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Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

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Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

Is Teva using (b) (4) form of atorvastatin and is this equivalent?

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FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-056; approved 6/17/09: The PI is now in PLR format.

   In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 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, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIV	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	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	––		PIV	Same As
	Jan 19, 2013 ped	__		PIV	Same As

6126971	July 19, 2013				
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	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

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period. TEVA filed 24 separate patent amendments addressing the same patent 7,790,197 which is NOT listed in the OB yet. TEVA wishes to provide certification with regard to this patent. The '197 patent was issued on 9/7/10. Thus, TEVA anticipates that Pfizer of Warner-Lambert would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration (b) (4)

	(b) (4)
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4) 30's Configuration
	(b) (4)
Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4) 30's Configuration
	(b) (4)

Count Container: 30 Bottle: (b) (4) bottle (b) (4) (HDPE) (b) (4) (b) (4) of desiccant and (b) (4)

(b) (4)

(b) (4)

In 8/18/10 AM: TEVA submitted (b) (4) information



However, TEVA will not market the (b) (4) at the time of approval.

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg. 208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Only DS is compendial
PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature

RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
10 mg: 30s, (b) (4)
20 mg: 30s, (b) (4)
40 mg: 30s, (b) (4)
80 mg: 30s, (b) (4)

[Vol B1.2, pg. 574] and 2.3.P.8 of AC dated 3/12/08

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7313" on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

Date of Review: March 4, 2011 Dates of Submission: February 23, and March 1, 2011

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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(b) (4)

(b) (4)

NDC 0093-7310-56

ATORVASTATIN CALCIUM Tablets

10 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

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

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7310-56 3

Reference ID: 2913789

(b) (4)

(b) (4)

(b) (4)

NDC 0093-7311-56

ATORVASTATIN CALCIUM Tablets 20 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7311-56 0

Reference ID: 2913789

(b) (4)

(b) (4)

(b) (4)

NDC 0093-7312-56

ATORVASTATIN CALCIUM Tablets

40 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

*Each tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7312-56 7

323[illegible] 9/2011

Reference ID: 2913789

(b) (4)

(b) (4)

(b) (4)

NDC 0093-7313-56

ATORVASTATIN CALCIUM Tablets

80 mg*

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

℞ only

30 TABLETS

TEVA

* Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.

Usual Dosage: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

323K0[illegible] Iss. 9/2010

Reference ID: 2913789

N 0093-7313-56

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
03/04/2011

JOHN F GRACE
03/08/2011

****TENTATIVE APPROVAL SUMMARY#2****
(Supercedes TA SUM#1 dated 11/28/08)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-773 Date of Submission: October 28, 2010

Applicant's Name: TEVA Pharmaceuticals USA

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

---

BASIS OF TENTATIVE APPROVAL:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

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, firm only submitted **draft** labeling.

Container Labels (10 mg, 20 mg and 40 mg: 30s, [redacted (b) (4)]; 80 mg: [redacted (b) (4)])
Draft labeling acceptable in 10/28/10 electronic submission

Professional Package Insert Labeling: Draft labeling acceptable in 10/28/10 electronic submission

Patient Information Sheet: Draft labeling acceptable in 10/28/10 electronic submission

Revisions needed before full approval: No

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:

Email from Haitao on 12/6/10:

Ann,

Based on my review note, 80 mg is only supplied in 30 ct, (b) (4) container. If they have (b) (4), they had better submit to me and I will have to look at the stability data in that container.

The firm called their API (b) (4). It's a mixture of (b) (4) and (b) (4) form. Teva's API indeed does not have hydrate form. From chemistry point view, if it is pure and stable, it is fine. I am not sure about legal's aspect.

I hope I have answered your questions. I cc this email to Laxma in case he wants to chime in. We all have to agree, this is a rather complicated ANDA.

Haitao

Ann,

(b) (4), Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)
Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks

Ann

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-056; approved 6/17/09: The PI is now in PLR format. .

   In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 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, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIV	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	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	––		PIV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	––		PIV	Same As
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	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

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that

Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period. TEVA filed 24 separate patent amendments addressing the same patent 7,790,197 which is NOT listed in the OB yet. TEVA wishes to provide certification with regard to this patent. The '197 patent was issued on 9/7/10. Thus, TEVA anticipates that Pfizer of Warner-Lambert would take steps to list the patent within 30 days of issue so as not to be considered late listed.

According to M. Holovac's email dated 12/6/10: Pfizer did NOT list the '197 patent yet.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	

[redacted]

80 mg:
30's: [redacted] bottle [redacted] (HDPE) [redacted]

[Vol B.1.3, pg. 574]

In 8/18/10 AM: TEVA submitted [redacted] information

[redacted]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, [redacted] (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg. 208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: DS proposed for USP
PACKAGING AND STORAGE: Preserve in well-closed containers, and store at room temperature

RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
10 mg: 30s, (b) (4)
20 mg: 30s, (b) (4)
40 mg: 30s, (b) (4)
80 mg: (b) (4)

[Vol B1.2, pg. 574] and 2.3.P.8 of AC dated 3/12/08

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7313" on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

Date of Review: December 7, 2010 Date of Submission: October 28, 2010

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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
12/07/2010

JOHN F GRACE
12/08/2010

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-773 Date of Submission: March 12, 2008

Applicant's Name: TEVA Pharmaceuticals USA

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

---

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? Yes, electronic submission dated 8/15/07 and 3/20/8

Container Labels (10 mg, 20 mg and 40 mg: 30s, (b) (4); 80 mg: (b) (4)) Yes, 3/12/08 electronic submission

Professional Package Insert Labeling: Yes, 3/12/08 electronic submission

Patient Information Sheet: Yes, 3/12/08 electronic submission

Revisions needed before full approval: Yes:

INSERT:

A. General comment: Please revise the footnotes associated with the Tables. A “1” is associated with all of the footnotes. As an example, in Table 1, the footnote in the table itself states “b1” while the footnote at the end of the Table states “b”.

B. Figure 3; please increase the resolution to increase readability. The title of the Figure 3 should be “...Calcium Tablets 80 mg/day vs. 10 mg/day on ...”

C. Patient Information, Before You Start Atorvastatin Calcium Tablets, paragraph beginning with “Some medicines should not...” add a space between “causing” and “serious”.

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:

Ann,

(b) (4), Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)
Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks
Ann

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-050; approved 9/26/07.

   In AC dated 3/12/8, TEVA added three new strengths: 10 mg, 20 mg and 40 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, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIV	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	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		PIV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-434	**JUL 30,2007**	PREVENTION OF CARDIOVASCULAR DISEASE IN ADULT PATIENTS WITHOUT CLINICALLY EVIDENT HEART DISEASE, BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE TO REDUCE RISK OF MI AND RISK FOR REVASCULARIZATION PROCEDURES AND ANGINA	None
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
M-36	**JUL 30,2007**	ADDITION OF INFORMATION TO CLINICAL STUDIES REGARDING PREVENTION OF CARDIOVASCULAR DISEASE	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

In AC dated 3/12/8: TEVA filed cert IV to '971, '156, '104 and '995. In XP dated 9/24/08 TEVA stated that Pfizer sued TEVA on the '995 patent (Civil Action No. 08-00237 filed on 4/25/08 in the US District Court for the District of Delaware). No suit filed on the '971, 156 and 104 patents within the 45 day period.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

Table 2.3.P.7-2 Packaging Configuration- AC dated 3/12/08, 2.3.P.7

Strength	How Supplied	Packaging Configuration
Atorvastatin calcium Eq. to 10 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 20 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	
Atorvastatin calcium Eq. to 40 mg strength	(b) (4) HDPE Bottle (b) (4)	30's Configuration
	(b) (4)	

80 mg:

(b) (4)

[Vol B.1.3, pg. 574]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyethylene glycol) [Vol. B1.2, pg.

208-367]

Note that in AC dated 3/12/08, the new strengths have the same inactive ingredients as above.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not USP
RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

RLD: 90s, 500s and 8x8 unit dose blisters

ANDA:
10 mg: 30s, (b) (4)
20 mg: 30s, (b) (4)
40 mg: 30s, (b) (4)
80 mg: (b) (4)

[Vol B1.2, pg. 574] and 2.3.P.8 of AC dated 3/12/08

11. FINISHED DOSAGE FORM

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

ANDA:

10 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet.

20 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet.

40 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet.

80 mg: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7313" on the other side of the tablet.

[Vol B1.3, pg. 702] and 2.3.P.5 of AC dated 3/12/08

Date of Review: November 25, 2008 Date of Submission: March 12, 2008

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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
11/28/2008 09:58:41 AM
LABELING REVIEWER

John Grace
11/28/2008 02:19:29 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-773 Dates of Submission: December 29, 2006

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Atorvastatin Calcium Tablets, 80 mg

Labeling Deficiencies:

1. CONTAINER [redacted] (b) (4)

   Add a statement to the pharmacist to dispense patient leaflet with medication.

2. INSERT:

   A. Your product uses the [redacted] (b) (4) while the reference listed drug uses trihydrate. Please comment on your product and why you consider it to be the same as the reference listed drug.

   B. Revise your product to be in accord with the recent supplement approval for the reference listed drug; as of this review the NDA/20-702/S-047 approved 3/2/2007. Please visit www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm site for the most recent approved labeling.

3. PATIENT INFORMATION SHEET:

   Please submit the patient information sheet. Also state the number of sheets you intend on providing with your bottles of [redacted] (b) (4).

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://www.fda.gov/cder/cdernew/listserv.html

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.

SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-773
Date of Submission	
Applicant	TEVA Pharmaceuticals USA
Drug Name	Atorvastatin Calcium Tablets
Strength(s)	80 mg (base)

Approval Summary

Container Labels	**Submitted**
80 mg,	(b) (4),
Package Insert Labeling	
Patient leaflet	

Reference Listed Drug

RLD on the 356(h) form	LIPITOR
NDA Number	20702
RLD established name	Atorvastatin Calcium Tablets USP
Firm	(b) (4)
Currently approved PI	S-047
AP Date	Approved 3/2/07

Note: The applicant\ is using (b) (4) form while the RLD has the trihydrate form. We have asked the firm to comment on the discrepancies and revise accordingly.

NOTE TO CHEMIST:
Ann,

(b) (4), Teva used (b) (4) form. Another firm used (b) (4) form of atorvasatin calcium. I think they have possible citizen petition.

I will give Jacket 1 to you once I finished it.

Wenlei

From: Vu, Thuyanh (Ann)

Sent: Tuesday, June 26, 2007 8:30 AM
To: Jiang, Wenlei
Subject: 78-773

Wenlei,

Teva's insert did not include the 3 H2O in the structural formula:

Teva's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ M.W. 1155.36

RLD's insert: $(C_{33}H_{34}FN_2O_5)_2Ca$ 3H2O M.W. 1209.42

Is Teva using (b) (4) form of atorvastatin and is this equivalent?

Thanks
Ann

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, s-047; approved 3/2/07

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	PIII	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	PIII	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	––		PIII	Same As
6126971	Jan 19, 2013 ped July 19, 2013	––		PIII	Same As

Exclusivity Data For NDA 20702

Code/sup	Expiration	Description	*Labeling impact*
I-434	**JUL 30,2007**	PREVENTION OF CARDIOVASCULAR DISEASE IN ADULT PATIENTS WITHOUT CLINICALLY EVIDENT HEART DISEASE, BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE TO REDUCE RISK OF MI AND RISK FOR REVASCULARIZATION PROCEDURES AND ANGINA	None
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
M-36	**JUL 30,2007**	ADDITION OF INFORMATION TO CLINICAL STUDIES REGARDING PREVENTION OF CARDIOVASCULAR DISEASE	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

[Vol. B1.1, pg. 12]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

TEVA Pharmaceuitcal Industries Ltd.
(b) (4)

[Vol B1.2, pg. 370]

4. CONTAINER/CLOSURE

(b) (4)

[Vol B.1.3, pg. 574]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: lactose monohydrate, crospovidone, magnesium carbonate, colloidal silicon dioxide, magnesium stearate, (b) (4) (polydextrose, titanium dioxide, hypromellose, polyehylene glycol) [Vol. B1.2, pg. 208-367]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: Not USP
   RLD: store at CRT (20-25°C (68-77°F) [see USP].
   ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

7. DISPENSING STATEMENTS COMPARISON

   RLD: Dispense in tight containers (USP)
   ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

8. BIOAVAILABILITY/BIOEQUIVALENCE: the firm uses the (b) (4) form rather than the trihydrate

9. SCORING

   RLD: Not scored
   ANDA: Not scored

10. PACKAGE CONFIGURATION

    RLD: 90s, 500s and 8x8 unit dose blisters

    ANDA: (b) (4)

    [Vol B1.2, pg. 574]

11. FINISHED DOSAGE FORM

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

    ANDA: White to off white, capsule shaped, film coated tablet, debossed with “93” on one side and “7313” on the other side of the tablet.

    [Vol B1.3, pg. 702]

Date of Review: June 25, 2007 Date of Submission: December 29, 2006

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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
6/29/2007 01:49:15 PM
LABELING REVIEWER

John Grace
7/2/2007 09:52:41 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

CHEMISTRY REVIEWS

Addendum # 1

ANDA 078773

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Teva Pharmaceuticals USA

Haitao Li, Ph.D.
Chemistry Division III

The addendum #1 is generated for ANDA 078773 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg in response to the firm's Minor Amendment dated April 10, 2012 for Request for Full Approval upon expiration of the first PIV applicant's 180-day exclusivity period. The firm requests final approval of this ANDA on May 28, 2012, the date of expiry of Ranbaxy's PC exclusivity.

The following details are provided by the firm:

Chemistry, Manufacturing, and Controls:
The firm requests withdrawal of a contract labeling facility which was previously proposed in this application. This site has not been used in support of this application.

(b) (4)

This has been communicated to the PM and the site is withdrawn from EES.

Applicant has provided an updated summary of establishment information for all facilities proposed in this application.

Site of Drug Substance Manufacturing ((b) (4)

Assia Chemical Industries Ltd. (Teva API Division) Teva Tech Site Ramat Hovav, Emek-Sara P.O. Box 2049 Be'er Sheva 84874 Israel FEI: 3004096736 DUNS #: 514678507 Site Ready for Inspection: Yes	US Agent for Assia Chemical Industries Ltd. (Teva API Division): Teva API, Inc. 400 Chestnut Ridge Road Woodcliff Lake, NJ 07677-7604 Ms. Kerri McCullough Wood Vice President Phone: (201)-307-6900 Fax: (201)-307-6909 email: elizabeth.heil@tevapharm.com

Site of Drug Product Manufacturing, Processing, Packaging, Labeling and Testing:

Teva Pharmaceutical Industries, Ltd.
Jerusalem OSD Form Production Plant
24 Prof. Hartum Street
Har Hotzvim
Jerusalem 97775
Israel
FEI: 3005202697
DUNS #: 533065806

Yael Brenner, Director, OA
Phone: 011-972-2-5895573
Fax: 011-972-9-7638849
email: yael.brenner@teva.co.il

Site Ready for Inspection: Yes

Additional Site of Finished Packaged Product Labeling:

Teva Pharmaceuticals USA, Inc.
650 Cathill Road
Sellersville, PA 18960
FEI: 2517175
DUNS #: 118234421

John M. Abt, Vice President, North American Quality Systems & Compliance
Phone: 215-591-8603
Fax: 215-591-8811
email: john.abt@tevapharm.com

Site Ready for Inspection: Yes

Sites of Analytical Testing of Raw Materials and Finished Drug Product (Release & Stability):

Teva Pharmaceutical Industries, Ltd.

Kfar Saba Site:	Jerusalem Site:	Jerusalem Site:
64 Hashikma St. Industrial Zone Kfar Saba 44102 Israel FEI: 3002721084 DUNS #: 533065814	2 Hamarpe St. Industrial Zone Jerusalem 97774 Israel FEI: 3003414719 DUNS #: 533065822	Jerusalem OSD Form Production Plant 24 Prof. Hartum Street Har Hotzvim Jerusalem 97775 Israel FEI: 3005202697 DUNS #: 533065806

Reference ID: 3135749

Jerusalem (Hamarpe St.) Site:
Mark Kessler, Ph.D., Executive Director, Quality Assurance
Phone: 011-972-9-7648112
Fax: 011-972-9-7638849
email: mark.kessler@teva.co.il

Kfar Saba & Jerusalem OSD Sites:
Yael Brenner, Director, OA
Phone: 011-972-2-5895573
Fax: 011-972-9-7638849
email: yael.brenner@teva.co.il

Sites Ready for Inspection: Yes

Site of Drug Product Clinical Studies:

Clinical Facility:

Cetero Research
4801 Amber Valley Parkway
Fargo, ND 58104

Herb Smith, Vice President, QA
Phone: 919-468-7149
Fax: 919-468-6850
e-mail: herb.smith@cetero.com

Site Ready for Inspection: Yes

Analytical Facility:

(b) (4)

Site Ready for Inspection: Yes

Contract Testing Facilities

At this time we do not propose the use of any contract testing laboratories. If a contract laboratory is desired in the future, the appropriate documentation will be submitted to this ANDA.

Stability Data

Controlled room temperature stability data ((b) (4) months) were submitted to this file in an August 4, 2011 minor amendment. In a November 17, 2011 telephone amendment, the firm reduced the shelf life for this product to 18 months and submitted stability data for three commercial batches of each strength of drug product. Updated stability data for these commercial batches are provided. All data are with in the spec. There is slight increase of (b) (4) content and total impurities for some batches of the DP but all data meet the current specification.

Based on the following updated information, this application meets the requirement for full approval.

1. Satisfactory EES
2. DMF is adequate with IR as of 5/24/2012
3. DS meets the current USP monograph
4. No CMC changes since TA

Reference ID: 3135749

30. MICROBIOLOGY
NA

31. SAMPLES AND RESULTS/METHODS VALIDATIONs·
NA

32. LABELING
Acceptable on 5/12/2012

33. ESTABLISHMENT INSPECTION
Acceptable 7/5/2011

34. BIOEQUIV ALENCE
Acceptable 08/19/2008.

Type of Letter: Approvable

Endorsement
HFD-630/H. Li /Reviewer /5/22/2012
HFD-630/L. Nagavelli/5/24/2012
HFD-617/LA Sears/5/24/2012

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TYPE OF LETTER: APPROVABLE

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/s/

HAITAO LI
05/24/2012

LAXMA R NAGAVELLI
05/24/2012

LEIGH A SEARS
05/24/2012

ANDA 078773

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Teva Pharmaceuticals USA

Haitao Li, Ph.D.
Chemistry Division III

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Chemistry Review Data Sheet

1. ANDA 078773

2. REVIEW # 6

3. REVIEW DATE: 9/1/2011; revised 11/18/2011; 11/30/2011

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 29, 2006
Amendment*	March 12, 2008
Amendment	February 15, 2010
Amendment	8/18/2010
Amendment	8/24/2010
Amendment	11/24/2010
Amendment	2/18/2011
Amendment (Telephone Deficiency)	4/22/2011
Amendment	6/20/2011

* The original submission is for 80 mg strength only. This gratuitous amendment is for 10, 20 and 40 mg strength. However, all the amended strengths are based on deficient specifications, therefore this amendment was not reviewed. Updated information for all strengths was provided in the subsequent amendment dated Feb 15, 2010.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	8/4/2011
Amendment	9/28/2011
Amendment	9/29/2011
Amendment	10/10/2011
Amendment	10/18/2011
Amendment	10/21/2011
Amendment	11/17/2011
Method Validation Report	11/18/2011
Amendment	11/23/2011

Reference ID: 3052066

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Telephone:	(215) 591-3000
Fax:	(215) 591-8812

Representative:	Philip Erickson, R. Ph., Senior Director, Regulatory Affairs
Telephone:	(215) 591-3141
Fax:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Teva Pharmaceuticals USA proposed ANDA for Atorvastatin Calcium Tablets, 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.
b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, , 22nd Edition (2006), the RLD is covered by 5 patents.

	Paragraph III certification	
US patent no.	Expiration date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	November 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Teva Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of these patents and their associated pediatric exlusivities.

c. Exclusivity statement is provided (p. 13).

Reference ID: 3052066

I-350	Expires on October 18, 2005
PED	Expires on April 18, 2006
I-471	Expires on September 21, 2008
M-36	Expires on July 30, 2007
I-434	Expires on July 30, 2007

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20mg, 40 mg and 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__X___Not a NANO product

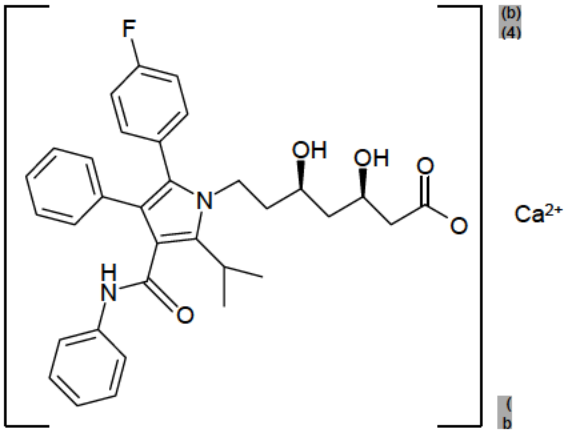
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atorvastatin Calcium, $(C_{33}H_{34}FN_2O_5)_2Ca$, CAS 134523-03-8
Atorvastatin, CAS 134523-00-5

(b) (4) = 1155.3 (b) (4)

1*H*-Pyrrole-heptanoic acid, 2-(4-flourophenyl)-β,-δ-hydroxy-5-(b) (4)-3-phenyl-4-[(phenylamino)-carbonyl]-,calcium salt (2:1),[*R*-(*R**,*R**)]-

Reference ID: 3052066



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20069	II	Teva		1	Adequate IR	11/28/2011	Reviewed by H. Li
See Section 26	III	See Section 26	(b) (4)	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		

Reference ID: 3052066

EES	Acceptable	2/23/2011	7/5/2011
Methods Validation	N/A		
Labeling	Acceptable	8/16/2011	T. Vu
Bioequivalence	Acceptable	8/19/2008	S. Dandamudi
EA	Adequate	Rev #1	
Radiopharmaceutical	N/A		

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: 3052066

The Chemistry Review for ANDA 078773

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol. The DS exhibit many polymorphic forms. The manufacturer for this ANDA product states that their drug substance (DS) is (b) (4) whereas the Pfizer's Lipitor is manufactured using (b) (4). The DS is preserved in well closed containers, at a temperature of (b) (4) packed with (b) (4).

Drug substance meets the IR identification test under the modified <197K> conditions to the current USP monograph. The results have been confirmed by the Agency laboratories at St. Louis, Missouri. Therefore the agency concludes that Teva's drug substance meets the USP monograph for the ID test per the API Sameness memorandum in DARRTS dated Nov 30, 2011.

There are references made to the USP pending monograph in the current review and earlier review cycles. However, referencing to pending monograph in the current and earlier review cycles has no impact on the satisfactory outcome for the drug substance per addendum darrts dated Nov 30, 2011.

Reference ID: 3052066

Drug Product:
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: colloidal silicon dioxide; crospovidone; hypromellose; lactose monohydrate; magnesium carbonate; magnesium stearate; polydextrose; polyethylene glycol; titanium dioxide. The API loading in the DP is (b) (4)%. All ingredients in the DP are (b) (4). The DP is manufactured by (b) (4) (b) (4)

Atorvastatin calcium is supplied as follows:

10 mg tablets :White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet; packed in bottles of 30 count.

20 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet, packed in bottles of 30 count.

40 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet, packed in bottles of 30 count.

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet; packed in bottles of 30 ct.

The firm withdraws the (b) (4) proposed previously to this application in the fourth review cycle. The firm withdrew the (b) (4) bottle for 10, 20 and 40 mg strengths in the AM dated 4/22/2011 due to stability issues.

The firm further withdrew all other (b) (4) packages in AM dated 8/4/2011.

The expiry date for the drug product is proposed for 18 month per AM dated 11/17/2011.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

B. Description of How the Drug Product is Intended to be Used

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium. The maximum daily dose of Atorvastatin calcium is 80 mg.

Based on ICH Q3A, for DS, Identification threshold is 0.10%; Qualification threshold is 0.15%. Based on ICH Q3B, for DP, Identification threshold: 0.2%; Qualification threshold: (b) (4)%.

Reference ID: 3052066

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.

Reference ID: 3052066

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/s/

HAITAO LI
11/30/2011

LAXMA R NAGAVELLI
11/30/2011

LEIGH A SEARS
11/30/2011

Addendum

ANDA 078773 - Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, 80 mg
Teva Pharmaceuticals USA

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
11/30/2011

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: 3047016

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: 3047016

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: 3047016

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: 3047016

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/s/

JAMES F ALLGIRE
11/18/2011

ANDA 078773

Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg

Teva Pharmaceuticals USA

Haitao Li, Ph.D.
Chemistry Division III

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22. SYNTHESIS: 17

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A. Drug Substance(s): 18

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26. CONTAINER: 25

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29. STABILITY: 34

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Reference ID: 2979791

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35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: ...35

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**Error! Bookmark not defined.**

Reference ID: 2979791

Chemistry Review Data Sheet

1. ANDA 078773

2. REVIEW #5

3. REVIEW DATE: 6/30/2010

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 29, 2006
Amendment*	March 12, 2008
Amendment	February 15, 2010
Amendment	8/18/2010
Amendment	8/24/2010
Amendment	2/18/2011
Amendment (Telephone Deficiency)	4/22/2011

* The original submission is for 80 mg strength only. This gratuitous amendment is for 10, 20 and 40 mg strength. However, all the amended strengths are based on deficient specifications, therefore this amendment was not reviewed. Updated information for all strengths was provided in the subsequent amendment dated Feb 15, 2010.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	6/20/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Telephone: (215) 591-3000

Reference ID: 2979791

Fax: (215) 591-8812

Representative: Philip Erickson, R. Ph., Senior Director, Regulatory Affairs
Telephone: (215) 591-3141
Fax: (215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Teva Pharmaceuticals USA proposed ANDA for Atorvastatin Calcium Tablets, 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.
b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, , 22nd Edition (2006), the RLD is covered by 5 patents.

	Paragraph III certification	
US patent no.	Expiration date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	November 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Teva Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of these patents and their associated pediatric exlusivities.

c. Exclusivity statement is provided (p. 13).

I-350	Expires on October 18, 2005
PED	Expires on April 18, 2006
I-471	Expires on September 21, 2008
M-36	Expires on July 30, 2007
I-434	Expires on July 30, 2007

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

Reference ID: 2979791

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20mg, 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

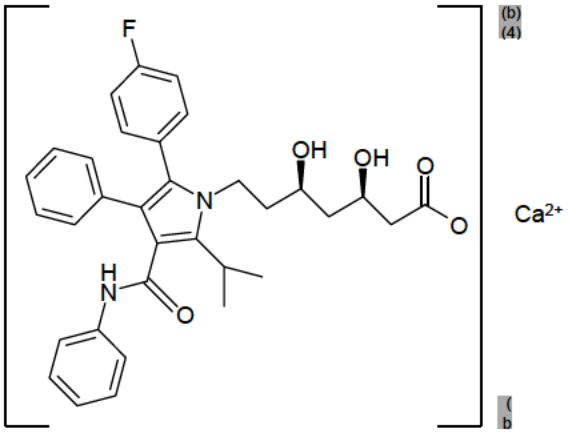
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atorvastatin Calcium, $(C_{33}H_{34}FN_2O_5)_2Ca$, CAS 134523-03-8
Atorvastatin, CAS 134523-00-5

(b) (4) = 1155.3(b) (4), (b) (4)

1*H*-Pyrrole-heptanoic acid, 2-(4-flourophenyl)-β,-δ-hydroxy-5-(b) (4)-3-phenyl-4-[(phenylamino)-carbonyl]-,calcium salt (2:1),[*R*-(*R**,*R**)]-



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20069	II	Teva		1	Inadequate	5/9/2011	Reviewed by H. Li
See Section 26	III	See Section 26	(b) (4)	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		

Reference ID: 2979791

EES	Acceptable	2/23/2011	7/5/2011
Methods Validation	N/A		
Labeling	Acceptable	3/8/2011	T. Vu
Bioequivalence	Acceptable	8/19/2008	S. Dandamudi
EA	Adequate	Rev #1	
Radiopharmaceutical	N/A		

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: 2979791

The Chemistry Review for ANDA 078773

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (NA Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their DS is (b) (4) The firm that manufactures the CDER approved product refers the polymorph as (b) (4) form.

Drug Product:
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: colloidal silicon dioxide; crospovidone; hypromellose; lactose monohydrate; magnesium carbonate; magnesium stearate; polydextrose; polyethylene glycol; titanium dioxide. The API loading in the DP is (b) (4)%. All ingredients in the DP are (b) (4). The DP is manufactured by (b) (4) (b) (4).

Reference ID: 2979791

Atorvastatin calcium is supplied as follows:

10 mg tablets :White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet; packed in bottles of 30, (b) (4) .

20 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet, packed in bottles of 30, (b) (4)

40 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet, packed in bottles of 30, (b) (4) .

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet; packed in bottles of 30, (b) (4)

The firm withdraws the (b) (4) proposed previously to this application in the fourth review cycle.

The firm withdrew the (b) (4) bottle for 10, 20 and 40 mg strengths in the AM dated 4/22/2011 due to stability issues.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

B. Description of How the Drug Product is Intended to be Used

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium. The maximum daily dose of Atorvastatin calcium is 80 mg.

Based on ICH Q3A, for DS, Identification threshold is 0.10%; Qualification threshold is 0.15%.

Based on ICH Q3B, for DP, Identification threshold: 0.2%; Qualification threshold: (b) (4) %

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies (NA Minor).

Reference ID: 2979791
29 PAGES 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/

HAITAO LI
07/27/2011

LEIGH A SEARS
07/27/2011

LAXMA R NAGAVELLI
07/27/2011

ANDA 078773

Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg

Teva Pharmaceuticals USA

Haitao Li, Ph.D.
Chemistry Division III

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A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation ..... 9.

Chemistry Assessment **10**

20. COMPONENTS AND COMPOSITION: 31

21. FACILITIES: 34

22. SYNTHESIS: 34

23. RAW MATERIAL CONTROLS 35

A. Drug Substance(s): 35

B. Inactive Ingredients: 39

24. OTHER FIRM(s): 39

25. MANUFACTURING AND PROCESSING: 39

26. CONTAINER: 42

27. PACKAGING AND LABELING 43

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM) 43

29. STABILITY: 51

30. MICROBIOLOGY 52

Reference ID: 2958052

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS 52

32. LABELING.....52

33. ESTABLISHMENT INSPECTION 52

34. BIOEQUIVALENCE 52

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: ...53

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 54

Reference ID: 2958052

Chemistry Review Data Sheet

1. ANDA 078773

2. REVIEW #4

3. REVIEW DATE: 3/7/2011, review of Telephone Deficiency on 5/4/11

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 29, 2006
Amendment*	March 12, 2008
Amendment	February 15, 2010
Amendment	8/18/2010
Amendment	8/24/2010

* The original submission is for 80 mg strength only. This gratuitous amendment is for 10, 20 and 40 mg strength. However, all the amended strengths are based on deficient specifications, therefore this amendment was not reviewed. Updated information for all strengths was provided in the subsequent amendment dated Feb 15, 2010.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	2/18/2011
Amendment (Telephone Deficiency)	4/22/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Telephone: (215) 591-3000

Fax: (215) 591-8812

Reference ID: 2958052

Representative:	Philip Erickson, R. Ph., Senior Director, Regulatory Affairs
Telephone:	(215) 591-3141
Fax:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Teva Pharmaceuticals USA proposed ANDA for Atorvastatin Calcium Tablets, 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.
b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, , 22nd Edition (2006), the RLD is covered by 5 patents.

	Paragraph III certification	
US patent no.	Expiration date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	November 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Teva Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of these patents and their associated pediatric exlusivities.

c. Exclusivity statement is provided (p. 13).

I-350	Expires on October 18, 2005
PED	Expires on April 18, 2006
I-471	Expires on September 21, 2008
M-36	Expires on July 30, 2007
I-434	Expires on July 30, 2007

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

Reference ID: 2958052

12. STRENGTH/POTENCY: 10 mg, 20mg, 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

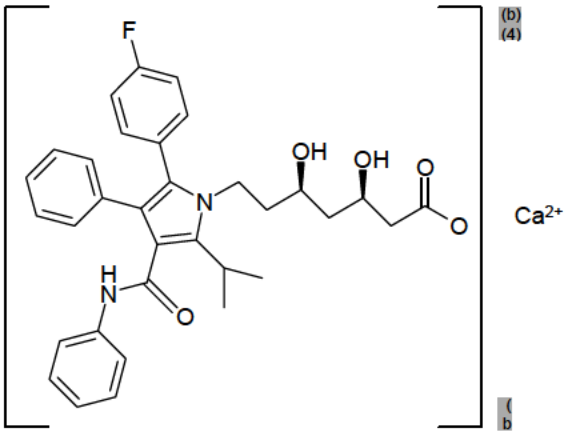
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atorvastatin Calcium, $(C_{33}H_{34}FN_2O_5)_2Ca$, CAS 134523-03-8
Atorvastatin, CAS 134523-00-5

(b) (4) = 1155.3(b), (b) (4)

1*H*-Pyrrole-heptanoic acid, 2-(4-flourophenyl)-β,-δ-hydroxy-5-(b) (4)-3-phenyl-4-[(phenylamino)-carbonyl]-,calcium salt (2:1),[*R*-(*R**,*R**)]-



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20069	II	Teva		1	Inadequate	5/9/2011	Reviewed by H. Li
See Section 26	III	See Section 26	(b) (4)	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Withhold	2/23/2011	
Methods Validation	N/A		
Labeling	Acceptable	3/8/2011	T. Vu
Bioequivalence	Acceptable	8/19/2008	S. Dandamudi
EA	Adequate	Rev #1	
Radiopharmaceutical	N/A		

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: 2958052

The Chemistry Review for ANDA 078773

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor), qualification of one of the epoxides is required.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their DS is (b) (4) The firm that manufactures the CDER approved product refers the polymorph as (b) (4) form.

Drug Product:
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: colloidal silicon dioxide; crospovidone; hypromellose; lactose monohydrate; magnesium carbonate; magnesium stearate; polydextrose; polyethylene glycol; titanium dioxide. The API loading in the DP is (b) (4) %. All ingredients in the DP are (b) (4) . The DP is manufactured by (b) (4) (b) (4)

Reference ID: 2958052

Atorvastatin calcium is supplied as follows:

10 mg tablets :White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet; packed in bottles of 30, (b) (4)

20 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet, packed in bottles of 30, (b) (4)

40 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet, packed in bottles of 30, (b) (4)

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet; packed in bottles of 30, (b) (4)

The firm withdraws the (b) (4) proposed previously to this application in the fourth review cycle.

The firm withdrew the (b) (4) bottle for 10, 20 and 40 mg strengths in the AM dated 4/22/2011 due to stability issues.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

B. Description of How the Drug Product is Intended to be Used

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium. The maximum daily dose of Atorvastatin calcium is 80 mg.

Based on ICH Q3A, for DS, Identification threshold is 0.10%; Qualification threshold is 0.15%.

Based on ICH Q3B, for DP, Identification threshold: 0.2%; Qualification threshold: (b) (4)%

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies (NA Minor).

Reference ID: 2958052
46 PAGES 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/

HAITAO LI
06/08/2011

LEIGH A SEARS
06/08/2011

MOHAMMED K AHMED
06/09/2011

ANDA 078773

Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg

Teva Pharmaceuticals USA

Haitao Li, Ph.D.
Chemistry Division III

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A. Recommendation and Conclusion on Approvability 9

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 9

II. Summary of Chemistry Assessments 9

A. Description of the Drug Product(s) and Drug Substance(s) 9

B. Description of How the Drug Product is Intended to be Used 10

C. Basis for Approvability or Not-Approval Recommendation ..... 10.

Chemistry Assessment **11**

20. COMPONENTS AND COMPOSITION: 29

21. FACILITIES: 32

22. SYNTHESIS: 32

23. RAW MATERIAL CONTROLS 32

A. Drug Substance(s): 32

B. Inactive Ingredients: 37

24. OTHER FIRM(s): 37

25. MANUFACTURING AND PROCESSING: 37

26. CONTAINER: 39

27. PACKAGING AND LABELING 41

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM) 41

29. STABILITY: 47

30. MICROBIOLOGY 48

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS 48

32. LABELING.....48

33. ESTABLISHMENT INSPECTION 49

34. BIOEQUIVALENCE 49

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: ...49

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 50

Chemistry Review Data Sheet

1. ANDA 078773

2. REVIEW #3

3. REVIEW DATE: 10/12/2010

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 29, 2006
Amendment*	March 12, 2008
Amendment	February 15, 2010

* The original submission is for 80 mg strength only. This gratuitous amendment is for 10, 20 and 40 mg strength. However, all the amended strengths are based on deficient specifications, therefore this amendment was not reviewed. Updated information for all strengths was provided in the subsequent amendment dated Feb 15, 2010.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	8/18/2010
Amendment	8/24/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Telephone: (215) 591-3000

Fax: (215) 591-8812

Chemistry Review Data Sheet

Representative:	Philip Erickson, R. Ph., Senior Director, Regulatory Affairs
Telephone:	(215) 591-3141
Fax:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Teva Pharmaceuticals USA proposed ANDA for Atorvastatin Calcium Tablets, 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.
b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, , 22nd Edition (2006), the RLD is covered by 5 patents.

Paragraph III certification

US patent no.	Expiration date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	Novemeber 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Teva Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of these patents and their associated pediatric exlusivities.

c. Exclusivity statement is provided (p. 13).

I-350	Expires on October 18, 2005
PED	Expires on April 18, 2006
I-471	Expires on September 21, 2008
M-36	Expires on July 30, 2007
I-434	Expires on July 30, 2007

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20mg, 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

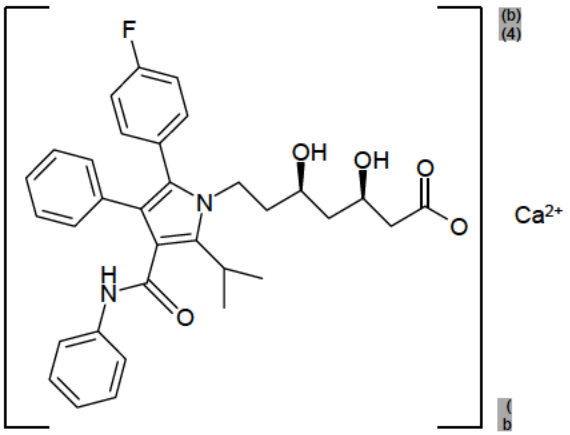
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atorvastatin Calcium, $(C_{33}H_{34}FN_2O_5)_2Ca$, CAS 134523-03-8
Atorvastatin, CAS 134523-00-5

(b) (4) = 1155.3(b) (4), (b) (4)

1*H*-Pyrrole-heptanoic acid, 2-(4-flourophenyl)-β,-δ-hydroxy-5-(b) (4)-3-phenyl-4-[(phenylamino)-carbonyl]-,calcium salt (2:1),[*R*-(*R**,*R**)]-



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20069	II	Teva		1	Inadequate	12/21/2010	Reviewed by H. Li
See Section 26	III	See Section 26	(b) (4)	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefor-e the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable[#]	04/18/2007	
Methods Validation	N/A		
Labeling	TA*	11/28/2008	T. Vu
Bioequivalence	Acceptable	8/19/2008	S. Dandamudi
EA	Adequate	Rev #1	
Radiopharmaceutical	N/A		

[#] New sites for the API manufacturer needs to be included in EES per recent API manufacturer's amendment.
* The packaging approved has been changed by the firm. The firm also added (b) (4) for each strengths in current amendment, this has been communicated to the labeling reviewer.

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 Chemistry Review for ANDA 078773

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their DS is (b) (4) The firm that manufactures the CDER approved product refers the polymorph as (b) (4) form.

Drug Product:
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: colloidal silicon dioxide; crospovidone; hypromellose; lactose monohydrate; magnesium carbonate; magnesium stearate; polydextrose; polyethylene glycol; titanium dioxide. All ingredients in the DP are (b) (4). The DP is manufactured by (b) (4).

Atorvastatin calcium is supplied as follows:

10 mg tablets :White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7310" on the other side of the tablet; packed in bottles of 30, (b) (4)

20 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7311" on the other side of the tablet, packed in bottles of 30, (b) (4)

40 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet, packed in bottles of 30, (b) (4)

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet; packed in bottles of 30, (b) (4)

A (b) (4) which integrates an (b) (4) has been proposed for all strengths of the DP.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

B. Description of How the Drug Product is Intended to be Used

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium. The maximum daily dose of Atorvastatin calcium is 80 mg.

Based on ICH Q3A, for DS, Identification threshold is 0.10%; Qualification threshold is 0.15%.
Based on ICH Q3B, for DP, Identification threshold: 0.2%; Qualification threshold: (b) (4)%

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies (NA Minor).

43 PAGES 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/

HAITAO LI
01/10/2011

LEIGH A SEARS
01/13/2011

LAXMA R NAGAVELLI
01/13/2011

ANDA 078773

Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg

Teva Pharmaceuticals USA

Haitao Li, Ph.D.
Chemistry Division III

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II. Summary of Chemistry Assessments 9

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C. Basis for Approvability or Not-Approval Recommendation ..... 10.

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20. COMPONENTS AND COMPOSITION: 36

21. FACILITIES: 38

22. SYNTHESIS: 38

23. RAW MATERIAL CONTROLS 38

A. Drug Substance(s): 38

B. Inactive Ingredients: 42

24. OTHER FIRM(s): 42

25. MANUFACTURING AND PROCESSING: 43

26. CONTAINER: 49

27. PACKAGING AND LABELING 50

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM) 50

29. STABILITY: 58

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Chemistry Review Data Sheet

1. ANDA 078773

2. REVIEW #2

3. REVIEW DATE: 03/19/2010

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	December 29, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment*	March 12, 2008
Amendment	February 15, 2010

* The original submission is for 80 mg strength only. This gratuitous amendment is for 10, 20 and 40 mg strength. However, all the amended strengths are based on deficient specifications, therefore this amendment was not reviewed. Updated information for all strengths was provided in the subsequent amendment (see below).

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Telephone: (215) 591-3000

Fax: (215) 591-8812

Representative:	Philip Erickson, R. Ph., Senior Director, Regulatory Affairs
Telephone:	(215) 591-3141

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Teva Pharmaceuticals USA proposed ANDA for Atorvastatin Calcium Tablets, 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.
b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, , 22nd Edition (2006), the RLD is covered by 5 patents.

	Paragraph III certification	
US patent no.	Expiration date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	Novemeber 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Teva Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of these patents and their associated pediatric exlusivities.

c. Exclusivity statement is provided (p. 13).

I-350	Expires on October 18, 2005
PED	Expires on April 18, 2006
I-471	Expires on September 21, 2008
M-36	Expires on July 30, 2007
I-434	Expires on July 30, 2007

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20mg, 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

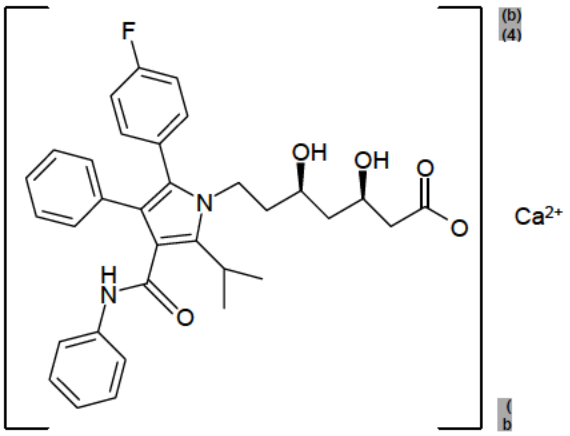
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atorvastatin Calcium, $(C_{33}H_{34}FN_2O_5)_2Ca$, CAS 134523-03-8
Atorvastatin, CAS 134523-00-5

(b) (4) = 1155.3(b) (4), (b) (4)

1*H*-Pyrrole-heptanoic acid, 2-(4-flourophenyl)-β,-δ-hydroxy-5-(b) (4)-3-phenyl-4-[(phenylamino)-carbonyl]-,calcium salt (2:1),[*R*-(*R**,*R**)]-



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20069	II	Teva		1	Inadequate	03/18/2010	Reviewed by H. Li
See Section 26	III	See Section 26	(b) (4)	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefor-e the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	04/18/2007	
Methods Validation	N/A		
Labeling	TA*	11/28/2008	T. Vu
Bioequivalence	Acceptable	8/19/2008	S. Dandamudi
EA	Adequate	Rev #1	
Radiopharmaceutical	N/A		
* The packaging approved has been changed by the firm. The firm also added (b) (4) for each strengths in current amendment, this has been communicated to the labeling reviewer.			

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 Chemistry Review for ANDA 078773

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their DS is (b) (4) The firm that manufactures the CDER approved product refers the polymorph as (b) (4) form.

Drug Product:
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: colloidal silicon dioxide; crospovidone; hypromellose; lactose monohydrate; magnesium carbonate; magnesium stearate; polydextrose; polyethylene glycol; titanium dioxide. All ingredients in the DP are (b) (4).

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40 mg tablets: White to off white, capsule shaped, film coated tablet, debossed with "93" on one side and "7312" on the other side of the tablet, packed in bottles of 30, (b) (4) .

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet; packed in bottles of 30, (b) (4)

A (b) (4) which integrates an (b) (4) has been proposed for all strengths of the DP.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

B. Description of How the Drug Product is Intended to be Used

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium. The maximum daily dose of Atorvastatin calcium is 80 mg.

Based on ICH Q3A, for DS, Identification threshold is 0.10%; Qualification threshold is 0.15%.
Based on ICH Q3B, for DP, Identification threshold: 0.2%; Qualification threshold: (b) (4)%

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78773	ORIG-1	TEVA PHARMACEUTICALS USA	ATORVASTATIN CALCIUM

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/s/

HAITAO LI
05/14/2010

LEIGH A BRADFORD
05/14/2010

ROBERT L ISER
05/17/2010

ANDA 78-773

Atorvastatin Calcium Tablets, 80 mg (Base)

Teva Pharmaceuticals USA

Wenlei Jiang, Ph.D.
Chemistry Division III

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II. Summary of Chemistry Assessments 9

A. Description of the Drug Product(s) and Drug Substance(s) 9

B. Description of How the Drug Product is Intended to be Used 10

C. Basis for Approvability or Not-Approval Recommendation ..... 10.

Chemistry Assessment **11**

20. COMPONENTS AND COMPOSITION: 11

21. FACILITIES: 13

22. SYNTHESIS: 13

23. RAW MATERIAL CONTROLS 14

A. Drug Substance(s): 14

B. Inactive Ingredients: 21

24. OTHER FIRM(s): 21

25. MANUFACTURING AND PROCESSING: 22

26. CONTAINER: 24

27. PACKAGING AND LABELING 25

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM) 26

29. STABILITY: 36

30. MICROBIOLOGY 38

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS 38

32. LABELING.....38

33. ESTABLISHMENT INSPECTION 38

34. BIOEQUIVALENCE 38

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: ...38

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 39

Chemistry Review Data Sheet

1. ANDA 78-773

2. REVIEW #1

3. REVIEW DATE: 06/08/2007

4. REVIEWER: Wenlei Jiang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	December 29, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Address: 1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Telephone: (215) 591-3000

Fax: (215) 591-8812

Chemistry Review Data Sheet

Representative: Philip Erickson, R. Ph., Senior Director, Regulatory Affairs

Telephone: (215) 591-3141

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Teva Pharmaceuticals USA proposed ANDA for Atorvastatin Calcium Tablets, 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.
b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, , 22nd Edition (2006), the RLD is covered by 5 patents.

	Paragraph III certification	
US patent no.	Expiration date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	Novemeber 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Teva Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of these patents and their associated pediatric exlusivities.

c. Exclusivity statement is provided (p. 13).

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PED	Expires on April 18, 2006
I-471	Expires on September 21, 2008
M-36	Expires on July 30, 2007
I-434	Expires on July 30, 2007

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 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

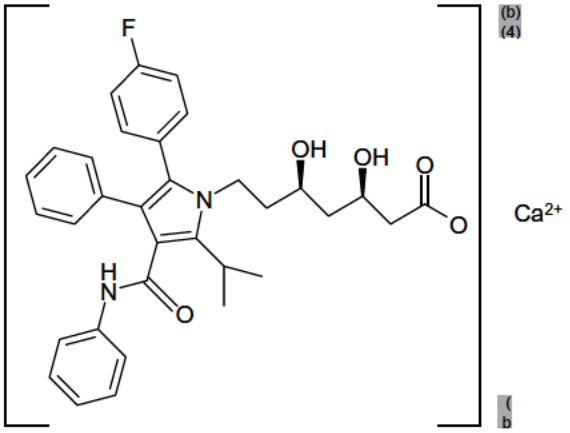
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Atorvastatin Calcium, $(C_{33}H_{34}FN_2O_5)_2Ca$, CAS 134523-03-8
Atorvastatin, CAS 134523-00-5

(b) (4) = 1155.3(b) (4), (b) (4)

1*H*-Pyrrole-heptanoic acid, 2-(4-flourophenyl)-β,-δ-hydroxy-5-(b) (4)-3-phenyl-4-[(phenylamino)-carbonyl]-,calcium salt (2:1),[*R*-(*R**,*R**)]-



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
20069	II	Teva		1	Inadequate	06/18/07	
See Section 26	III	See Section 26	(b) (4)	4			

[1] Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
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3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefor-e the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		-
EES	Acceptable	04/18/2007	
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

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 Chemistry Review for ANDA 78-773

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin calcium is a white to off-white powder that is insoluble in aqueous solutions of pH 4 and below, very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Drug Product:
Atorvastatin calcium tablets for oral administration contain 80 mg atorvastatin and the following inactive ingredients: colloidal silicon dioxide; crospovidone; hypromellose; lactose monohydrate; magnesium carbonate; magnesium stearate; polydextrose; polyethylene glycol; titanium dioxide.

Atorvastatin calcium is supplied as follows:

80 mg tablets – white to off-white, capsule-shaped, film-coated tablets debossed with "93" on one side and "7313" on the other side of the tablet in bottles of (b) (4)

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

B. Description of How the Drug Product is Intended to be Used

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium. The maximum daily dose of atorvastatin calcium is 80 mg.

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies and pending bioequivalence review. EES is pending.

32 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Weniel Jiang
7/26/2007 04:08:19 PM
CHEMIST

Jeanne Skanchy
7/30/2007 06:02:16 PM
CSO

Hossein Khorshidi
8/1/2007 02:10:47 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	78-773
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	EQ 10 mg, 20 mg, 40 mg and 80 mg Base
Applicant Name	TEVA Pharmaceuticals USA
Address	1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, Senior Director, Regulatory Affairs
Contact's Telephone Number	215-591-3141
Contact's Fax Number	215-591-8812
Original Submission Date(s)	December 29, 2006 (Original Application) September 14, 2007 (Amendment)
Submission Date(s) of Amendment(s) Under Review	March 12, 2008
Reviewer	Suman Dandamudi, Ph.D.
Outcome Decision	**ACCEPTABLE**

I. Executive Summary

TEVA Pharmaceuticals submitted an amendment to the original application for its Atorvastatin Calcium Tablets, EQ 80 mg Base, to propose addition of the new strengths, EQ 10 mg, 20 mg and 40 mg Base. In the current amendment, the firm requests for the waivers of the in vivo bioavailability study requirements for the 10 mg, 20 mg and 40 mg strengths. The firm submitted the formulations and the comparative dissolution testing results of all the lower strengths, EQ 10 mg, 20 mg and 40 mg Base. The dissolution testing is acceptable. The formulations of the Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg and 40 mg Base, are proportionally similar to that of the Atorvastatin Calcium Tablets, EQ 80 mg Base. The waiver requests for *in vivo* BE study requirements of Atorvastatin Calcium Tablets for the EQ 10 mg, 20 mg and 40 mg Base strengths are granted and the amendment is **acceptable.**

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D. In vitro Dissolution 3
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ii. Dissolution data....7
VI. Outcome Page 12

III. Background

1. The firm submitted its original application on December 29, 2006. DBE had done a "dissolution only" review on this ANDA (DFS N 078773 N 000 29-Dec-2006). The firm conducted its dissolution testing using the FDA- recommended dissolution method:

   Medium: 900 mL of 0.05M Phosphate buffer, pH 6.8
   Apparatus: USP apparatus II (Paddle)
   Speed: 75 RPM

   The firm's dissolution testing was found incomplete. The proposed specification of "NLT (b)(4)% (Q) in (b)(4) min" was not acceptable. DBE has requested the firm to acknowledge the FDA-recommended specification of "NLT (b)(4)% (Q) in 15 minutes".

2. On Sep 14, 2007, the firm acknowledged the FDA-recommended dissolution method and specification.

3. The firm, in its original application, also submitted the fasting and fed bioequivalence studies comparing its Atorvastatin Calcium Tablets, EQ 80 mg Base, to the Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg. The BE studies were found acceptable (DFS N 078773 N 000 29-Dec-2006 and N 078773 N 000 AB 14-Sep-2007).

4. In the current amendment, the firm submitted its dissolution comparison data for lower strengths EQ 10 mg, 20 mg and 40 mg Base, and requested for waivers of in vivo bioavailability studies for these strengths.

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See the review of the original submission DFS N 078773 N 000 29-Dec-2006 and N 078773 N 000 AB 14-Sep-2007.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	3
Waiver requests	Yes	3
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Formulation

Location in appendix	Section V (i), Formulation data
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

D. In vitro Dissolution

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
DBE-recommended specifications	NLT (b)(4)% (Q) in 15 minutes
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 dissolved
Is method acceptable?	**ACCEPTABLE**
If not then why?	

E. Waiver Requests

Strengths for which waivers are requested	EQ 10 mg, 20 mg and 40 mg Base
Proportional to strength tested *in vivo*?	Yes

Is dissolution acceptable?	Yes
Waivers granted?	**Yes**
If not then why?	

F. Deficiency Comments

None.

G. Recommendations

The Division of Bioequivalence (DBE) agrees that the information submitted by Teva Pharmaceuticals demonstrates that its Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg and 40 mg Base, meets the requirements of Section 21 CFR § 320.22 (d) (2). The DBE recommends the waivers of in vivo bioequivalence study requirements for the lower strengths of Teva's Atorvastatin Calcium Tablets to be granted based on (a) an acceptable bioequivalence study on the EQ 80 mg Base strength, (b) acceptable dissolution testing of the EQ 10 mg, 20 mg, 40 mg and 80 mg Base strengths, and (c) proportional similarity in the formulations of the EQ 10 mg, 20 mg, 40 mg and 80 mg Base strengths.

V. Appendix

i. Formulation data

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet			
	10 mg	20 mg	40 mg	80 mg †	10 mg	20 mg	40 mg	80 mg †
(b) (4)	(b) (4)							
Atorvastatin Calcium (b) (4)								
Lactose Monohydrate (b) (4)								
Crospovidone (b) (4)								
Magnesium Carbonate (b) (4)								
Colloidal Silicon Dioxide (b) (4)								
Magnesium Stearate, (b) (4)								
(b) (4)								
(b) (4)								
(b) (4)								
Total								

† Bio-strength from the original ANDA for Atorvastatin Calcium EQ 80 mg Base

1 [redacted] is equivalent to 10, 20, 40 and 80 mg of Atorvastatin respectively.

* [redacted]

[redacted]

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet			
	10 mg	20 mg	40 mg	80 mg †	10 mg	20 mg	40 mg	80 mg †
Hypromellose [redacted]	[redacted]							
Polydextrose [redacted]								
Titanium Dioxide [redacted]								
Polyethylene Glycol [redacted]								
Total								

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

Comments on the drug product formulation:	1. The amounts of all inactive ingredients in the tablet are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products. 2. The formulation of the 10 mg, 20 mg and 40 mg strength products are proportionally similar to the formulation of the 80 mg biostudy strength product. 3. The formulations are acceptable.

ii. Dissolution data

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate Buffer
	Volume:	900 mL
	Temperature:	37.0° C ± 0.5° C
Firm's Proposed Specifications	NLT (b) (4)% (Q) at 15 minutes	

Study Ref No.	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	Study Report Location
CDP 1620/01	Test Product Atorvastatin Tablets Lot # K-38319	EQ 10 mg Base Tablet	12	Mean	97	99	99	99	Unsolicited amendment Addition of 10 mg, 20 mg and 40 mg strengths Section VI.3
				Range	(b) (4)				
				%CV	2.3	1.1	1.1	1.1	
	Reference Product Lipitor ® Tablets Lot # 10605V	10 mg Tablet	12	Mean	104	103	104	103	
				Range	(b) (4)				
				%CV	1.6	1.2	1.1	1.1	
CDP 1621/01	Test Product Atorvastatin Tablets	EQ 20 mg Base Tablet	12	Mean	95	97	97	97	
				Range	(b) (4)				

	Lot # K-38320			%CV	3.6	1.6	1.3	1.1	
	Reference Product Lipitor ® Tablets Lot # 0508055	20 mg Tablet	12	Mean	100	99	99	99	
				Range	(b) (4)				
				%CV	1.1	0.6	0.8	0.7	
CDP 1622/01	Test Product Atorvastatin Tablets Lot # K-38321	EQ 40 mg Base Tablet	12	Mean	92	94	95	94	
				Range	(b) (4)				
				%CV	3.0	1.8	1.6	1.6	
	Reference Product Lipitor ® Tablets Lot # 0324075	40 mg Tablet	12	Mean	98	99	99	99	
				Range	(b) (4)				
				%CV	1.1	0.6	0.5	0.7	
CDP 1485/02	Test Product Atorvastatin Tablets Lot # K-37191	EQ 80 mg Base Tablet	12	Mean	93	95	95	95	Original ANDA Pg 87-89
				Range	(b) (4)				
				%CV	2.7	2.3	2.3	2.3	
	Reference Product Lipitor ® Tablets Lot # 07625V	80 mg Tablet	12	Mean	94	97	94	95	
				Range	(b) (4)				
				%CV	3.2	3.2	3.1	2.4	

Comparative Dissolution profile of Atorvastatin Calcium Tablets, EQ 10 mg Base



Comparative Dissolution profile of Atorvastatin Calcium Tablets, EQ 20 mg Base



Comparative Dissolution profile of Atorvastatin Calcium Tablets, EQ 40 mg Base



Comments on Dissolution testing data

The firm conducted its dissolution testing, using the FDA-recommended method for its Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg Base comparing them with Pfizer's Lipitor® Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg Base, respectively. The dissolution data for all the strengths of test product met the FDA-recommended specification of "NLT (b) (4) % (Q) in 15 minutes" at S1 level.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-773

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, EQ 10 mg, 20 mg, 40 mg and 80 mg Base

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page and has no further question at this time.

We acknowledge that you will conduct dissolution testing using the following FDA-recommended dissolution method and specification:

The dissolution testing should be conducted in 900 mL of 0.05M Phosphate buffer, pH 6.8 at 37°C ± 0.5°C using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specification:

NLT (b)(4)% (Q) of Atorvastatin 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

VI. Outcome Page

ANDA: 78-773

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5971	3/12/2008	Other	Dissolution Waiver	1	1
5971	3/12/2008	Other	Dissolution Waiver	1	1
5971	3/12/2008	Other	Dissolution Waiver	1	1
				Bean Total:	3

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

/s/

Suman Dandamudi
8/18/2008 03:45:58 PM
BIOPHARMACEUTICS

Bing Li
8/18/2008 04:02:51 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
8/19/2008 08:35:39 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-773
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	EQ 80 mg Base
Applicant Name	TEVA Pharmaceuticals USA
Address	1090 Horsham Road, PO Box 1090, North Wales, PA 19454
Applicant's Point of Contact	Philip Erickson, R.Ph., Senior Director, Regulatory Affairs
Contact's Telephone Number	215-591-3141
Contact's Fax Number	215-591-8812
Original Submission Date(s)	29 Dec 2006
Submission Date(s) of Amendment(s) Under Review	14 Sept 2007
Reviewer	April C. Braddy, Ph.D.
Study Number (s)	R06-1030
Study Type (s)	Fasting (STF)
Strength (s)	EQ 80 mg Base
Clinical Site	PRACS Institute, Ltd.
Clinical Site Address	625 DeMers Avenue, East Grand Forks, MN 56721
Analytical Site	(b) (4)
Analytical Site Address	
Study Number (s)	R06-1031
Study Type (s)	Fed (STP)
Strength (s)	EQ 80 mg Base
Clinical Site	PRACS Institute, Ltd.
Clinical Site Address	4801 Amber Valley Fargo, ND 58104
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**ACCEPTABLE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Atorvastatin Calcium Tables, EQ 80 mg Base to the corresponding reference product, Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg Base. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

1 x EQ 80 mg Base Tablets Fasting Bioequivalence Study No. R06-1030, N=78 (Male=17 and Female=61) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	163.58	150.25	1.09	104.51-	113.42
AUC∞ (ng·hr/mL)	166.44	153.05	1.09	104.51	113.16
Cmax (ng/mL)	38.60	34.62	1.12	101.65	122.34

	Ortho-Hydroxyatrovastatin			Para-Hydroxyatorvastatin		
Parameter (units)	**Test**	**Reference**	**Ratio**	**Test**	**Reference**	**Ratio**
AUC0-t (ng·hr/mL)	215.33	201.04	1.07	29.57	25.78	1.15
AUC∞ (ng·hr/mL)	219.14	204.69	1.07	31.25	27.52	1.14
Cmax (ng/mL)	31.50	29.99	1.05	1.56	1.13	**1.38**

1 x EQ 80 mg Base Tablets Fed Bioequivalence Study No. R06-1031, N=77 (Male=71 and Female=6) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Atorvastatin					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	154.27	155.05	0.99	96.08	103.03
AUC∞ (ng·hr/mL)	158.08	158.80	1.00	96.18	103.03
Cmax (ng/mL)	29.22	31.52	0.93	83.43	103.01

	Ortho-Hydroxyatrovastatin			Para-Hydroxyatorvastatin		
Parameter (units)	**Test**	**Reference**	**Ratio**	**Test**	**Reference**	**Ratio**
AUC0-t (ng·hr/mL)	170.21	169.79	1.00	27.62	27.38	1.01
AUC∞ (ng·hr/mL)	173.87	174.25	1.00	29.87	29.34	1.02
Cmax (ng/mL)	21.62	23.01	0.94	1.33	1.31	1.02

In the fasting BE study, the point estimate for the active metabolite, para-hydroxyatorvastatin did not meet the BE limits (0.80 to 1.25) for the C_{max}. This is due to the high intrasubject variability for C_{max}, the low plasma levels of the metabolite as compared to the parent, atorvastatin and the other active metabolite, ortho-hydroxyatorvastatin, along with the fact that the study was not powered to show

bioequivalence for a metabolite present at low concentrations with high variability in bioequivalence parameters. Therefore, the Division of Bioequivalence bases bioequivalence determination on the 90% CIs data of AUC_{0-t}, AUC_{∞} and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolite, ortho-hydroxyatorvastatin, and concludes that the parahydroxyatorvastatin PK results are acceptable.

The firm has conducted acceptable comparative dissolution testing on its test product using the FDA-recommended dissolution method, (Division of System Files v 2.0. Bioequivalence Dissolution Review N 078773 N 000 29-Dec-2006.). On 14 Sep 2007, the firm acknowledged the FDA-recommended dissolution method and specification.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is acceptable with no deficiencies.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Atorvastatin Calcium Tablets, EQ 80 mg Base
Reference Product	Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg Base
RLD Manufacturer	Pfizer
NDA No.	020702
RLD Approval Date	07 Apr 2000
Indication	*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 *Hypercholesterolemia* It 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

3.2 PK/PD Information[1]

Bioavailability	Atorvastatin is rapidly absorbed after oral administration. The absolute bioavailability of atorvastatin (parent) is approximately 14%. Low systemic availability (~ 30%) is attributed to presystemic clearance in the gastrointestinal mucosa and/or hepatic first-pass metabolism.
Food Effect	C_{max} decreases by 25% AUC decreases by 9%
Tmax	1 to 2 hrs
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 coadministration

[1] 1.External database: CDER Drugs@ FDA database. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Search: Lipitor. Label approved: 26 Sep 2007. Last accessed: 04 Feb 2008.
2. Online-Physicians' Desk Reference Electronic Library™. (2008). http://www.thomsonhc.com. Thomson Micromedex: Keyword Search: Lipitor. Last accessed: 13 Feb 2008.

	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. 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.
Half-life	Atorvastatin: 14 hrs
Drug Specific Issues (if any)	**WARNINGS** **Liver Dysfunction** 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 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 function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, 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. 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). **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.** Uncomplicated myalgia has been reported in atorvastatin- treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, 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, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering 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. 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. **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 (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

3.3 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:	EQ 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Parent drug: Atorvastatin Active metabolites: Ortho- and parahydroxylated atorvastatin
Bioequivalence based on:	90% CI: $LAUC_T$, $LAUC_I$, LC_{max} – **only** Atorvastatin
Waiver request of in-vivo testing:	EQ 10 mg Base, EQ 20 mg Base, and EQ 40 mg Base
Source of most recent recommendations:	Controlled Correspondence # 07-0036, letter date: 03 Apr 2007. \\cdsnas\OGDS6\CONTROLS\2007-docs\07-0036.pdf, reference protocol # 01-205.
Summary of OGD or DBE History (for details, see Appendix 4.4):	According to the Electronic Orange Book (current through December 2007), there are currently no approved generic products for Atorvastatin Calcium Tablets on the market. To date, the DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets:

ANDA	Firm	Submission Date
76-477	Ranbaxy	19 Aug 2002
77-575	Lek	11 Feb 2005

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	1
Waiver requests	No	0
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Report location	Section 7.0, Page(s):
Analyte (Drug/Metabolite 1/Metabolite 2)	Atorvastatin/4-hydroxyatorvastatin/2-hydroxyatorvastatin (pg 1351) of the Addendum to the Method Validation
Internal standard (IS)	(b) (4) (pg 1351) of the Addendum to the Method Validation
Method description	Solid Phase Extraction Procedure (pg 1353 & 1354) of the Addendum to the Method Validation Analytical Procedure (AP) Sheet included in Appendix A of the Second Addendum to the Method Validation AP LC/MS/MS 052.102
Limit of quantitation (ng/mL)	0.1000/0.02000/0.1000 (LLOQ) to 50.00/10.00/50.00 (ULOQ) (pg 1310) of the Second Addendum to the Method Validation
Average recovery of drug (%)	106/76.6/73.9 (pg 1431) of the Method Validation (b) (4)
Average recovery of IS (%)	83.1 (pg 1431) of the Method Validation (b) (4)
Standard curve concentrations (ng/mL)	0.1000/0.02000/0.1000, 0.2000/0.04000/0.2000, 0.5000/0.1000/0.5000, 1.000/0.2000/1.000, 2.000/0.4000/2.000, 5.000/1.000/5.000, 10.00/2.000/10.00, 20.00/4.000/20.00, 40.00/8.000/40.00 and 50.00/10.00/50.00 (pg 1310) of the Second Addendum to the Method Validation
QC concentrations (ng/mL)	0.3000/0.06000/0.3000 (LQC), 0.7500/0.1500/0.7500 (MQC-1), 3.750/0.7500/3.750 (MQC-2) and 37.50/7.500/37.50 (HQC) (pg 1310) of the Second Addendum to the Method Validation
QC Intraday precision range (%)	1.3 to 5.2/3.1 to 7.0/2.2 to 5.3 (pg 1312) of the Second Addendum to the Method Validation
QC Intraday accuracy range (%)	90.7 to 99.4/90.3 to 99.9/91.8 to 103 (pg 1312) of the Second Addendum to the Method Validation
QC Interday precision range (%)	4.5 to 6.5/6.9 to 7.3/5.3 to 8.0 (pg 1356) of the Addendum to the Method Validation
QC Interday accuracy range (%)	95.4 to 99.5/99.9 to 102/98.7 to 101 (pg 1356) of the Addendum to the Method Validation
Bench-top stability in biological matrix (hrs)	25 hours for drug and metabolites in human plasma at room temperature (pg 1434) of the Method Validation (b) (4)
Stock stability (days)	21 hours at room temperature for drug and metabolites (pg 1357) of the Addendum to the Method Validation 6 hours at room temperature for internal standard (pg 1433) of the Method Validation (b) (4) 78 days for drug and metabolite-2 and 85 days for metabolite-1 at 4°C ± 6°C (pg 1357 & 1358) of the Addendum to the Method Validation 34 days for internal standard at 4°C ± 6°C (pg 1357 & 1358) of the Addendum to the Method Validation Intermediate stock solution stability for drug and metabolites is 7 days at 4°C ± 6°C (pg 1358) of the Addendum to the Method Validation
Processed stability (hrs)	123 hours for drug and metabolites at room temperature (pg 1293) of the Fourth Addendum to the Method Validation 76 hours for drug and metabolites at 4°C ±6°C (pg 1435) of the Method Validation (b) (4)
Freeze-thaw stability (cycles)	6 cycles (pg 1433 & 1434) of the Method Validation (b) (4) (b) (4)
Long-term storage stability (days)	66 days at -70°C ±20°C (pg 1301) of the Third Addendum to the Method Validation
Dilution integrity	DIS 250.0/50.00/250.0 ng/mL and DHQC 37.50/7.500/37.50 ng/mL diluted 10 times (pg 1432) of the Method Validation (b) (4)
Selectivity	No interfering peaks noted in blank plasma samples (pg 1356 & 1357) of the Addendum to the Method Validation

SOPs submitted	Yes	SOP AP LC/MS/MS 242.100 (Effective date: 11 Apr 2006)
Bioanalytical method is acceptable	Yes	

Comments on the Pre-Study Method Validation:

Acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

A. Atorvastatin

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hrs)	AUC_{0-t} (ng x hr/mL)	AUC_{∞} (ng x hr/mL)	T½ (hrs)	K_{el} (1/hr)	
Study # B0606576 (R06-1030)	A bioequivalence study of atorvastatin calcium 80 mg tablets under fasting conditions	Single-dose, randomized, three-group, two-period, two-treatment, crossover study design	Test: Atorvastatin Calcium 80 mg Tablets, p.o. [Batch No. K-37191]	80 Subjects (63 M/17 F) Healthy subjects Age (yrs): 31.8 (18 – 67) Weight (lbs): 174.0 (105.0 – 229.0)	44.947 ± 30.281	1.458	182.919 ± 96.641	185.578 ± 96.910	9.380	0.085	Section 2, pg. 11, pg. 13
			Reference: LIPITOR® 80 mg Tablets, p.o. [Lot No. 07625V]		40.964 ± 32.889	1.163	170.100 ± 105.828	172.798 ± 106.007	10.507	0.077	
Study # B0606577 (R06-1031)	A bioequivalence study of atorvastatin calcium 80 mg tablets under non-fasting conditions	Single-dose, randomized, two-period, two-treatment, crossover study design	Test: Atorvastatin Calcium 80 mg Tablets, p.o. [Batch No. K-37191]	78 Subjects (72 M/6 F) Healthy subjects Age (yrs): 25.4 (18 – 68) Weight (lbs): 176.2 (126.0 – 236.0)	35.597 ± 24.825	2.133	176.959 ± 100.704	181.399 ± 101.032	10.943	0.068	Section 2, pg. 8, pg. 10
			Reference: LIPITOR® 80 mg Tablets, p.o. [Lot No. 07625V]		37.007 ± 21.287	2.081	176.600 ± 102.684	180.692 ± 103.472	11.284	0.067	

B. Ortho-Hydroxyatorvastatin

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hrs)	AUC_{0-t} (ng x hr/mL)	AUC_{∞} (ng x hr/mL)	$T½$ (hrs)	K_{el} (1/hr)	
Study # B0606576 (R06-1030)	A bioequivalence study of atorvastatin calcium 80 mg tablets under fasting conditions	Single-dose, randomized, three-group, two-period, two-treatment, crossover study design	Test: Atorvastatin Calcium 80 mg Tablets, p.o. [Batch No. K-37191]	80 Subjects (63 M/17 F) Healthy subjects Age (yrs): 31.8 (18 – 67) Weight (lbs): 174.0 (105.0 – 229.0)	35.604 ± 20.481	2.132	228.703 ± 86.174	232.385 ± 86.421	11.797	0.066	Section 2, pg. 31, pg. 33
			Reference: LIPITOR® 80 mg Tablets, p.o. [Lot No. 07625V]		34.079 ± 19.463	1.561	217.138 ± 93.818	220.643 ± 94.262	12.390	0.065	
Study # B0606577 (R06-1031)	A bioequivalence study of atorvastatin calcium 80 mg tablets under non-fasting conditions	Single-dose, randomized, two-period, two-treatment, crossover study design	Test: Atorvastatin Calcium 80 mg Tablets, p.o. [Batch No. K-37191]	78 Subjects (72 M/6 F) Healthy subjects Age (yrs): 25.4 (18 – 68) Weight (lbs): 176.2 (126.0 – 236.0)	24.150 ± 11.615	2.773	185.393 ± 78.486	188.795 ± 78.591	12.339	0.061	Section 2, pg. 16, pg. 18
			Reference: LIPITOR® 80 mg Tablets, p.o. [Lot No. 07625V]		25.565 ± 11.360	2.851	185.577 ± 82.167	189.835 ± 82.231	13.331	0.058	

C. Para-Hydroxyatorvastatin

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hrs)	AUC_{0-t} (ng x hr/mL)	AUC_{∞} (ng x hr/mL)	$T½$ (hrs)	K_{el} (1/hr)	
Study # B0606576 (R06-1030)	A bioequivalence study of atorvastatin calcium 80 mg tablets under fasting conditions	Single-dose, randomized, three-group, two-period, two-treatment, crossover study design	Test: Atorvastatin Calcium 80 mg Tablets, p.o. [Batch No. K-37191]	80 Subjects (63 M/17 F) Healthy subjects Age (yrs): 31.8 (18 – 67) Weight (lbs): 174.0 (105.0 – 229.0)	1.886 ± 1.367	4.379	32.654 ± 14.964	34.536 ± 15.924	20.874	0.035	Section 2, pg. 15, pg. 17
			Reference: LIPITOR® 80 mg Tablets, p.o. [Lot No. 07625V]		1.501 ± 1.877	4.939	29.388 ± 16.811	31.258 ± 17.494	21.903	0.034	
Study # B0606577 (R06-1031)	A bioequivalence study of atorvastatin calcium 80 mg tablets under non-fasting conditions	Single-dose, randomized, two-period, two-treatment, crossover study design	Test: Atorvastatin Calcium 80 mg Tablets, p.o. [Batch No. K-37191]	78 Subjects (72 M/6 F) Healthy subjects Age (yrs): 25.4 (18 – 68) Weight (lbs): 176.2 (126.0 – 236.0)	1.642 ± 1.099	5.531	32.057 ± 17.894	34.280 ± 19.489	23.484	0.032	Section 2, pg. 12, pg. 14
			Reference: LIPITOR® 80 mg Tablets, p.o. [Lot No. 07625V]		1.642 ± 1.334	5.846	31.632 ± 18.642	34.019 ± 19.668	22.836	0.032	

Table 2. Statisitical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Fasting BE Study No. R06-1030

Atorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-1030					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	163.58	150.25	1.09	104.51	113.42
AUC∞ (hr *ng/ml)	166.44	153.05	1.09	104.51	113.16
Cmax (ng/ml)	38.60	34.62	1.12	101.65	122.34

Ortho-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-1030					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	215.33	201.04	1.07	102.65	111.76
AUC∞ (hr *ng/ml)	219.14	204.69	1.07	102.70	111.61
Cmax (ng/ml)	31.50	29.99	1.05	96.57	114.23

Para-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-1030					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	29.57	25.78	1.15	109.92	119.69
AUC∞ (hr *ng/ml)	31.25	27.52	1.14	108.95	118.36
Cmax (ng/ml)	1.56	1.13	1.38	126.76	150.96

Fed Bioequivalence Study No. R06-1031

Atorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-1031					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	154.27	155.05	0.99	96.08	103.03
AUC∞ (hr *ng/ml)	158.08	158.80	1.00	96.18	103.03
Cmax (ng/ml)	29.22	31.52	0.93	83.43	103.01

Ortho-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-1031					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	170.21	169.79	1.00	97.06	103.55
AUC∞ (hr *ng/ml)	173.87	174.25	1.00	96.67	103.00
Cmax (ng/ml)	21.62	23.01	0.94	87.30	101.17

Para-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-1031					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	27.62	27.38	1.01	97.90	103.93
AUC∞ (hr *ng/ml)	29.87	29.34	1.02	98.64	105.09
Cmax (ng/ml)	1.33	1.31	1.02	94.77	108.94

Table 3. Reanalysis of Study Samples

A. Fasting BE Study No. R06-1030

Study No. B0606576/R06-1030 Additional Information in Section 8.0, Pages 1574, 1599-1607								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Above limit of quantitation (D)	26	16	0.62	0.38	26	16	0.62	0.38
Above limit of quantitation (D/M1/M2)	0	6	0.00	0.14	0	6	0.00	0.14
Above limit of quantitation (D/M2)	27	17	0.64	0.40	27	17	0.64	0.40
Above limit of quantitation (M2)	16	13	0.38	0.31	16	13	0.38	0.31
Air bubble in sample (D/M1)	1	0	0.02	0.00	1	0	0.02	0.00
Extraction error (D/M1/M2)	1	0	0.02	0.00	1	0	0.02	0.00
High internal standard (D/M1/M2)	13	7	0.31	0.17	13	7	0.31	0.17
High internal standard (M1/M2)	2	0	0.05	0.00	2	0	0.05	0.00
High internal standard (M2)	4	1	0.10	0.02	4	1	0.10	0.02
Incomplete data acquisition (D/M1/M2)	1	0	0.02	0.00	1	0	0.02	0.00
Low internal standard (D/M1/M2)	2	4	0.05	0.10	2	4	0.05	0.10
Low internal standard (M1/M2)	5	6	0.12	0.14	5	6	0.12	0.14
Low internal standard (M2)	1	0	0.02	0.00	1	0	0.02	0.00
No internal standard added (M1/M2)	1	0	0.02	0.00	1	0	0.02	0.00
Peak in pre-dose (D/M1/M2)	1	0	0.02	0.00	1	0	0.02	0.00
Peak in pre-dose (M1)	2	5	0.05	0.12	2	5	0.05	0.12
Sample lost during extraction procedure (D/M1/M2)	1	0	0.02	0.00	1	0	0.02	0.00
Sample not injected (D/M1/M2)	10	11	0.24	0.26	10	11	0.24	0.26
Sample tube broken during extraction (D/M1/M2)	2	0	0.05	0.00	2	0	0.05	0.00

D = Parent drug: Atorvastatin
M1 = Metabolite 1: Para-Hydroxyatorvastatin
M2 = Metabolite 2: Ortho-Hydroxyatorvastatin

B. Fed BE Study No. R06-1031

Study No. B0606577/R06-1031 Additional Information in Section 8.0, Pages 1437, 1438 and 1462-1470								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Above limit of quantitation (D)	39	54	0.91	1.25	39	54	0.91	1.25
Above limit of quantitation (D/M2)	5	9	0.12	0.21	5	9	0.12	0.21
Above limit of quantitation (M2)	1	0	0.02	0.00	1	0	0.02	0.00
Air bubble in sample (M1)	1	0	0.02	0.00	1	0	0.02	0.00
Air bubble in sample (D/M1/M2)	1	1	0.02	0.02	1	1	0.02	0.02
High internal standard (D/M1/M2)	14	22	0.33	0.51	14	22	0.33	0.51
High internal standard (D/M2)	1	2	0.02	0.05	1	2	0.02	0.05
High internal standard (M1)	1	1	0.02	0.02	1	1	0.02	0.02
Low internal standard (D/M1/M2)	10	9	0.23	0.21	10	9	0.23	0.21
Low internal standard (M1)	1	1	0.02	0.02	1	1	0.02	0.02
No internal standard peak (D/M1/M2)	1	0	0.02	0.00	1	0	0.02	0.00
Peak in pre-dose (M1)	10	4	0.23	0.09	10	4	0.23	0.09
Peak in pre-dose (M1) and high internal standard	1	0	0.02	0.00	1	0	0.02	0.00

D = Parent drug: Atorvastatin
M1 = Metabolite 1: 4-Hydroxyatorvastatin
M2 = Metabolite 2: 2-Hydroxyatorvastatin

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

Fasting BE Study No. R06-1030

1. Seventy-eight (78) of the eighty (80) healthy adult male and female subjects enrolled in the study, completed the fasting BE study.

2. The 80 subjects were dosed in three (3) groups. Treatment group I consisted of subject Nos. 01 to 28 (N=28), treatment group II consisted of subject Nos. 29 to 54 (N=26) and treatment group III consisted of subject Nos. 55-80 (N=26).

3. The firm stated in its clinical report that the study was composed of the 3 groups due to the size of the study. **The subjects were dosed at the same clinical site.**

4. Each of the 80 subjects were recruited from the community at large ((b) (4)) and consisted of both male and female subjects. According to their respective genders, the subjects had similar demographic profiles. The screening, dosing, and analysis dates for the subjects that were dosed in the study are as follows:

Treatment Group	Screening Dates	Dosing Dates		Analysis Dates***	
		Period I	Period II	Start	End**
I	10/10/06 to 10/27/06	10/28/06	11/04/06	11/10/06	11/18/06
II	10/20/06 to 11/02/06	11/04/06	11/11/06	11/18/06	11/25/06
III	10/24/06 to 11/09/06	11/11/06	11/18/06*	11/25/06	11/29/06

* Last sample collected for Group III, Period II was on 11/22/06
** Repeat analysis was from 11/30/06 to 12/01/06
*** Analysis started on 11/10/06 and ended on 12/10/06

5. The firm started analysis of the samples while still conducting the clinical portion of its fasting BE study. The analysis of the samples were performed for thirty-one (31) consecutive days, which started after the samples had been collected for at least 24 hrs for Group II. The firm will be informed that for future applications, they should wait until all samples are collected before beginning analysis.

6. The Division of Bioequivalence (DBE) recommended that the firm measure the plasma concentration for the parent drug, atorvastatin and its active metabolites, ortho-hydroxyatrovastatin and para-hydroxyatorvastatin. However, **only** atorvastatin should be subject to the 90% confidence interval (CI) approach. Based on this recommendation, the 90% confidence intervals for log-transformed AUC_T, AUC_I, and C_{max} for atorvastatin are within the acceptable range of 80.00-125.00%.

7. Two-hundred and one (201) plasma samples were reanalyzed in the fasting BE study. Of these samples, one-hundred and ninety-three (193) of the samples were reanalyzed for analytical reasons. Whereas, for atorvastatin (D), para-hydroxyatorvastatin (M1), ortho-hydroxyatrovastatin (M2) were reanalyzed for PK reasons (peak in pre-dose), 1, 1, 8 respectively. For atorvastatin and para-hydroxyatorvastin, the use of the original values do not have an impact on the outcome of the study. For seven (7) of the ortho-hydroxyatrovastatin samples, the original and recalculated values were below the limit of quantitation (0.1000 ng/mL). Therefore, the recalculated values were not used in BE statistical evaluations. The reviewer agrees with the firm's decision.

8. The fasting BE study is acceptable.

Fed BE Study No. R06-1031

1. Seventy-seven (77) of the seventy-eight (78) healthy male and female subjects enrolled in the fed BE study, completed the study.

2. A total of one-hundred and eighty-nine (189) samples were reanalyzed in the fed BE study. Of these samples, one-hundred and seventy-four (174) of the samples were reanalyzed for analytical reasons. Whereas, fifteen (15) ortho-hydroxyatorvastatin samples were reanalyzed for a PK reason (peak in pre-dose). The use of the original values for the samples repeated for the PK reason were below the limit of quantitation and will not have an impact on the outcome of the study.

3. The 90% CI for log-transformed AUC_T, AUC_I, and C_{max} are within the acceptable range of 80.00-125.00% for atorvastatin.

4. The fed BE study is acceptable.

3.7 Formulation

Location in appendix	Section 4.2, Page 71
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION IS ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Division of System Files v 2.0. Bioequivalence Dissolution Review N 078773 N 000 29-Dec-2006.
Source of Method (USP, FDA or Firm)	FDA
Medium	0.05M Phosphate Buffer, pH 6.8
Volume (mL)	900
USP Apparatus type	11 (Paddle)
Rotation (rpm)	75
DBE-recommended specifications	NLT (b)(4)% (Q) in 15 minutes
If a modified-release tablet, was testing done on ½ tablets?	No
F2 metric calculated?	No
If no, reason why F2 not calculated	It is rapidly dissolved
Is method acceptable?	**METHOD IS ACCEPTABLE**
If not then why?	

3.9 Waiver Request(s)

None.

3.10 Deficiency Comment

None.

3.11 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study No. R06-1030 conducted by the TEVA Pharmaceuticals USA on its Atorvastatin Calcium Tablets, EQ 80 mg Base, lot # K-37191 comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg Base, lot # 07625V.

2. The Division of Bioequivalence accepts the fed BE study No. R06-1031 conducted by the TEVA Pharmaceuticals USA on its Atorvastatin Calcium Tablets, EQ 80 mg Base, lot # K-37191 comparing it to Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, EQ 80 mg Base, lot # 07625V.

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.05M Phosphate Buffer, pH 6.8 at 37ºC ± 0.5ºC using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) of atorvastatin dissolved in 15 min

4. The Division of Bioequivalence deems the test product, Atorvastatin Calcium Tablets manufactured by TEVA Pharmaceuticals USA, to be bioequivalent to the reference product, Lipitor® (Atorvastatin Calcium) Tablets, manufactured by Pfizer.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	N/A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	R06-1030
Study Title	A Bioequivalence Study of Atorvastatin Calcium 80 mg Tablets under Fasting Conditions
Clinical Site (Name & Address)	PRACS Institute, Ltd. 625 DeMers Avenue, East Grand Forks, MN 56721, USA
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	**Period I** (Group 1) : 28 Oct 2006 – 01 Nov 2006 (Subjects 01-28) (Group 2): 04 Nov 2006 – 08 Nov 2006 (Subjects 29-54) (Group 3): 11 Nov 2006 – 15 Nov 2006-11-24 (Subjects 55-80)
	Period II (Group 1): 04 Nov 2006 – 08 Nov2006 (Subjects 01-28) (Group 2): 11 Nov 2006 – 15 Nov 2006 (Subjects 29-54) (Group 3): 18 Nov 2006 – 22 Nov2006 (Subjects 55-80)
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Group I: 10 Nov 2006 to 18 Nov 2006 Group II: 18 Nov 2006 to 25 Nov 2006 Group III: 25 Nov 2006 to 29 Nov 2006
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)	Group I: 28 Oct 2006 to 18 Nov 2006 (22 days) Group II: 04 Nov 2006 to 25 Nov 2006 (22 days) Group III: 11 Nov 2006 to 29 Nov 2006 (19 days)

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium Tablets	Lipitor®
Manufacturer	TEVA Pharmaceutical Industries, Ltd.	Pfizer Ireland Pharmaceuticals
Batch/Lot No.	K-37191	07625V
Manufacture Date	09 Aug 2006	
Expiration Date		Apr 2008
Strength	EQ 80 mg Base	EQ 80 mg Base
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	
Production Batch Size	(b) (4)	
Potency (Assay)	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	101.6%, 1.0%	
Dose Administered	1 x EQ 80 mg Base	1 x EQ 80 mg Base
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 80 Dosed: 80 Completed: 78 Analyzed: 78		
No. of Sequences	2		
No. of Periods	2		
No. of Treatments	2		
No. of Groups	3		
Washout Period	7 days		
Randomization Scheme	Group I: Sequence AB: 01, 04, 05, 06, 07, 08, 09, 10, 12, 14, 15, 16, 18, 21, and 24 Sequence BA: 02, 03, 11, 13, 17, 19, 20, 22, 23, 25, 26, 27, and 28	Group II: Sequence AB: 33, 34, 37, 39, 42, 43, 44, 45, 46, 47, 48, 50, and 52 Sequence BA: 29, 30, 31, 32, 35, 36, 38, 40, 41, 49, 51, 53, and 54	Group III: Sequence AB: 55, 56, 57, 58, 62, 63, 65, 68, 69, 73, 77, and 78 Sequence BA: 59, 60, 61, 64, 66, 67, 70, 71, 72, 74, 75, 76, 79, and 80

Blood Sampling Times	0.0 hrs (pre-dose), 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 72 and 96 hrs (post-dose)
Blood Volume Collected/Sample	1 x 6 mL each (27 samples)
Blood Sample Processing/Storage	Samples were collected by direct venipuncture and centrifuged at approximately 3000 RPM and 4°C for 10 minutes. The plasma was then pipetted into duplicate polypropylene tubes, frozen and stored at -70°C until shipment transfer for analysis. Upon completion of the clinical study, the plasma samples were transferred to the bioanalytical laboratory at [redacted] (b) (4) for sample analysis.
IRB Approval	20 Sep 2006
Informed Consent	28 June 2006
Length of Fasting	The subjects fasted overnight and until at least 4 hrs after dose administration.
Length of Confinement	The subjects checked into the clinical facility on the day prior to dosing. The subject were allowed to leave the clinical facility after the 24 hour blood sample collection.
Safety Monitoring	Sitting blood pressure and radial heart rate were measured prior to dosing and at 2 (± 30 minutes) hours after dosing, before discharge from the clinic, and at the last return visit each study period. Any additional blood pressure and heart rate evaluations were collected at the discretion of the clinical investigators.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study R06-1030		
	Treatment Groups	
	Test Product N=78[1]	Reference Product N=78[1]
Age (years)		
Mean ± SD	32.05 ± 13.66	32.05 ± 13.66
Range	18 - 67	18 - 67
Groups		
<18	-	-
18-39	53 (67.95%)	53 (67.95%)
40-64	24 (30.77%)	24 (30.77%)
65-75	1 (1.28%)	1 (1.28%)
>75	-	-
Sex		
Female	17 (21.79%)	17 (21.79%)
Male	61 (78.21%)	61 (78.21%)
Hispanic or Latino		
Race		
N	-	-
A	-	-
B	-	-
I	-	-
W	1 (1.28%)	1 (1.28%)
Not Hispanic or Latino		
Race		
N	2 (2.56%)	2 (2.56%)
A	1 (1.28%)	1 (1.28%)
B	2 (2.56%)	2 (2.56%)
I	-	-
W	71 (91.03%)	71 (91.03%)
WN	1 (1.28%)	1 (1.28%)

RACE:
American Indian or Alaskan Native N
Asian A
Black or African American B
Native Hawaiian or Other Pacific Islander I
White W

[1]Subjects Used in Final Statistical Report

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
25	Subject elected to withdraw prior to Period II dose administration for personal reasons.	I	No
65	Subject elected to withdraw prior to Period II dose administration for personal reasons.	I	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups			
	Fasting Bioequivalence Study R06-1030		Non-Fasting Bioequivalence Study R06-1031	
	Test N=79[2]	Reference N=79[2]	Test N=78[2]	Reference N=77[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Eye disorders				
Eye irritation	1 (1.27%)	-	-	-
Gastrointestinal disorders				
Abdominal distension	-	1 (1.27%)	-	-
Abdominal pain upper	1 (1.27%)	-	-	-
Diarrhoea	-	-	1 (1.28%)	-
Flatulence	-	-	1 (1.28%)	-
Nausea	-	1 (1.27%)	-	-
Oral mucosal blistering	-	-	1 (1.28%)	-
Toothache	-	-	-	1 (1.30%)
General disorders and administration site conditions				
Feeling drunk	1 (1.27%)	-	-	-
Infections and infestations				
Acute rhino sinusitis	-	-	1 (1.28%)	-
Musculoskeletal and connective tissue disorders				
Back pain	-	-	-	1 (1.30%)

(To be continued)
[1] MedDRA Version 9.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups			
	Fasting Bioequivalence Study R06-1030		Non-Fasting Bioequivalence Study R06-1031	
	Test N=79[2]	Reference N=79[2]	Test N=78[2]	Reference N=77[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Nervous system disorders				
Dizziness	3 (3.80%)	3 (3.80%)	-	-
Headache	2 (2.53%)	7 (8.86%)	3 (3.85%)	6 (7.79%)
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	-	-	-	1 (1.30%)
Pharyngolaryngeal pain	1 (1.27%)	1 (1.27%)	-	-
Skin and subcutaneous disorders				
Rash papular	-	-	-	2 (2.60%)
Rash	1 (1.27%)	-	-	-
Total Subjects Reporting at Least One Adverse Event	9 (11.39%)	11 (13.92%)	7 (8.97%)	10 (12.99%)

[1] MedDRA Version 9.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s
Did not meet the height and weight restrictions	09, 26, and 73
Used tobacco within the 3 month abstinence window	61
Was not postmenopausal for at least one year prior to dose administration	26
Reported having an influenza vaccination shot within 7 days prior to initial dose administration	10
Reported medication use within 7 days prior to initial dose administration	27
Reported multivitamin use within 7 days prior to initial dose administration	49
Reported medication use over the course of the study	29 and 54
Sampling time deviations	02, 09, 14, 16, 18, 24, 25, 30, 31, 51, 53, 55, 56, 58, 66, 68, 69, and 79

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. The two (2) subjects (Nos. 25 and 65) that elected to withdraw from the study prior to Period II dose administration were not replaced in the study.

2. No subjects reported experiencing emesis during the fasting BE study.

3. No serious adverse events (SAEs) were reported during the fasting BE study.

4. The reported discontinued subjects, adverse events (AEs) and protocol deviations do not have an impact on the outcome of the fasting BE study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.1000	0.2000	0.5000	1.000	2.00	5.000	10.00	20.00	40.00	50.00
Inter day Precision (%CV)	2.0	3.7	3.6	3.5	2.7	2.7	2.8	2.6	3.5	4.6
Inter day Accuracy (%Actual)	99.3	101	100	101	103	104	102	99.1	96.6	95.5
Linearity	0.9989 (0.9979-0.9997)									
Linearity Range (ng/mL)	0.100 to 50.00 ng/mL									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.3000	0.75000	3.750	37.50
Inter day Precision (%CV)	5.1	5.6	4.6	4.8
Inter day Accuracy (%Actual)	104	103	106	102

Ortho-Hydroxyatorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.1000	0.2000	0.5000	1.000	2.000	5.000	10.00	20.00	40.00	50.00
Inter day Precision (%CV)	2.6	5.0	4.1	2.8	2.3	3.0	2.6	2.5	3.3	4.1
Inter day Accuracy (%Actual)	99.8	101	98.6	101	100	101	101	99.7	99.0	99.4
Linearity	0.9992 (0.9974-0.9998)									
Linearity Range (ng/mL)	0.1000 to 50.00									
Sensitivity/LOQ (ng/mL)	0.1000									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.3000	0.7500	3.750	37.50
Inter day Precision (%CV)	5.6	5.3	4.6	4.3
Inter day Accuracy (%Actual)	101	99.6	101	102

Para-Hydroxyatorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.02000	0.04000	0.1000	0.2000	0.4000	1.000	2.000	4.000	8.000	10.00
Inter day Precision (%CV)	3.8	7.2	4.7	4.9	3.3	3.5	2.2	2.4	2.8	3.9
Inter day Accuracy (%Actual)	99.5	102	98.0	99.7	99.6	99.6	99.9	99.9	100	102
Linearity	0.9987 (0.9968 to 0.9996)									
Linearity Range (ng/mL)	0.02000 to 10.00									
Sensitivity/LOQ (ng/mL)	0.02000									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.06000	0.1500	0.7500	7.500
Inter day Precision (%CV)	7.9	6.4	4.8	4.6
Inter day Accuracy (%Actual)	99.8	97.9	98.8	102

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
L10.000	01 Feb 2006	Sample Reanalysis and Reporting Criteria

Table 13. 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:

1. The firm began analysis of its samples prior to completion of its clinical study. The clinical study was performed in 3 groups and the samples were analyzed on consecutive days. The firm will be informed that for future applications, they should complete the clinical portion of its study prior to beginning analysis.

2. The study assays are acceptable.

4.1.1.4 Pharmacokinetic Results

A. Atorvastatin

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 26 and Figure 1

Fasting Bioequivalence Study No. R06-1030										
Atorvastatin										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng.hr/mL	182.92	52.83	52.95	674.70	170.10	62.22	55.88	807.75	1.08
AUCI	ng.hr/mL	185.58	52.22	54.14	680.31	172.80	61.35	57.29	809.85	1.07
CMAX	ng/mL	44.95	67.37	13.13	217.70	40.96	80.29	11.38	257.30	1.10
TMAX	hr	1.00	.	0.33	5.00	0.67	.	0.33	5.00	1.50
KE	hr-1	0.08	41.94	0.04	0.24	0.08	39.34	0.02	0.23	1.10
THALF	hr	9.38	36.63	2.94	19.64	10.51	45.34	2.96	29.72	0.89

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study No. R06-1030				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	164.629	150.634	1.09	105-114
AUC∞ (hr *ng/ml)	167.503	153.457	1.09	105-114
Cmax (ng/ml)	38.657	34.695	1.11	101-122

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-1030					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	163.58	150.25	1.09	104.51-	113.42
AUC∞ (hr *ng/ml)	166.44	153.05	1.09	104.51	113.16
Cmax (ng/ml)	38.60	34.62	1.12	101.65	122.34

Table 17. Additional Study Information, Fasting Bioequivalence Study No. R06-1030

Root mean square error, AUC0-t	0.1534	
Root mean square error, AUC∞	0.1490	
Root mean square error, Cmax	0.3475	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	78	78
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	3	3

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	78	0.98	0.87	1.00
Reference	78	0.98	0.94	1.00

B. Ortho-Hydroxyatorvastatin

Table 18. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 27 and Figure 2

Fasting Bioequivalence Study No. R06-1030										
Ortho-Hydroxyatorvastatin										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng.hr/mL	228.70	37.68	100.39	612.29	217.14	43.21	80.11	668.53	1.05
AUCI	ng.hr/mL	232.39	37.19	103.41	615.30	220.64	42.72	83.94	671.01	1.05
CMAX	ng/mL	35.60	57.53	11.21	140.60	34.08	57.11	7.64	130.10	1.04
TMAX	hr	2.00	.	0.50	7.00	1.00	.	0.50	5.00	2.00
KE	hr-1	0.07	33.47	0.03	0.11	0.06	33.60	0.02	0.11	1.03
THALF	hr	11.80	36.21	6.25	21.79	12.39	45.34	6.36	32.29	0.95

* Tmax values are presented as median, range

Table 19. Geometric Means and 90% Confidence Intervals - Firm Calculated

Ortho-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study No. R06-1030				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	216.90	201.97	1.07	103-112
AUC∞ (hr *ng/ml)	220.71	205.63	1.07	103-112
Cmax (ng/ml)	31.51	30.01	1.05	96.4-114

Table 20. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Ortho-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-1030					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	215.33	201.04	1.07	102.65	111.76
AUC∞ (hr *ng/ml)	219.14	204.69	1.07	102.70	111.61
Cmax (ng/ml)	31.50	29.99	1.05	96.57	114.23

Table 21. Additional Study Information, Fasting Bioequivalence Study No. R06-1030

Root mean square error, AUC0-t	0.1594	
Root mean square error, AUC∞	0.1559	
Root mean square error, Cmax	0.3149	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	78	78
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	3	3

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	78	0.98	0.93	1.00
Reference	78	0.98	0.93	1.00

C. Para-Hydroxyatorvastatin

Table 22. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 28 and Figure 3

Fasting Bioequivalence Study No. R06-1030										
Para-Hydroxyatorvastatin										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng.hr/mL	32.65	45.83	8.56	94.67	29.39	57.20	6.84	116.73	1.11
AUCI	ng.hr/mL	34.54	46.11	9.42	99.80	31.26	55.97	7.74	121.87	1.10
CMAX	ng/mL	1.89	72.45	0.35	9.00	1.50	125.10	0.29	16.25	1.26
TMAX	hr	3.00	.	0.50	36.00	5.00	.	0.33	12.00	0.60
KE	hr-1	0.04	25.81	0.02	0.07	0.03	27.83	0.02	0.06	1.03
THALF	hr	20.87	26.28	10.34	37.69	21.90	29.49	11.81	44.46	0.95

* Tmax values are presented as median, range

Table 23. Geometric Means and 90% Confidence Intervals - Firm Calculated

Para-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study No. R06-1030				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	29.69	25.84	1.15	110-120
AUC∞ (hr *ng/ml)	31.41	27.63	1.14	109-118
Cmax (ng/ml)	1.55	1.11	1.38	127-151

Table 24. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Para-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-1030					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	29.57	25.78	1.15	109.92	119.69
AUC∞ (hr *ng/ml)	31.25	27.52	1.14	108.95	118.36
Cmax (ng/ml)	1.56	1.13	1.38	126.76	150.96

Table 25. Additional Study Information, Fasting Bioequivalence Study No. R06-1030

Root mean square error, AUC0-t	0.1597	
Root mean square error, AUC∞	0.1534	
Root mean square error, Cmax	0.3276	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	78	78
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	3	3

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	78	0.98	0.87	1.00
Reference	78	0.98	0.94	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm assayed the plasma concentration data for atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin. The firm also provided the plasma profiles for atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin.

2. The point estimate for para-hydroxyatorvastatin did not meet the point estimate of 0.80-1.25 for C_{max}. This is due to (1) the high intrasubject variability of the drug product for C_{max} (atorvastatin: 34.75%, ortho-hydroxaytovastatin: 31.49%, and para-hydroxyatrovastatin: 32.76%), (2) low plasma levels of the para-hydroxyatrovastatin as compared to the atorvastatin and ortho-hydroxyatorvastatin, along with the under powering of the study. Therefore, bioequivalence determination is based on the 90% CIs data of AUC_{0-t}, AUC_{∞} and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolite, ortho-hydroxyatorvastatin.

3. The firm and reviewer calculated the PK parameters (AUC_T, AUC_I, C_{max}, T_{max}, K_{el}, $t_{½}$) for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval.

4. The reviewer agrees with the firm's results.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study is acceptable.

Table 26. Mean Atorvastatin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin					
	Test (n=78)		Reference (n=78)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	883.18	0.00	.	.
0.17	2.79	160.27	0.72	180.18	3.87
0.33	19.01	92.78	13.86	117.73	1.37
0.50	25.48	86.00	26.12	99.90	0.98
0.67	24.00	82.99	26.87	99.01	0.89
0.83	22.50	82.15	25.19	104.40	0.89
1.00	23.45	108.94	23.85	102.97	0.98
1.25	24.33	118.97	22.05	101.30	1.10
1.50	22.00	111.34	21.59	134.30	1.02
2.00	21.33	85.36	19.66	112.92	1.08
2.50	19.05	79.30	16.86	92.99	1.13
3.00	19.74	85.36	14.96	88.30	1.32
3.50	16.31	71.13	13.54	82.28	1.20
4.00	15.59	68.63	12.28	72.97	1.27
5.00	14.50	51.05	13.03	56.62	1.11
6.00	11.34	47.15	10.23	51.81	1.11
7.00	8.59	52.48	7.67	53.03	1.12
8.00	6.72	49.55	6.23	54.23	1.08
10.00	4.98	53.70	4.66	60.13	1.07
12.00	4.45	57.55	4.25	61.86	1.05
14.00	2.94	59.40	2.85	63.25	1.03
16.00	2.07	64.89	2.06	68.48	1.00
24.00	0.95	69.12	0.97	71.29	0.98
36.00	0.54	76.95	0.62	88.63	0.88
48.00	0.19	100.44	0.21	98.93	0.91
72.00	0.04	203.84	0.04	185.23	0.82
96.00	0.00	616.56	0.01	355.47	0.27

Table 27. Mean Ortho-Hydroxyatrovastatin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Ortho-Hydroxyatorvastatin					
	Test (n=78)		Reference (n=78)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	883.18	0.00	.	.
0.17	0.28	229.08	0.04	361.90	7.04
0.33	6.67	127.90	4.02	135.91	1.66
0.50	15.05	115.72	13.99	106.74	1.08
0.67	18.50	110.69	20.12	81.20	0.92
0.83	18.96	94.95	22.22	69.45	0.85
1.00	20.71	89.81	23.68	64.12	0.87
1.25	21.47	83.39	24.36	65.71	0.88
1.50	21.82	83.20	24.56	75.41	0.89
2.00	22.84	69.27	24.03	75.09	0.95
2.50	22.17	62.73	21.24	67.31	1.04
3.00	22.20	58.18	19.52	67.14	1.14
3.50	20.38	54.95	17.99	62.16	1.13
4.00	19.61	50.92	16.76	57.53	1.17
5.00	17.94	38.26	16.12	45.05	1.11
6.00	14.83	38.41	13.19	41.86	1.12
7.00	11.74	37.20	10.46	40.75	1.12
8.00	9.72	34.48	8.83	42.64	1.10
10.00	7.26	34.71	6.64	41.55	1.09
12.00	6.16	40.48	5.78	44.61	1.06
14.00	4.34	39.84	4.10	44.84	1.06
16.00	3.22	43.16	3.08	47.57	1.05
24.00	1.43	41.56	1.41	48.11	1.01
36.00	0.93	61.12	0.92	61.54	1.01
48.00	0.34	63.46	0.33	58.27	1.03
0.00	0.00	883.18	0.00	.	.
0.17	0.28	229.08	0.04	361.90	7.04

Table 28. Mean Para-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Para-Hydroxyatorvastatin					
	Test (n=78)		Reference (n=78)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	544.46	0.00	438.37	1.23
0.17	0.01	225.36	0.00	327.32	4.97
0.33	0.26	217.24	0.16	155.01	1.61
0.50	0.51	196.05	0.43	133.40	1.18
0.67	0.52	162.60	0.54	108.14	0.97
0.83	0.53	125.16	0.56	106.64	0.94
1.00	0.61	111.15	0.62	124.37	0.98
1.25	0.77	121.85	0.69	129.31	1.12
1.50	0.85	122.55	0.80	193.88	1.07
2.00	1.03	98.05	0.91	199.50	1.13
2.50	1.12	96.18	0.94	171.04	1.19
3.00	1.34	89.94	1.00	169.97	1.34
3.50	1.27	82.77	1.07	156.73	1.19
4.00	1.35	82.60	1.06	123.33	1.28
5.00	1.31	61.40	1.15	88.48	1.14
6.00	1.13	53.42	0.95	70.85	1.18
7.00	1.00	50.95	0.81	62.91	1.23
8.00	0.91	45.39	0.77	60.12	1.18
10.00	1.02	55.08	0.89	66.99	1.15
12.00	0.95	46.42	0.85	62.71	1.11
14.00	0.72	45.17	0.66	55.47	1.09
16.00	0.62	45.86	0.57	52.26	1.09
24.00	0.46	47.50	0.42	50.04	1.08
36.00	0.36	46.18	0.35	71.00	1.01
48.00	0.19	56.80	0.17	65.54	1.09
72.00	0.09	70.40	0.08	60.46	1.09
96.00	0.05	83.54	0.04	76.06	1.15

Figure 1. Mean Atorvastatin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

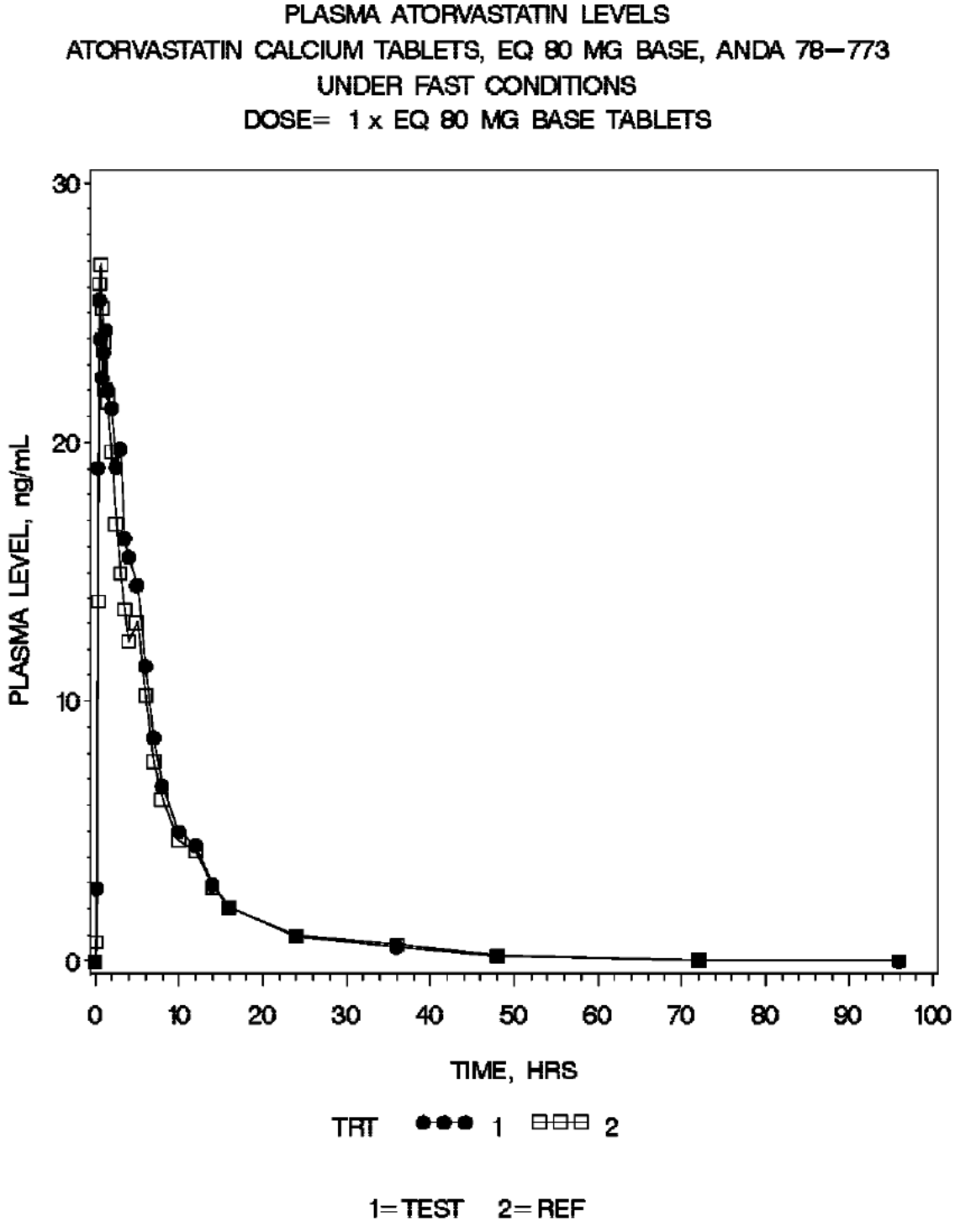


Figure 2. Mean Ortho-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

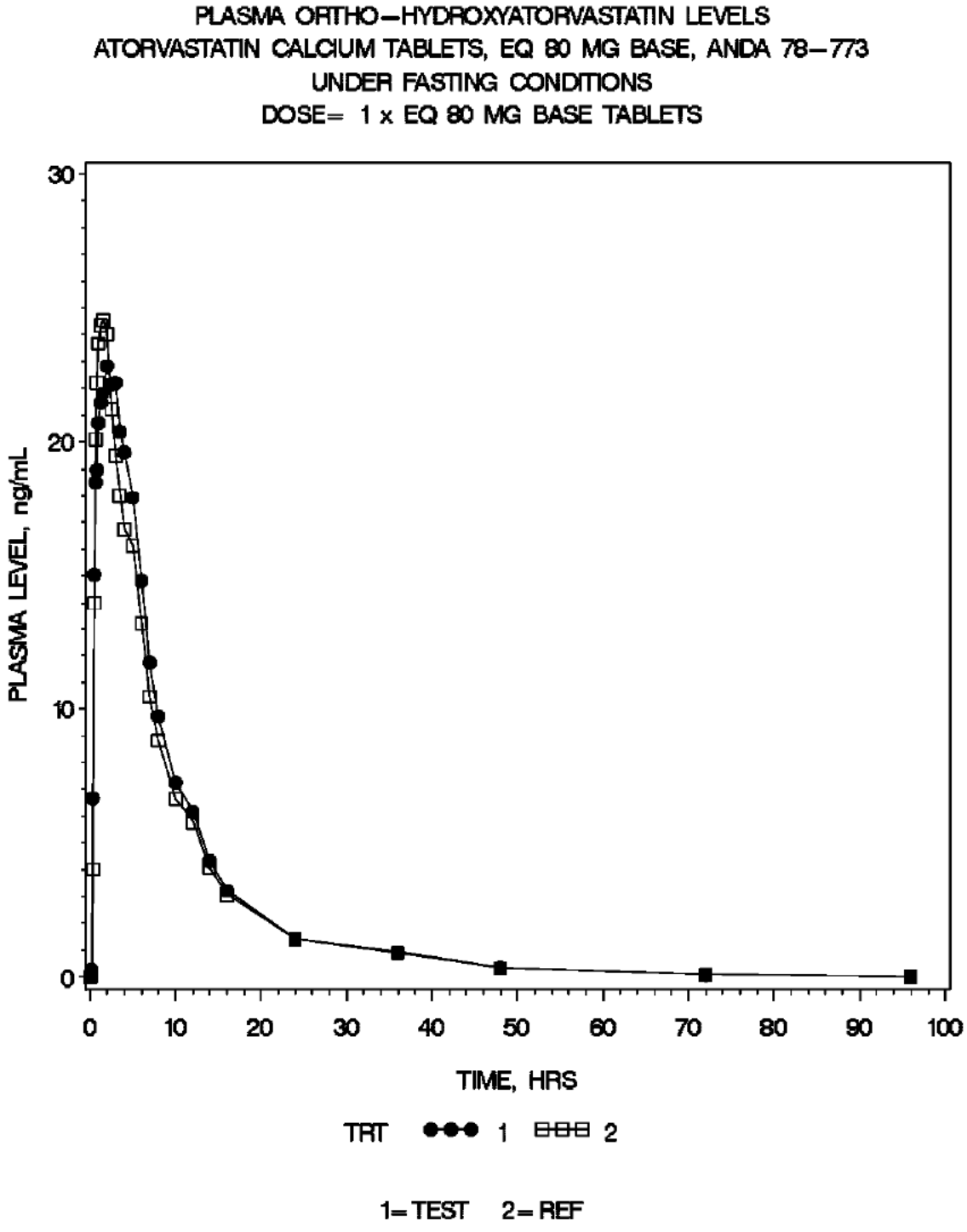
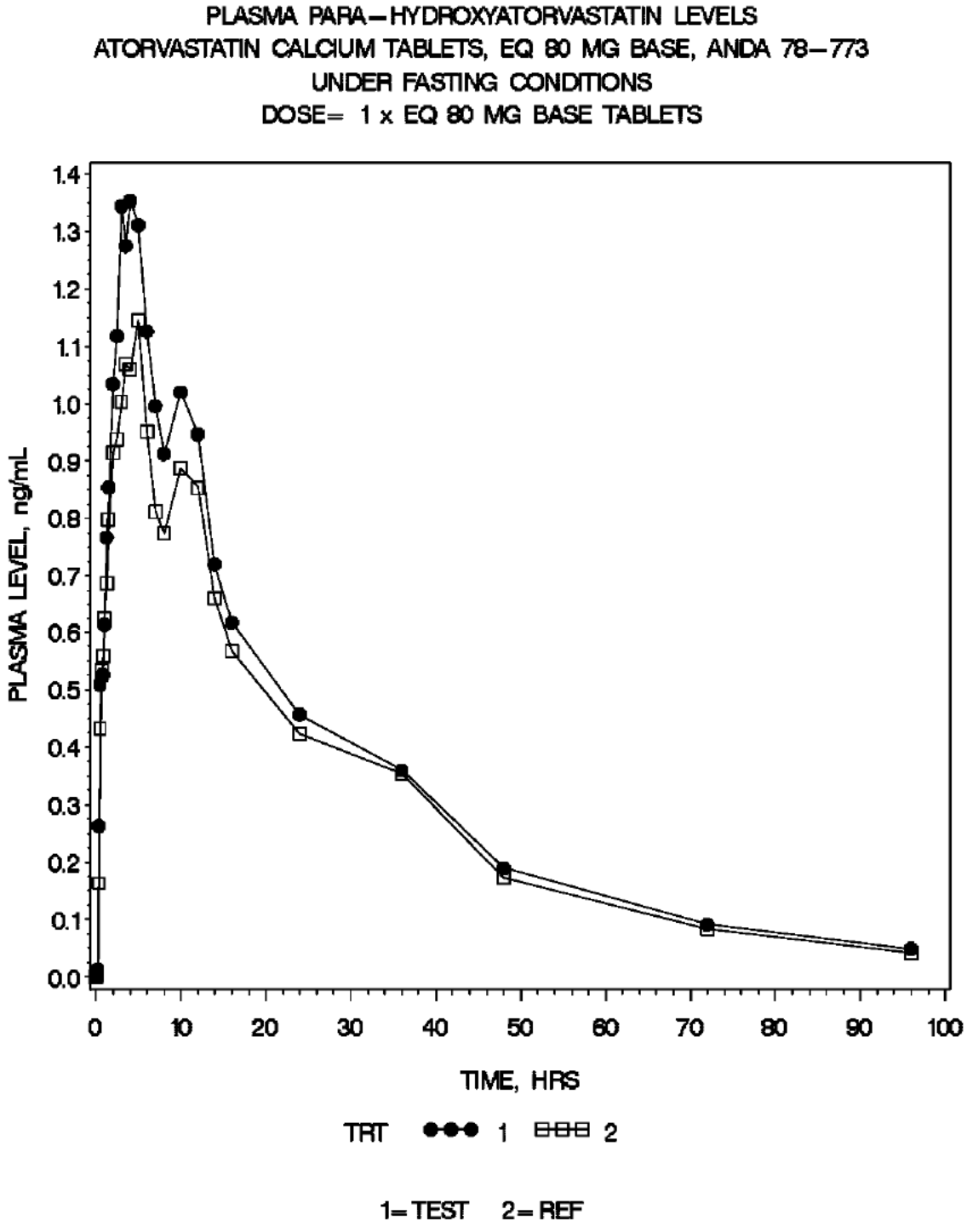


Figure 3. Mean Para-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 29. Study Information

Study Number	R06-1031
Study Title	A Bioequivalence Study of Atorvastatin Calcium 80 mg Tablets under Non-Fasting Conditions
Clinical Site (Name & Address)	4801 Amber Valley Parkway Fargo, ND 58104, USA
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I 11 Nov 2006 . 15 Nov 2006 Period II 18 Nov 2006 . 22 Nov 2006
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	29 Nov 2006 to 15 Dec 2006
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)	11 Nov 2006 to 15 Dec 2006 (35 days)

Table 30. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium Tablets	Lipitor®
Manufacturer	TEVA Pharmaceutical Industries, Ltd.	Pfizer Ireland Pharmaceuticals
Batch/Lot No.	K-37191	07625V
Manufacture Date	09 Aug 2006	
Expiration Date		Apr 2008
Strength	EQ 80 mg Base	EQ 80 mg Base
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	
Production Batch Size	(b) (4)	
Potency (Assay)	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	101.6%, 1.0%	
Dose Administered	1 x EQ 80 mg Base	1 x EQ 80 mg Base
Route of Administration	Oral	Oral

Table 31. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Enrolled: 78 Dosed: 78 Completed: 77 Analyzed: 77
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Sequence AB: 02, 03, 06, 07, 08, 10, 11, 12, 15, 16, 19, 21, 22, 24, 26, 27, 28, 30, 33, 35, 38, 43, 46, 50, 53, 54, 56, 58, 63, 64, 66, 68, 70, 72, 73, 75, and 78 Sequence BA: 01, 04, 05, 09, 13, 14, 17, 18, 20, 23, 25, 29, 31, 32, 34, 36, 37, 39, 40, 41, 42, 44, 45, 47, 48, 49, 51, 52, 55, 57, 59, 60, 61, 62, 65, 67, 69, 71, 74, 76, and 77.
Blood Sampling Times	0.00 hrs (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48, 72, and 96 hours (post-dose)
Blood Volume Collected/Sample	1 x 6 mL each (28 samples)
Blood Sample Processing/Storage	Samples were collected by direct venipuncture and centrifuged at approximately 3000 RPM and 4°C for 10 minutes. The plasma was then pipetted into duplicate polypropylene tubes, frozen and stored at -70°C until shipment transfer for analysis. Upon completion of the clinical study, the plasma samples were transferred to the bioanalytical laboratory at (b) (4) for sample analysis.
IRB Approval	20 Sep 2006
Informed Consent	28 Jun 2006
Length of Fasting Before Meal	The subjects fasted overnight, and were served a standardized, high fat breakfast 30 minutes prior to dose administration
Length of Confinement	Subjects checked into the clinical facility on the day prior to dosing. The subjects were allowed to leave the clinical facility after the 24 hour blood sample collection.
Safety Monitoring	Sitting blood pressure and radial heart rate were measured prior to dosing and at 2 (± 30 minutes) hours after dosing, before discharge from the clinic, and at the last return visit each study period. Any additional blood pressure and heart rate evaluations were collected at the discretion of the clinical investigators.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 32. Demographics Profile of Subjects Completing the Bioequivalence Study

Non-Fasting Bioequivalence Study R06-1031		
	Treatment Groups	
	Test Product N=76[1]	Reference Product N=76[1]
Age (years)		
Mean ± SD	25.51 ± 9.21	25.51 ± 9.21
Range	18 - 68	18 - 68
Groups		
<18	-	-
18-39	69 (90.79%)	69 (90.79%)
40-64	6 (7.89%)	6 (7.89%)
65-75	1 (1.32%)	1 (1.32%)
>75	-	-
Sex		
Female	6 (7.89%)	6 (7.89%)
Male	70 (92.11%)	70 (92.11%)
Hispanic or Latino		
Race		
N	1 (1.32%)	1 (1.32%)
A	-	-
B	-	-
I	-	-
W	1 (1.32%)	1 (1.32%)
Not Hispanic or Latino		
Race		
N	2 (2.63%)	2 (2.63%)
A	2 (2.63%)	2 (2.63%)
B	4 (5.26%)	4 (5.26%)
I	-	-
W	65 (85.53%)	65 (85.53%)
WB	1 (1.32%)	1 (1.32%)

RACE:
American Indian or Alaskan Native N
Asian A
Black or African American B
Native Hawaiian or Other Pacific Islander I
White W

[1]Subjects Used in Final Statistical Report

Table 33. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
72	Dropped per Medical Investigator prior to Period II dosing due to adverse event	I	No

Table 34. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups			
	Fasting Bioequivalence Study R06-1030		Non-Fasting Bioequivalence Study R06-1031	
	Test N=79[2]	Reference N=79[2]	Test N=78[2]	Reference N=77[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Eye disorders				
Eye irritation	1 (1.27%)	-	-	-
Gastrointestinal disorders				
Abdominal distension	-	1 (1.27%)	-	-
Abdominal pain upper	1 (1.27%)	-	-	-
Diarrhoea	-	-	1 (1.28%)	-
Flatulence	-	-	1 (1.28%)	-
Nausea	-	1 (1.27%)	-	-
Oral mucosal blistering	-	-	1 (1.28%)	-
Toothache	-	-	-	1 (1.30%)
General disorders and administration site conditions				
Feeling drunk	1 (1.27%)	-	-	-
Infections and infestations				
Acute rhino sinusitis	-	-	1 (1.28%)	-
Musculoskeletal and connective tissue disorders				
Back pain	-	-	-	1 (1.30%)

(To be continued)
[1] MedDRA Version 9.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups			
	Fasting Bioequivalence Study R06-1030		Non-Fasting Bioequivalence Study R06-1031	
	Test N=79[2]	Reference N=79[2]	Test N=78[2]	Reference N=77[2]
	n (%)[3]	n (%)[3]	n (%)[3]	n (%)[3]
Nervous system disorders				
Dizziness	3 (3.80%)	3 (3.80%)	-	-
Headache	2 (2.53%)	7 (8.86%)	3 (3.85%)	6 (7.79%)
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	-	-	-	1 (1.30%)
Pharyngolaryngeal pain	1 (1.27%)	1 (1.27%)	-	-
Skin and subcutaneous disorders				
Rash papular	-	-	-	2 (2.60%)
Rash	1 (1.27%)	-	-	-
Total Subjects Reporting at Least One Adverse Event	9 (11.39%)	11 (13.92%)	7 (8.97%)	10 (12.99%)

[1] MedDRA Version 9.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 35. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Due to enrollment difficulty, only seventy-eight (78) subjects were dosed in contrast to the protocol which specified that eighty (80) subjects were to dose.	--	--
Subject No: 19 Initials: (b) (6) Combo Drug Name / Start Date / Time / End Date / Time / Med / Strength / Unit / Route / Frequency / Reason acetaminophen / 11/21/2006 / 10:30 / 11/21/2006 / 10:31 / No / 500.00 / mg / Oral / 1 Time Daily / AE(s): headache Subject took 2x 500 mg acetaminophen tablets. *** (b) (6) 11/22/2006 1450 *** *** (b) (6) 1/27/2006 1117 *** *** (b) (6) 1/27/2006 1627 *** Subject No: 62 Initials: (b) (6) Combo Drug Name / Start Date / Time / End Date / Time / Med / Strength / Unit / Route / Frequency / Reason Tylenol Extra Strength / 11/13/2006 / 2:00 / 11/13/2006 / 2:00 / No / 500.00 / mg / Oral / 1 Time Daily / AE(s): tooth ache 2 x 500 mg rapid release gels *** (b) (6) 1/13/2006 0751 *** Subject No: 72 Initials: (b) (6) Dropped From Study Combo Drug Name / Start Date / Time / End Date / Time / Med / Strength / Unit / Route / Frequency / Reason azithromycin / 11/18/2006 / 8:00 / 11/25/2006 / 20:00 / No / 250.00 / mg / Oral / 2 Times Daily / AE(s): Acute rhino sinusitis Z-pack x 8 days (8 - 250 mg tabs) *** (b) (6) 11/18/2006 0946 ***		
Blood sampling time deviations.	**Subjects:**	01, 03, 04, 05, 06, 07, 10, 11, 13, 14, 18, 19, 20, 22, 23, 24, 25, 26, 28, 29, 32, 34, 37, 38, 39, 40, 43, 45, 46, 47, 48, 50, 51, 52, 53, 54, 55, 56, 59, 60, 63, 64, 65, 66, 67, 68, 69, 70, 72, 73, 74, 76, 77, and 78

Comments on Adverse Events/Protocol Deviations:

1. The one (1) subject (No. 72) that was withdrawn from the due to an AE (acute rhino sinusitis) was not replaced in the study, see Table 33. This subject also took concomitant medication, azithromycin as pharmacotherapy for its reported AE, see Table 35.

2. No subjects reported experiencing emesis during the fed BE study.

3. No serious adverse events (SAEs) were reported during the fed BE study.

4. Two (2) subjects (Nos. 19 and 62) took concomitant medication for pharmacotherapy of their reported AEs, headache and toothache, respectively (Table 35).

5. The reported discontinued subjects, adverse events (AEs) and protocol deviations do not have an impact on the outcome of the fed BE study.

4.1.2.3 Bioanalytical Results

Table 36. Assay Validation – Within the Fed Bioequivalence Study

Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.1000	0.2000	0.5000	1.000	2.00	5.000	10.00	20.00	40.00	50.00
Inter day Precision (%CV)	2.1	3.8	4.0	3.5	4.4	3.9	2.7	3.3	4.1	4.5
Inter day Accuracy (%Actual)	99.4	101	99.6	99.6	103	105	102	99.5	96.4	95.5
Linearity	0.9986 (0.9973-0.9996)									
Linearity Range (ng/mL)	0.1000 to 50.00									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.3000	0.75000	3.750	37.50
Inter day Precision (%CV)	6.7	5.6	5.0	6.1
Inter day Accuracy (%Actual)	106	103	107	101

Ortho-Hydroxyatorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.1000	0.2000	0.5000	1.000	2.000	5.000	10.00	20.00	40.00	50.00
Inter day Precision (%CV)	3.0	5.9	5.7	4.1	5.1	3.6	3.4	3.6	4.5	4.3
Inter day Accuracy (%Actual)	100	101	97.5	98.5	100	102	99.6	101	99.5	101
Linearity	0.9986 (0.9959 to 0.9997)									
Linearity Range (ng/mL)	0.1000 to 50.00									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.3000	0.7500	3.750	37.50
Inter day Precision (%CV)	7.3	6.1	5.1	5.9
Inter day Accuracy (%Actual)	101	99.4	101	102

Para-Hydroxyatorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.02000	0.04000	0.1000	0.2000	0.4000	1.000	2.000	4.000	8.000	10.00
Inter day Precision (%CV)	3.0	6.6	6.2	4.9	4.7	4.7	3.7	3.5	4.2	3.4
Inter day Accuracy (%Actual)	101	99.4	96.1	97.5	99.6	99.9	99.5	101	102	104
Linearity	0.9983 (0.9948-0.9994)									
Linearity Range (ng/mL)	0.02000 to 10.00									
Sensitivity/LOQ (ng/mL)	0.02000									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.06000	0.1500	0.7500	7.500
Inter day Precision (%CV)	12.7	8.2	5.9	5.7
Inter day Accuracy (%Actual)	99.1	98.2	98.3	105

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable/Incomplete.

Table 37. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
L10.000	01 Feb 2006	Sample Reanalysis and Reporting Criteria

Table 38. 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:

The study assays are acceptable.

4.1.2.4 Pharmacokinetic Results

A. Atorvastatin

Table 39. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 51 and Figure 4

Fed Bioequivalence Study No. R06-1031										
Atorvastatin										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng.hr/mL	176.96	56.91	56.05	527.87	176.60	58.15	55.31	605.81	1.00
AUCI	ng.hr/mL	181.40	55.70	62.59	530.08	180.69	57.26	56.73	614.19	1.00
CMAX	ng/mL	35.60	69.74	9.45	119.00	37.01	57.52	7.14	112.50	0.96
TMAX	hr	1.25	.	0.50	5.00	1.50	.	0.50	11.00	0.83
KE	hr-1	0.07	25.86	0.03	0.11	0.07	27.70	0.03	0.11	1.02
THALF	hr	10.94	31.67	6.18	25.39	11.28	32.50	6.26	24.84	0.97

* Tmax values are presented as median, range

Table 40. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study No. R06-1031				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	154.268	155.052	0.99	96.1-103
AUC∞ (hr *ng/ml)	158.083	158.804	0.99	96.2-103
Cmax (ng/ml)	29.221	31.519	0.93	83.4-103

Table 41. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-1031					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	154.27	155.05	0.99	96.08	103.03
AUC∞ (hr *ng/ml)	158.08	158.80	1.00	96.18	103.03
Cmax (ng/ml)	29.22	31.52	0.93	83.43	103.01

Table 42. Additional Study Information, Fed Bioequivalence Study No. R06-1031

Root mean square error, AUC0-t	0.1298	
Root mean square error, AUC∞	0.1263	
Root mean square error, Cmax	0.3924	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	76	76
Do you agree or disagree with firm's decision?	Yes	Yes
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	76	0.98	0.90	1.00
Reference	76	0.98	0.94	1.00

B. Ortho-Hydroxyatorvastatin

Table 43. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 52 and Figure 5

Fed Bioequivalence Study No. R06-1031										
Ortho-Hydroxyatorvastatin										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng.hr/mL	185.39	42.34	64.47	454.17	185.58	44.28	65.06	460.95	1.00
AUCI	ng.hr/mL	188.79	41.63	65.91	460.21	189.83	43.32	66.40	464.25	0.99
CMAX	ng/mL	24.15	48.10	7.88	69.34	25.56	44.44	6.36	55.80	0.94
TMAX	hr	2.50	.	0.75	5.00	2.00	.	0.75	11.00	1.25
KE	hr-1	0.06	27.91	0.03	0.10	0.06	31.58	0.02	0.11	1.05
THALF	hr	12.34	29.77	7.06	23.79	13.33	37.90	6.43	38.45	0.93

* Tmax values are presented as median, range

Table 44. Geometric Means and 90% Confidence Intervals - Firm Calculated

Ortho-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study No. R06-1031				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	170.215	169.970	1.00	97.1-104
AUC∞ (hr *ng/ml)	173.873	174.247	0.99	96.7-103
Cmax (ng/ml)	21.622	23.008	0.94	87.3-101

Table 45. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Ortho-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-1031					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	170.21	169.79	1.00	97.06	103.55
AUC∞ (hr *ng/ml)	173.87	174.25	1.00	96.67	103.00
Cmax (ng/ml)	21.62	23.01	0.94	87.30	101.17

Table 46. Additional Study Information, Fed Bioequivalence Study No. R06-1031

Root mean square error, AUC0-t	0.1205	
Root mean square error, AUC∞	0.1182	
Root mean square error, Cmax	0.2746	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	77	77
Do you agree or disagree with firm's decision?	Yes	Yes
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	77	0.98	0.93	1.00
Reference	77	0.97	0.84	1.00

C. Para-Hydroxyatorvastatin

Table 47. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 53 and Figure 6

Fed Bioequivalence Study No. R06-1031										
Para-Hydroxyatrovastatin										
		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng.hr/mL	32.06	55.82	7.98	100.54	31.63	58.93	8.12	115.53	1.01
AUCI	ng.hr/mL	34.28	56.85	9.13	102.67	34.02	57.81	8.59	117.88	1.01
CMAX	ng/mL	1.64	66.98	0.37	6.60	1.64	81.24	0.38	9.23	1.00
TMAX	hr	5.00	.	0.50	11.00	5.00	.	0.75	12.00	1.00
KE	hr-1	0.03	28.23	0.01	0.06	0.03	23.55	0.01	0.06	1.00
THALF	hr	23.48	33.96	12.34	57.39	22.84	27.39	12.31	51.25	1.03

* Tmax values are presented as median, range

Table 48. Geometric Means and 90% Confidence Intervals - Firm Calculated

Para-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study No. R06-1031 (N=77)				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	27.6193	27.3807	1.01	97.9-104
AUC∞ (hr *ng/ml)	29.8693	29.3378	1.02	98.6-105
Cmax (ng/ml)	1.333	1.3121	1.02	94.8-109

Table 49. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Para-Hydroxyatorvastatin 1 x EQ 80 mg Base Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-1031 (N=76)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	27.62	27.38	1.01	97.90	103.93
AUC∞ (hr *ng/ml)	29.87	29.34	1.02	98.64	105.09
Cmax (ng/ml)	1.33	1.31	1.02	94.77	108.94

Table 50. Additional Study Information, Fed Bioequivalence Study No. R06-1031

Root mean square error, AUC0-t	0.1105	
Root mean square error, AUC∞	0.1154	
Root mean square error, Cmax	0.2574	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	75	75
Do you agree or disagree with firm's decision?	Yes	Yes
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	75	0.93	0.58	0.98
Reference	75	0.93	0.69	0.99

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm assayed the plasma concentration data for atorvastatin, ortho-atorvastatin and para-hydroxyatorvastatin. The firm also provided the plasma profiles for atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin.

2. Ortho-hydroxyatrovastatin and para-hydroxyatorvastatin met the point estimate limits of 0.80-1.25.

3. According to the current BE recommendations, **only** atorvastatin should be analyzed using the confidence interval approach.

4. The firm and reviewer calculated the PK parameters (AUC_T, AUC_I, C_{max}, T_{max}, K_{el}, $t_{½}$) for atorvastatin, ortho-atorvastatin and para-hydroxyatorvastatin. Statistical analysis was performed on the PK parameters using the GLM procedure of SAS with a 90% confidence interval.

5. For atorvastatin, the firm did not calculate K_{el} and AUC_I for subject Nos. 28 (Period II, Treatment B) and 41 (Period II, Treatment A). The reviewer agrees with the firm's decision due to the subjects' individual plasma concentration data profiles for their respective investigational products.

6. For para-hydroxyatorvstatin, the firm did not calculate K_{el} and AUC_I for subject Nos. 57 (Period II, Treatment A) and 66 (Period II, Treatment B). The reviewer agrees

with the firm's decision due to the subjects' individual plasma concentration data profiles for their respective investigational products.

7. For para-hydroxyatorvastatin, the first measurable concentration for subject No. 27 in Period II was 0.05277 after receiving a single-oral dose of the reference product. This value is 5% of the subjects' C_{max} (0.6958); therefore, the subject was excluded from PK and statistical analysis.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study is acceptable.

Table 51. Mean Atorvastatin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin					
	Test (n=77)		Reference (n=77)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.25	2.66	257.66	0.59	322.15	4.53
0.50	17.26	160.82	10.12	187.42	1.71
0.75	20.87	119.36	18.01	121.97	1.16
1.00	21.76	90.91	21.83	94.65	1.00
1.25	21.43	74.04	23.24	81.76	0.92
1.50	20.42	70.41	23.07	76.38	0.89
2.00	19.45	65.86	22.84	73.51	0.85
2.50	18.60	62.86	20.74	68.62	0.90
3.00	17.30	65.30	19.15	71.45	0.90
3.50	16.41	64.46	17.34	73.24	0.95
4.00	15.43	65.30	15.76	75.14	0.98
4.50	18.28	59.65	18.80	72.56	0.97
5.00	16.05	70.11	15.71	74.52	1.02
5.50	13.37	64.23	12.97	69.89	1.03
6.00	11.51	68.12	11.22	70.29	1.03
7.00	8.06	67.56	7.87	71.71	1.02
8.00	6.59	64.72	6.41	66.42	1.03
9.00	5.29	64.61	5.32	67.88	0.99
10.00	4.64	67.13	4.56	75.13	1.02
11.00	5.36	61.91	5.40	66.34	0.99
12.00	4.12	68.37	4.01	69.40	1.03
16.00	2.09	73.79	1.93	69.13	1.08
24.00	0.94	72.87	0.91	74.57	1.04
36.00	0.61	73.46	0.57	66.32	1.07
48.00	0.23	101.87	0.21	84.73	1.08
72.00	0.04	260.90	0.03	237.19	1.06
96.00	0.01	502.06	0.00	620.47	1.57

Table 52. Mean Ortho-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Ortho-Hydroxyatrovastatin					
	Test (n=77)		Reference (n=77)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	394.08	0.00	326.67	0.85
0.25	0.19	356.36	0.04	516.20	4.24
0.50	5.10	173.11	3.42	251.99	1.49
0.75	11.22	116.89	8.29	158.87	1.35
1.00	14.65	93.96	11.05	112.20	1.33
1.25	15.04	81.19	13.09	97.30	1.15
1.50	15.78	74.16	12.97	84.99	1.22
2.00	16.64	66.90	14.62	71.19	1.14
2.50	17.12	59.55	15.12	59.75	1.13
3.00	17.29	55.56	15.22	60.37	1.14
3.50	16.65	52.73	15.15	60.44	1.10
4.00	16.56	49.28	15.51	58.37	1.07
4.50	19.37	46.87	16.91	51.61	1.15
5.00	16.06	48.12	14.62	56.39	1.10
5.50	14.35	47.96	12.78	55.36	1.12
6.00	13.02	46.32	11.55	58.22	1.13
7.00	10.10	45.12	9.41	58.31	1.07
8.00	8.89	43.20	7.84	56.99	1.13
9.00	7.63	44.65	6.48	56.41	1.18
10.00	6.85	46.88	5.46	55.64	1.25
11.00	6.92	44.04	5.87	52.17	1.18
12.00	5.47	43.57	4.98	58.42	1.10
16.00	2.96	38.95	2.60	55.31	1.14
24.00	1.42	45.65	1.17	52.60	1.21
36.00	0.93	45.14	0.80	52.43	1.17
48.00	0.40	56.41	0.34	67.04	1.19
72.00	0.09	120.13	0.08	148.47	1.13
96.00	0.02	281.95	0.02	303.51	0.95

Table 53. Mean Para-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Para-Hydroxyatrovastatin					
	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	318.80	0.00	614.07	2.41
0.25	0.02	292.57	0.00	379.73	6.39
0.50	0.28	206.80	0.11	250.80	2.52
0.75	0.43	167.87	0.27	164.88	1.60
1.00	0.48	134.77	0.35	124.29	1.35
1.25	0.50	106.33	0.41	110.58	1.20
1.50	0.50	97.42	0.44	101.46	1.14
2.00	0.63	90.44	0.58	99.71	1.07
2.50	0.73	79.88	0.69	88.95	1.06
3.00	0.83	85.98	0.84	92.39	0.99
3.50	0.94	72.19	0.93	89.20	1.02
4.00	1.04	65.68	1.01	87.43	1.03
4.50	1.41	69.21	1.42	93.21	0.99
5.00	1.36	66.17	1.36	91.38	1.00
5.50	1.30	63.38	1.30	88.51	1.00
6.00	1.23	62.67	1.24	88.18	0.99
7.00	0.98	59.55	1.00	88.09	0.98
8.00	0.93	59.22	0.93	73.63	1.00
9.00	0.88	58.00	0.89	73.85	0.98
10.00	0.90	61.46	0.91	69.14	0.99
11.00	1.14	58.56	1.16	62.55	0.98
12.00	0.95	60.19	0.95	63.09	0.99
16.00	0.65	60.55	0.62	55.09	1.04
24.00	0.42	51.10	0.43	57.04	0.97
36.00	0.37	53.91	0.37	57.05	0.99
48.00	0.21	82.25	0.21	61.77	1.03
72.00	0.10	75.39	0.10	68.21	1.05
96.00	0.06	105.58	0.05	85.56	1.06

Figure 4. Mean Atorvastatin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

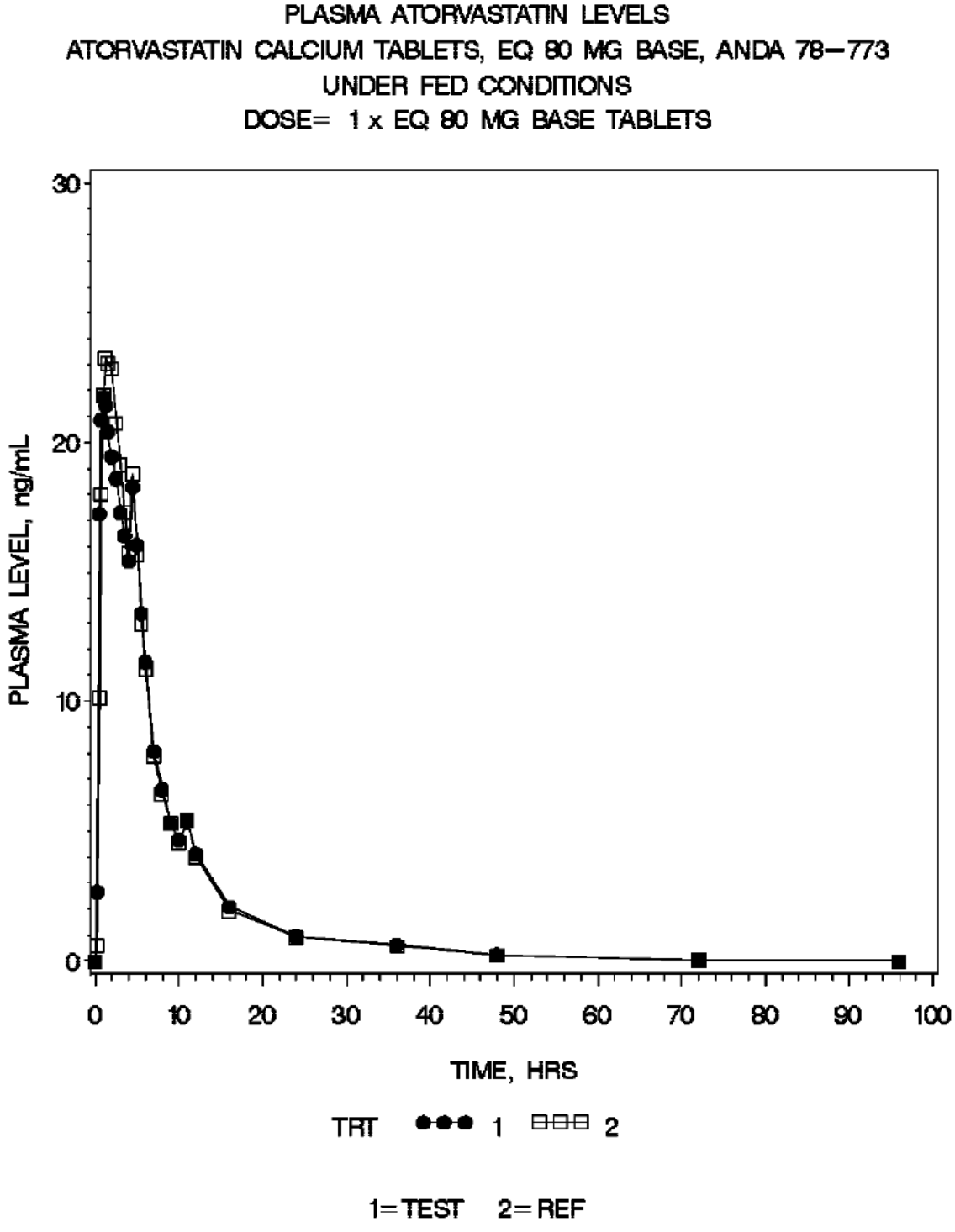


Figure 5. Mean Ortho-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

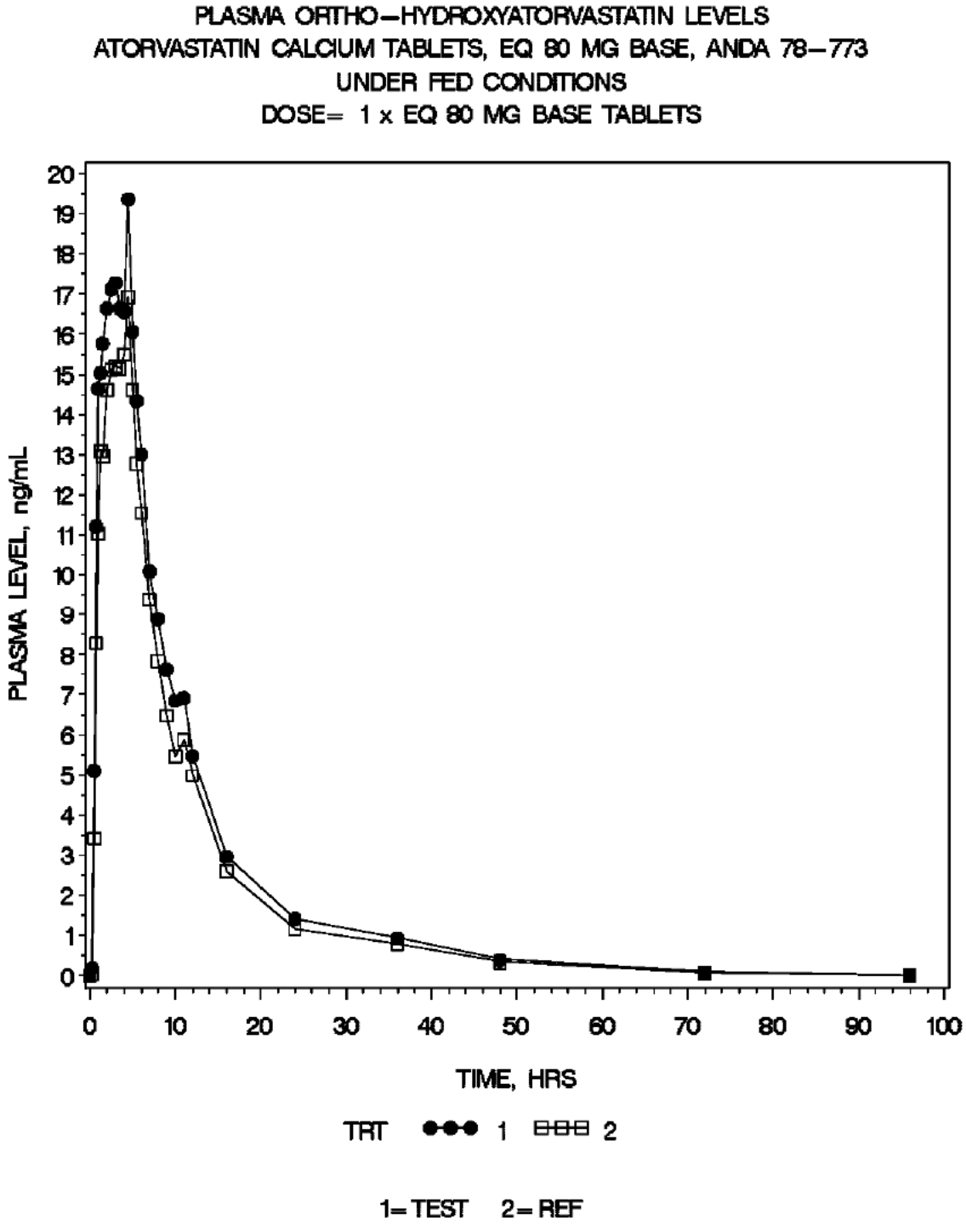
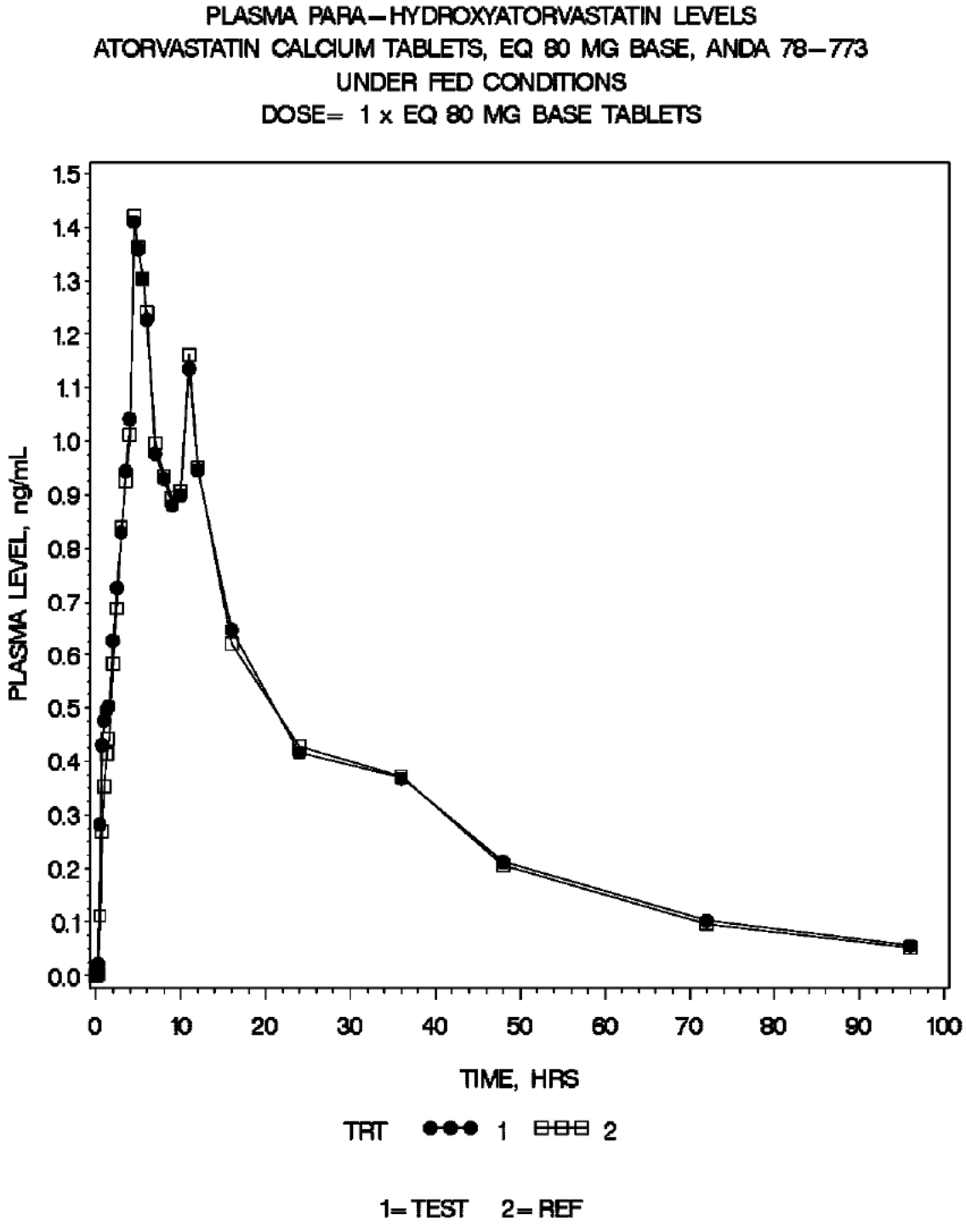


Figure 6. Mean Para-Hydroxyatorvastatin Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet
(b) (4)		
Atorvastatin Calcium (b) (4)	(b) (4)	
Lactose Monohydrate (b) (4)		
Crospovidone (b) (4)		
Magnesium Carbonate (b) (4)		
Colloidal Silicon Dioxide (b) (4)		
Magnesium Stearate (b) (4)		
(b) (4)		
(b) (4)		
Total	(b) (4)	
(b) (4)		

(b) (4)

Ingredient	Amount (mg) / tablet	Amount (%)/ tablet
Hypromellose (b) (4) (b) (4)		(b) (4)
Polydextrose (b) (4)		
Titanium Dioxide (b) (4)		
Polyethylene Glycol (b) (4)		
Total		

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?	NO
Comments on the drug product formulation:	The inactive ingredients in TEVA's Atorvastatin Calcium Tablets, EQ 80 mg Base are acceptable. The inactive ingredients are within the FDAs inactive ingredient guide (IIG limits).

4.3 Dissolution Data

Dissolution Review Path	Division of System Files v 2.0. Bioequivalence Dissolution Review N 078773 N 000 29-Dec-2006.

Table 54. Dissolution Data

Dissolution Conditions	**Apparatus:**	II (Paddle)
	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	NLT (b)(4)% (Q) in (b)(4) minutes	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
						15 min	30 min	45 min	60 min	
CDP 1485/02	Atorvastatin Calcium K-37191	Eq. to 80 mg Base Tablets	Dissolution: Apparatus 2 (paddles) Speed of Rotation: 75 rpm Medium: Buffer phosphate pH 6.8 Volume: 900 mL Temperature: 37 ± 0.5 °C Tolerance: NLT (b)(4)% (Q) dissolved in (b)(4) minutes.	12		93	95	95	95	Original ANDA Section VI.3
						(b) (4)				
					RSD (%)	2.7	2.3	2.3	2.3	
	Lipitor® 07625V	80 mg Tablets		12		94	97	94	95	
						(b) (4)				
					RSD (%)	3.2	3.2	3.1	2.4	

Figure 7. Dissolution Profiles

TEVA K-37191 vs. LIPITOR® 07625V



4.4 Detailed Regulatory History (If Applicable)

None.

4.5 Consult Reviews

None.

4.6 SAS Output

4.6.1 Fasting Study Data: Atorvastatin

(b) (4)

[redacted]

292 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

4.7 Additional Attachments

None.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-773

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, EQ 80 mg Base

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you will conduct dissolution testing on your Atorvastatin Calcium Tablets using the following FDA-recommended dissolution method and specification:

Medium:	0.05M Phosphate Buffer, pH 6.8
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	75 rpm

The test product should meet the following specification:

NLT (b)(4) % (Q) of the labeled amount of atorvastatin in the dosage form should be dissolved in 15 minutes

For future applications, you are advised to conduct the analysis of your study samples after all samples are collected.

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

4.8 Outcome Page

ANDA: 78-773

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4714	12/29/2006	Bioequivalence Study	Fasting Study	1	1
4714	12/29/2006	Bioequivalence Study	Fed Study	1	1
4714	9/14/2007	Dissolution Data	Dissolution Acknowledgement	0	0
				Bean Total:	2

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

/s/

April Braddy
3/10/2008 09:00:34 AM
BIOPHARMACEUTICS

Moheb H. Makary
3/10/2008 09:08:52 AM
BIOPHARMACEUTICS
For Dr. Dale P. Conner, Director, Division of Bioequivalence

Barbara Davit
3/10/2008 05:48:24 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-773	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength (s)	Eq. 80 mg Base	
Applicant Name	Teva Pharmaceuticals USA	
Address	1090 Horsham Road, PO Box 1090	
	North Wales, PA 19454-1090	
Applicant's Point of Contact	Philip Erickson, R.Ph. ,Sr. Director, Regulatory Affairs	
Contact's Phone Number	(215) 591-3141	
Contact's Fax Number	(215) 591-8812	
Submission Date(s)	December 29, 2006	
First Generic	No	
Reviewer	Sikta Pradhan, Ph.D.	
Study Number (s)	**B0606576**	**B0606577**
	(R06-1030)	**(R06-1031)**
Study Type (s)	**Fasting**	**Fed**
Strength(s)	**80 mg Tab.**	**80 mg Tab.**
Clinical Site	PRACS Institute, Ltd	
Clinical Site Address	4801 Amber Valley Parkway, Fargo, ND 58104	
Analytical Site	(b) (4)	
Analytical Address		

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. Firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). Firm's dissolution data meets the FDA-recommended dissolution specification (NLT (b)(4)% in 15 minutes). However, firm's proposed dissolution specification (NLT (b)(4)% (Q) in (b)(4) minutes) is not acceptable. The firm should acknowledge the FDA-recommended method and specification (NLT (b)(4)% (Q) in 15 minutes).

The DBE will review the fasted and fed BE studies at a later date.

TABLE 1. SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			X	☐	☐
Did the firm use the USP dissolution method			☐	☐	X
Did the firm use 12 units of both test and reference in dissolution testing			X	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			X	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	X	☐
Is FDA method in the public dissolution database (on the web)			X	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	X	☐	☐
		Plasma concentrations	X	☐	☐
	Fed BE study	PK parameters	X	☐	☐
		Plasma concentrations	X	☐	☐
	Other study	PK parameters	☐	☐	X
		Plasma concentrations	☐	☐	X
Are all eight electronic summary biotables present			X	☐	☐
Are electronic summary biotables in pdf format			X	☐	☐

If the answer to either of the last two questions is no, indicate which summary biotables are

- Not present: N/A
- Not in pdf format: N/A

RLD METHOD

Medium	0.05M Phosphate buffer at pH 6.8
Volume	900 ml
Temperature	37°C ± 0.5°C
Apparatus	USP 2 (Paddle)
Rotational Speed	75 rpm
Specification	NLT (b)(4)% (Q) dissolved in 15 minutes

Source of Method: [DBE Dissolution Database, modified on 1/15/2004]

TABLE 2. SUMMARY OF IN VITRO DISSOLUTION DATA

Study Ref. No.	Product ID/Batch No.	Dosage form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
						15 min	30 min	45 min	60 min	
CDP 1485/02	Atorvastatin Calcium K-37191	Eq. to 80 mg Base Tablets	Dissolution: Apparatus 2 (paddles) Speed of Rotation: 75 rpm Medium: Buffer phosphate pH 6.8 Volume: 900 mL Temperature: 37 ± 0.5 °C Tolerance: NLT (b) (4) % (Q) dissolved in (b) (4) minutes.	12		93	95	95	95 (b) (4)	Original ANDA Section VI.3
					RSD (%)	2.7	2.3	2.3	2.3	
	Lipitor® 07625V	80 mg Tablets		12		94	97	94	95 (b) (4)	
					RSD (%)	3.2	3.2	3.1	2.4	

COMMENTS:

The firm's dissolution testing data using the FDA-recommended method for Atorvastatin Calcium tablets, 80 mg are acceptable (at S1 level). Firm's dissolution data meet the FDA-recommended dissolution specification (NLT (b)(4)% in 15 minutes). However, firm's proposed dissolution specification (NLT (b)(4)% in (b)(4) minutes) is not acceptable. The firm should acknowledge the FDA- recommended method and specification (NLT (b)(4)% (Q) in 15 minutes).

DEFICIENCY COMMENTS:

Firm's proposed dissolution specification (NLT (b)(4)% in (b)(4) minutes) is not acceptable. The firm should acknowledge the FDA- recommended method and specification (NLT (b)(4)% (Q) in 15 minutes).

RECOMMENDATIONS:

The in vitro dissolution testing conducted by Teva Pharmaceuticals USA on its test product, Atorvastatin Calcium tablets, 80 mg comparing it to Lipitor® Tablets, 80 mg is acceptable. The dissolution data meet the FDA-recommended specification (NLT (b)(4)% (Q) in 15 minutes). The firm should acknowledge the FDA- recommended method and specification.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, Eq. 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 and has the following comment presented below. The review of the bioequivalence studies will be conducted later.

1. Your dissolution testing is acceptable. However, your proposed dissolution specification (NLT (b)(4)% (Q) in (b)(4) minutes) is not acceptable. Please acknowledge the following FDA- recommended method and specification:

The dissolution testing should be conducted in 900 mL of 0.05M Phosphate buffer at pH 6.8 using Paddle at 75 rpm. The test product should meet the following specification:

Not less than (b)(4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

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

ANDA #78-773
DISSOLUTION - INCOMPLETE Submission date: December 29, 2006

[NOTE: The in vitro testing is acceptable. However, the firm needs to acknowledge the FDA-recommended dissolution specification. The fasting and fed BE studies are pending review]

1. BDI -DISSOLUTION (Dissolution Data) Strength: 80 mg
Outcome: IC

Outcome Decisions: IC –Incomplete

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

/s/

Sikta Pradhan
7/10/2007 02:53:47 PM
BIOPHARMACEUTICS

Yih Chain Huang
7/10/2007 04:09:05 PM
BIOPHARMACEUTICS

Barbara Davit
7/12/2007 01:41:20 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078773

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 34	PM: Bob Gaines

Electronic ANDA: Yes ☒ No ☐

ANDA #:078773
Firm Name:Teva Pharmaceuticals USA
ANDA Name:Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base)
RLD Name:Lipitor Tablets (20702 by Pfizer)

Electronic AP Routing Summary Located:
V:\Chemistry Division III\Team 34\Electronic AP Summary\78773.ap.doc

AP/TA Letter Located:
V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\78773.apltr.DOC

Project Manager Evaluation: **Date: 5/16/12 Initials:** RG

☒ Previously reviewed and tentatively approved --- Date 12/1/2011
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 1/3/07	Date of Application 12/29/06	Date Acceptable for Filing 4/13/07
Patent Certification (type) PIV	Date Patent/Excl. expires 2015,2017,2013	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** 20069 (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☒ No ☐ Comment: Press release to be created by OCC. 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 8/19/08 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 5/10/12 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

Reference ID: 3136971

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:TA issued to this ANDA on 12/1/2011. At the time the TA was issued the reason cited for TA was another firm's (Ranbaxy) eligibility for 180 day exclusivity. TEVA had provided PIV certs to the unexpired '104, '156 and '971 patents and was not sued within 45 days. After TA, TEVA provided serial PIV certifications to the '488 patent which remains UNlisted in the OB. Since this patent was never listed I will not capture all of the submission dates in this RS. TEVA began these certifications on 12/27/2011 and continued for approximately 30 days. The last remaining barrier to the Full Approval of this ANDA is Ranbaxy's (76-477) eligibility for 180 day exclusivity. Ranbaxy triggered this exclusivity by commercially marketing all strengths. Their 180 day exclusivity period is set to expire on Monday the 28th of May which is a Federal Holiday. This ANDA is eligible for Full Approval on or after Tuesday the 29th of May.	

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 9:13 AM
To: Turner, Betty; Gaines, Robert
Subject: RE: ANDA 78773

I concur

Hi Bob,

Jean W. Zwicker is now listed at the point of contact in the most recent 356H

Do you need to add the following amendments? May 7, 2012 and April 10, 2012

Thanks,

Ruby

From: Turner, Betty
Sent: Thursday, May 17, 2012 8:51 AM
To: Gaines, Robert; Wu, Ruby (Chi-Ann)
Subject: RE: ANDA 78773

Good morning Bob,

I have checked the OB, USP, DARRTS, REMS, Drugs@fda and Medwatch for updates. No changes for the labeling since last review was completed.

Thanks,

Betty

From: Gaines, Robert
Sent: Wednesday, May 16, 2012 3:06 PM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 78773

Hello again Betty and Ruby.

Teva's Atorvastatin is also ready for approval on 5/29/12. Please provide labeling endorsement.

Thanks.

Bob

<< File: 78773.apltr.DOC >> << File: 78773 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 5/24/12**
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 11/30/11.

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 December 1, 2011. final approval was blocked at that time by Ranbaxy's ongoing 180-day exclusivity under ANDA 76-477. Refer to the administrative summary prepared at the time of the tentative approval. With the expiration of Ranbaxy's 180-day generic drug exclusivity on May 28, 2012, Teva's ANDA becomes eligible for final approval.

Final-printed labeling (FPL) found acceptable for approval 5/10/12, as endorsed 5/17/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #6 - Addendum #1) 5/24/12.

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 5/9/12 (Verified 5/25/12). No "OAI" Alerts noted.

Teva provided paragraph IV certifications to the '104, '156 and '971 patents, but was not sued within the 45-day period on any patent. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

With the expiration of Ranbaxy's 180-day generic drug exclusivity for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg on May 28, 2012, this ANDA is eligible for final approval. As May 28, 2012 falls on a Federal holiday, final approval will be granted on Tuesday, May 29, 2012.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS

Comments: RLWest for Keith Webber, Ph.D. 5/25/12.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

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

U.S. Generics

Jean W. Zwicker
Senior Director, Regulatory Affairs

May 7, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a labeling amendment to the above-referenced, tentatively approved Abbreviated New Drug Application in accord with an April 28, 2012 review letter from the Labeling Review Branch. For ease of review, a copy of the April 28, 2012 review letter is enclosed in **Attachment 1**. We have addressed your comments in the order in which they were presented.

LABELING DEFICIENCIES:

A. CONTAINER:

Revise "*Each tablet contains…" statement to read "*Each film-coated tablet contains..."

Response:
As requested, our container labels have been revised to read "*Each film-coated tablet contains...". Please find enclosed in **Attachment 2** our revised final print container labels (Iss. 5/2012) in Word and PDF formats. Comparisons to the last submitted container labels (Iss. 9/2010) are provided in PDF format.

Teva Pharmaceuticals
1090 Horsham Road | North Wales, PA 19454 | Tel. 215.591.8725 | Fax 215.591.8812 | jean.zwicker@tevapharm.com | www.tevapharm-na.com

B. INSERT:

1. HIGHLIGHTS:

Delete "and FDA Approved Patient Labeling" that appears at the end of the HIGHLIGHTS section.

Response:
In accord with 21CFR 201.57(a)(14), the highlights of Prescribing Information requirements for the Patient Counseling Information Statement "See 17 for Patient Counseling Information and (Insert either FDA-approved patient labeling or Medication Guide)." must appear in all FDA approved patient labeling. We therefore, respectfully decline to delete the "and FDA Approved Patient Labeling" that appears at the end of the HIGHLIGHTS section.

2. FULL PRESCRIBING INFORMATION: CONTENTS*:

i. Revise subtitle 2.1 and 2.2 to read as follows

2.1 Hyperlipidemia
2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

Response:
Please be advised that the content of labeling creates the highlight section in SPL and PLR. The table of contents match the content of labeling as per 21CFR 201.57(b). As such, we respectfully decline to revise our labeling in accord with your request.

ii. Under subtitle 4.1 revise "Elevations in" to read "Elevations of"

Response:
Please see Teva's response to FULL PRESCRIBING INFORMATION: CONTENTS 2(i) above.

iii. Revise subtitle "6.2 Postmarketing Experience" to read "Postintroduction Reports".

Response:
Please see Teva's response to FULL PRESCRIBING INFORMATION: CONTENTS 2(i) above.

iv. Revise subtitle 7.1 to read as follows:

7.1 Strong inhibitors of Cytochrome P450 3A4:
Clarithromycin
Combination of Protease Inhibitors
Itraconazole

Response:
Please see Teva's response to FULL PRESCRIBING INFORMATION: CONTENTS 2(i) above.

v. Revise subtitles 14.2, 14.3, and 14.4 to read as follows:

14.2 Hyperlipidemia and Mixed Dyslipidemia
14.3 Hypertriglyceridemia
14.4 Dysbetallpoproteinemia

Response:
Please see Teva's response to FULL PRESCRIBING INFORMATION: CONTENTS 2(i) above.

vi. Delete "PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS" that appears after subtitle 17.4 breastfeeding

Response:
Please be advised as the Patient Information is part of the content of labeling, the heading is included with the table of contents. Teva respectfully declines the request to delete "PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS" that appears after subtitle 17.4 breastfeeding.

3. FULL PRESCRIBING INFORMATION

i. GENERAL COMMENT:

Relocate the title for Figure 1; Figure 2, and Figure 3 that appears at the bottom of each figure, to appear at the top of the figure (Refer to the reference listed drug for guidance).

Response:
Teva respectfully declines the request to move the title of the figures, as it is Teva's format to position the figure title under the figure.

ii. 4 CONTRAINDICATIONS

a. Revise 4.1 to read as follows.

4.1 Active Liver Disease, which may include unexplained persistent elevations in hepatic transaminase levels

Response:
The RLD capitalizes some titles and uses upper and lower cases in others. It is our format to use capital letters throughout the headings to be consistent. As such, we respectfully decline to revise our labeling in accord with your request.

b. Revise 4.2 to read as follows.

4.2 Hypersensitivity to any component of this medication

Response:
Please see Teva's response to FULL PRESCRIBING INFORMATION 3(ii)(a) above.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the final approval of this ANDA on May 28, 2012. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /JMD

Jean W. Zwicker
Senior Director, Regulatory Affairs

5/7/2012

Date

Please send an email to the labeling reviewer (betty.turner@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 078773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8728)

TO: Teva Pharmaceuticals USA

TEL: (215) 591-1825

ATTN: Jean W. Zwicker

FAX: (215) 591-8812

FROM: Betty Turner

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, 20 mg, 40 mg and 80 mg.

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs 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.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 078773 Dates of Submission: April 10, 2012

Applicant's Name: TEVA Pharmaceuticals USA

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

---

LABELING DEFICIENCIES:

A. CONTAINER:

Revise "*Each tablet contains…" statement to read "*Each film-coated tablet contains…"

B. INSERT:

1. HIGHLIGHTS:
   Delete "and FDA Approved Patient Labeling" that appears at the end of the HIGHLIGHTS section.

2. FULL PRESCRIBING INFORMATION: CONTENTS*:

   i. Revise subtitle 2.1 and 2.2 to read as follows:

      2.1 Hyperlipidemia
      2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

   ii. Under subtitle 4.1 revise "Elevations in" to read "Elevations of"

   iii. Revise subtitle "6.2 Postmarketing Experience" to read "Postintroduction Reports".

   iv. Revise subtitle 7.1 to read as follows:

      7.1 Strong Inhibitors of Cytochrome P450 3A4:
      Clarithromycin
      Combination of Protease Inhibitors
      Itraconazole

   v. Revise subtitles 14.2, 14.3, and 14.4 to read as follows:

      14.2 Hyperlipidemia and Mixed Dyslipidemia
      14.3 Hypertriglyceridemia
      14.4 Dysbetalipoproteinemia

   vi. Delete "PATIENT INFORMATION FOR ATORVASTATIN CALCIUM TABLETS" that appears after subtitle 17.4 Breastfeeding

3. FULL PRESCRIBING INFORMATION:

   i. GENERAL COMMENT:
   Relocate the title for Figure 1; Figure 2, and Figure 3 that appears at the bottom of each figure, to appear at the top of the figure (Refer to the reference listed drug for guidance).

   ii. 4 CONTRAINDICATIONS

a. Revise 4.1 to read as follows.

   4.1 Active Liver Disease, which may include unexplained persistent elevations in hepatic transaminase levels

b. Revise 4.2 to read as follows.

   4.2 Hypersensitivity to any component of this medication

Submit revised insert 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.

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/

CHI-ANN Y WU
04/28/2012
For Wm. Peter Rickman

U.S. Generics

Jean W. Zwicker
Senior Director, Regulatory Affairs

April 10, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a minor amendment to the above-referenced, tentatively approved Abbreviated New Drug Application in accord with a December 1, 2011 tentative approval letter received for this file. As noted in the tentative approval letter, Teva's ANDA will be eligible for final approval upon expiration of the first PIV applicant's 180-day exclusivity period. Therefore, Teva respectfully requests final approval of this ANDA on May 28, 2012, the date of expiry of Ranbaxy's PC exclusivity. For your convenience, a copy of the December 1, 2011 tentative approval letter is enclosed in **Attachment 1**.

The following information is provided in support of our request for final approval:

Chemistry, Manufacturing, and Controls:
We hereby request withdrawal of a contract labeling facility which was previously proposed in this application. This site has not been used in support of this application.

(b) (4)

Please refer to the **fda-form-continued.pdf** for an updated summary of establishment information for all facilities proposed in this application.

Teva Pharmaceuticals
1090 Horsham Road | North Wales, PA 19454 | Tel. 215.591.8725 | Fax 215.591.8812 | jean.zwicker@tevapharm.com | www.tevapharm-na.com

Stability Data
Controlled room temperature stability data ((b) (4) months) were submitted to this file in an August 4, 2011 minor amendment. In a November 17, 2011 telephone amendment, Teva reduced the shelf life for this product to 18 months and submitted stability data for three commercial batches of each strength of drug product. Updated stability data for these commercial batches are provided herein (**Attachment 2**).

Labeling:
Please note that Teva's final print container labels were submitted in a labeling amendment dated February 23, 2011 and remain unchanged. Our final print package insert and patient package insert have been revised in accord with the most current labeling for the reference listed drug, Lipitor®, approved on February 28, 2012. Please find the following revised final print labeling in **Attachment 3**:

- Teva's final print package insert (Rev. D 2/2012) and patient package insert (Iss. 2/2012) in Word and PDF formats. A comparison of Teva's current package insert (Rev. D 2/2012) to that which was last submitted (Rev. B 2/2011) is provided in PDF format. In addition, a comparison of Teva's current patient package insert (Iss. 2/2012) to that which was last submitted (Iss. 4/2010) is also provided in PDF format.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 5 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has also been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA on May 28, 2012. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W Zwicker

Jean W Zwicker
Senior Director, Regulatory Affairs

04/10/12
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 26, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/26/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/26/2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 25, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/25/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson/gp

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/25/2012

Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591 3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 24, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/24/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/24/2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax. 215 591.8600 www.tevausa com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 23, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/23/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/23/2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone 215 591 3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/20/2012
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 20, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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Jean W. Zwicker
Senior Director, Regulatory Affairs

1/20/2012
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 19, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Enclosure

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

11/9/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson/gp
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/19/2012
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 18, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/18/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson/pp

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

1/18/2012

Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 17, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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{see appended signature page}

JWZ/jbp
Enclosure

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

11/17/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 17, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 16, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/16/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 16, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 13, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/31/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

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Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 13, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 12, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean Zwicker / gf

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/12/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 12 2012
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 11, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/11/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 11, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 10, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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{see appended signature page}

JWZ/jbp
Enclosure

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/10/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 10, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax. 215.591.8600 www tevausa com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 9, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
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{see appended signature page}

JWZ/jbp
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/9/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 9, 2012
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 6, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/6/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 6, 2012
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 5, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

1/5/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 5, 2012
Date

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1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 4, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
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Jean W. Zwicker
Senior Director, Regulatory Affairs

1/4/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 4, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

January 3, 2012

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker
Senior Director, Regulatory Affairs

1/31/2012
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Jan 3, 2012
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

December 30, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

12/30/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

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Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Dec 30, 2011
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

December 29, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced tentatively-approved ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,084,488, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,084,488 issued on December 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '488 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

12/29/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,084,488	September 14, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,084,488, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Dec 29, 2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

December 28, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,084,488

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Jean W. Zwicker
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Date

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_____ _____

Philip Erickson, R.Ph. Date
Vice President, Regulatory Affairs

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

December 27, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Dec 27, 2011
Date

Administrative Offices:
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Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

ROUTING SHEET

☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 34	PM: Leigh Ann Sears

Electronic ANDA: Yes ☒ No ☒

ANDA #:078773
Firm Name:TEVA Pharmaceuticals USA
ANDA Name:Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
RLD Name:Lipitor Tablets (NDA 20702 by Pfizer)

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 34\Electronic AP Summary\78773_AP-TA APRV ROUT SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\78773_TA.doc

Project Manager Evaluation: **Date: 11/17/2011 Initials:** LS

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 1/03/2007	Date of Application 12/29/2011	Date Acceptable for Filing 1/3/2007
Patent Certification (type) PIV	Date Patent/Excl. expires 2015, 2013, and 2017	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** _____ (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: 11/15/2011* ☐ 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) 11/30/2011 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 8/19/2008 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 8/16/2011 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: 11/21/11 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 11/23/11

☒ 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: 11/22/2011**

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 1/3/2007 for the 80 mg strength, BOS=Lipitor NDA 20702, PIII to '893, '995, '104, '156 and '971. Correspondence rec'd on 1/31/2007(before the ANDA was filed)-sponsor amended certs: PIII to '893, PIV to '995, '104, '156 and '971. ANDA ack for filing for the 80 mg strength on 1/3/2007(standard letter issued with LO on 4/13/2007). Patent Amendment rec'd on 11/16/2007-notice sent via Fed Ex to Warner-Lambert in Morris Plains NJ with notice delivered on 4/25/2007, notice sent via Fed Ex to Pfizer, Inc. in NY, NY with notice delivered on 4/25/2007, CA 07-360 filed in the D of DE on 6/7/2007 for infringement of the '995(not sued with respect to the '104, '156 and '971 patents), since suit was filed within 45 days the automatic 30 month stay of approval expired on 10/25/2009.

NSA submitted on 3/13/2008 for inclusion of the 10 mg, 20 mg and 40 mg strengths, BOS=Lipitor NDA 20702, PIII to '893, PIV to '995, '104, '156 and '971 patents. Patent Amendment rec'd on 9/25/2008-notice sent via Fed Ex to Pfizer in NY, NY with notice delivered on 3/13/2008, notice sent via Fed Ex to Warner-Lambert in Morris Plains, NJ with notice delivered on 3/13/2008, CA 08 CV 237 filed in the D of DE on 4/25/2008 for infringement of the '995 patent(not sued with respect to the '104, '156 and '971), since suit was filed within 45 days the automatic 30 month stay of approval expired on 9/13/2010.
Patent Amendment rec'd on 3/17/2009-PIV to the '667 patent for all strengths(with ped exclusivity this patent expired on 6/28/2011): again on 3/18/2009, 3/19. Patent Amendment rec'd on 7/19/2009-sponsor amends from PIV to PIII cert for the '995 and '667 patents which expire on 12/28/2010 and 6/28/2011 respectively.
Patent Amendment rec'd on 9/7/2010-PIV to '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,

9/27, 9/28, 9/29, 9/30, 10/1, 10/4, 10/5, 10/6, 10/7 and 10/8-to date this patent is not listed in the OB.
Patent Amendment rec'd on 9/27/2011-PIV to '376, again 9/27, 9/28, 9/29, 9/30, 10/3, 10/4, 10/5, 10/6, 10/7, 10/11, 10/12, 10/13, 10/14, 10/17, 10/18, 10/19, 10/20, 10/21, 10/24, 10/25, 10/26 and 10/27-to date this patent is not listed in the OB.

As thing currently stand the only barrier to the approval of TEVA's ANDA is Ranbaxy's continued eligibility for 180 day exclusivity. There are three remaining unexpired patents in the OB which cover Lipitor. These patents are the '104(exp 5/11/2015 with ped), '156(exp. 1/8/2017 with ped) and '971(exp. 7/19/2013 with ped). TEVA provided PIV certs to each of these patents and was not sued on any of the three. The only patent in which TEVA was sued was the '995 patent and this patent expired on 6/28/2011(again with ped exclusivity).
ANDA is eligible for immediate TA. (b) (4), (b) (5) [redacted]

2. ***Labeling Endorsement***

Reviewer, AV:
Date11/21/11
InitialsAV

Labeling Team Leader, JG:
Date11/22/11
InitialsJG

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Grace, John F
Sent: Tuesday, November 22, 2011 9:11 AM
To: Vu, Thuyanh (Ann); Sears, Leigh Ann
Subject: RE: Labeling sign-off for ANDA 078773 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg by TEVA)
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: Monday, November 21, 2011 2:41 PM
To: Sears, Leigh Ann; Grace, John F
Subject: RE: Labeling sign-off for ANDA 078773 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg by TEVA)
Please sign off for me. I checked OB,Drugs@ FDA and DAARTS.

Thanks
Ann

From: Sears, Leigh Ann
Sent: Monday, November 21, 2011 9:32 AM
To: Vu, Thuyanh (Ann); Grace, John F
Subject: Labeling sign-off for ANDA 078773 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg by TEVA)
Hello John and Ann,

Please perform labeling sign-off for this TA ANDA. It should be ready to TA, hopefully, before the end of this month.

Thanks,
Leigh Ann

Leigh Ann Sears, BSN, MAHS
CDR, U.S. Public Health Service
Chemistry Project Manager
Office of Generic Drugs, CDER, FDA
Phone: 240-276-8453 Fax: 240-276-8474
e-mail: leigh.sears@fda.hhs.gov

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read
OGD Regulatory Counsel

Date 23Nov2011
InitialsDTR

Pre-MMA Language included ☐
Post-MMA Language Included ☐

Comments:There are three patents remaining in the OB. Like all atorvastatin applicants, Teva filed PIV to these. Teva was not sued on any of these three. The basis of the TA is Ranbaxy's eligibility for 180-day exclusivity.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 11/30/11**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 11/30/11**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. By endorsing this tentative approval package, the CMC Division Director has oncurred that there are no precident setting issues associated with the CMC review and approval of this ANDA. Thus, no further CMC review is necessary.

OGD Office Management Evaluation

6. Peter Rickman **Date 11/30/11**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence study (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 to the 10 mg, 20 mg and 40 mg tablet strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 3/10/08, 8/19/08.

Final-printed labeling (FPL) found acceptable for approval (Approval Summary #3) 8/16/11, as endorsed 11/22/11. No REMS is required.

CMC found acceptable for approval (Chemistry Review #6) 11/30/11.

AND/OR

7. Robert L. West **Date 11/30/11**
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 11/15/11 (Verified 11/30/11). No "OAI" Alerts noted.

Teva provided paragraph IV certifications to the '995, '104, '156, '971 and '667 patents, Teva was sued within the 45-day period only on the '995 patent. The '995 patent expired on June 28, 2011 (with pediatric exclusivity extension). There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for tentative approval. Final approval of this ANDA is currently blocked by Ranbaxy's eligibility for 180-day generic drug exclusivity.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Keith Webber, Ph.D. 11/30/11.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 12/01/2011
Initials LS

Check Communication and Routing Summary into DARRTS

EER DATA:

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
12/01/2011

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 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.

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.

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
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 18, 2011

FROM: Paul Schwartz, Ph.D.
Associate Director for Product Quality Coordination
Office of Generic Drugs

THROUGH: Lawrence X. Yu, Ph.D.
Deputy Director for Science and Chemistry
Office of Generic Drugs

SUBJECT: API Sameness

TO: ANDA 078773 - Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, 80 mg
Teva Pharmaceuticals USA.

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 Teva in ANDA 078773 is atorvastatin calcium; it is (b) (4) and in a (b) (4) form designated as (b) (4).

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 Teva's ANDA meets the standards for identity in the monograph notwithstanding differences in polymorphic form.

Both the trihydrate and the anhydrous forms are listed in the USP monograph. The USP is silent, however, on the polymorphic 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 same wavelengths as the USP Reference Standard (USPRS). Since the drug substance used by Teva 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 Teva to use the modified IR method. When Teva 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 Teva 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 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 Teva's atorvastatin calcium tablets is in a different polymorphic form from that in the Pfizer Lipitor product, it is considered to be the same active ingredient because the Teva 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

From: CDER-OC-PLAIR
Sent: Monday, November 21, 2011 1:46 PM
To: gina.elton@tevausa.com
Cc: CDER-OC-PLAIR; Notzon, Stella; Philip.Erickson@tevausa.com
Subject: FW: PLAIR - ANDA#078773 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg base

Attachments: 2011-11-18 PLAIR - Atorvastatin Calcium Tabs-10 mg, 20 mg, 40 mg, and 80 mg base.pdf

Dear Gina,

At this time, FDA, Center for Drug Evaluation and Research (CDER) will exercise enforcement discretion to allow the importation of ANDA 78773 ATORVASTATIN Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg under the Pre-Launch Activities Importation Request (PLAIR).

Please make sure that your firm is registered and once the application has been approved you must list your drug product.

Stella Notzon (ORA contact above) must be notified, in advance, of the entry number involved that your company is importing under this PLAIR enforcement discretion. Please keep in mind that the amount of product imported into the US must match with what you stated in the PLAIR request. Otherwise, an amended PLAIR must be submitted to CDER-OC-PLAIR@fda.hhs.gov for an "enforcement discretion" which supersedes all enforcement discretion provided. You may make the changes on the initial PLAIR request, however please identify the document as an "amendment" to differentiate it from the initial PLAIR request which ensures expeditious review and response. Once your application has been approved, please provide us (CDER-OC-PLAIR and ORA/DIOP) with a copy of the approval letter.

Note: only one shipment ready for launching referring to one import entry regardless of the quantity, batches or lot numbers offered for imports will be acceptable.

Thanks,

ORA/DIOP Contact:

Stella Notzon

Import Operations and Policy Branch

Main no.: 301-796-6678

Fax: 301-827-4086

CDER contacts:

Marybet Lopez, CSO/CO

CDER/Import & Export Team

(301) 796-3213

CDER-OC-PLAIR@fda.hhs.gov

Michelle Dillahunt, CSO/CO

CDER/Import & Export Team

From: Gina Elton [mailto:Gina.Elton@tevapharm.com]
Sent: Friday, November 18, 2011 11:01 AM
To: CDER-OC-PLAIR
Cc: Philip Erickson; Debbie Jaskot
Subject: PLAIR - ANDA#078773 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg base

Attached please find the Prelaunch Activities Importation Request for ANDA#078773 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg base as a .pdf file. Please let me know if you have any difficulty opening this document.

Should you have any questions or need additional information, please contact Philip Erickson, Vice President, Regulatory Affairs at Philip.Erickson@tevapharm.com.

Thank you for your assistance.



Gina Elton
Project Specialist, North America Regulatory Affairs Policy & Governance
Tel: 215-591-8581 Fax: 215-591-8812 Gina.Elton@tevapharm.com http://www.tevapharm.com/

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/s/

LEIGH A SEARS
11/28/2011

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

November 23, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO A NOVEMBER 22, 2011 INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending ANDA in response to a November 22, 2011 telephone request received from Dr. Laxma Nagavelli of the Office of Generic Drugs. Specifically, Teva was asked to revise the drug substance limits for (b) (4) and (b) (4) in accord with the Related Compound D limit stated in the current USP monograph for atorvastatin calcium.

As requested, Teva has revised the drug substance impurity limits to control the sum of (b) (4) and (b) (4) at a limit of NMT (b) (4)%. Please find Teva's revised drug substance specification in **Attachment 1**. A certificate of analysis for a lot of API is provided in **Attachment 2**, demonstrating Teva's compliance with the revised limit.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately two megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has also been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevapharm.com
www.tevausa.com

{see appended signature page}

JWZ/jbp
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

11/23/11
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

November 17, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO NOVEMBER 16, 2011 INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending ANDA in response to a November 16, 2011 facsimile received from the Office of Generic Drugs, a copy of which is provided in **Attachment 1**. Comments presented in the facsimile are addressed in the order presented.

1. As requested, Teva will reduce the expiration dating on this product from (b) (4) months to 18 months. A revised stability protocol is provided in **Attachment 2**.

2. (b) (4)

3. All currently available stability data for three commercial batches of each strength are provided in **Attachment 3**. Further, Teva will provide the Agency with any additional stability data for these batches, via a gratuitous amendment, prior to final ANDA approval.

4. Teva hereby commits to place ten commercial batches of each strength of drug product on stability, and the data will be provided to the Agency via the annual report.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately two megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevapharm.com
www.tevausa.com

Teva Pharmaceuticals USA hereby certifies that a letter has also been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

11/17/2011
Date

TELEPHONE CONFERENCE FAX

ANDA 78773

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: Teva Pharmaceuticals, USA
ATTN: Philip Erickson

TEL: (215) 591-3141
FAX: (215) 591-8812

FROM: Haitao Li, Ph.D.

FDA CONTACT PHONE: 240-276-8462

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of the Chemist at 240-276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

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.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

The deficiencies presented below represent Telephone Deficiencies.

The deficiencies presented below represent Telephone Deficiencies.

1. Based on stability failures in the (b) (4) count containers, we recommend that you currently reduce the expiration date to 18 months. .

2. Please provide a (b) (4)

3. Please provide all available stability data on commercial batches of each strength and update the stability data through gratuitous amendment with notification to the division prior to full approval.

4. Please provide a commitment that you will place the first 10 batches of each strength on stability program and submit the results in annual report for the Agency review.

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

/s/

HAITAO LI
11/16/2011

LAXMA R NAGAVELLI
11/17/2011

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/27/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax. 215.591 8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 27, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/27/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson/gp
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/26/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 26, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/26/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/25/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone. 215.591 3000 Fax 215 591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 25, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/25/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/24/2011
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 24, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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JWZ/jbp
Enclosure

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Jean W. Zwicker
Senior Director, Regulatory Affairs

10/24/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/21/2011
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 21, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

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JWZ/jbp
Enclosure

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Jean Zwicker | JZ

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/21/2011
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 21, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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Document Control Room
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Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO OCTOBER 19, 2011 INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending ANDA in response to an October 19, 2011 request made by Dr. Laxma Nagavelli of the Office of Generic Drugs. Specifically, Teva was asked to provide drug substance ID by IR test data in accord with USP <197K>, both where the material was (b) (4) and where the material was dissolved in (b) (4) then evaporated to dryness before testing. Further, Teva is to provide a brief explanation for the need to dissolve the API in (b) (4) as part of the ID test procedure. Finally, Teva was asked to submit samples of the drug substance and USP reference standard to the St. Louis, Missouri district laboratory.

As excerpted from USP <197K>, "differences that may be observed in the spectra so obtained sometimes are attributed to the presence of polymorphs, which are not always acceptable …Unless otherwise directed in the individual monograph, therefore, continue as follows. If a difference appears in the IR spectra of the analyte and the standard, dissolve equal portions of the test specimen and the Reference Standard in equal volumes of a suitable solvent, evaporate the solution to dryness in similar containers under identical conditions, and repeat the test on the residues."

Teva has determined the "suitable solvent" for testing of our form of Atorvastatin calcium to be (b) (4), as reflected in our drug substance procedure manual (provided in **Attachment 1** for reference). Please refer to a report in **Attachment 2** which provides identification by IR test results for three lots of API, USP reference standard and in-house standard. Results reflect testing in accord with USP <197K>, both with and without (b) (4) using (b) (4). As requested by Dr. Nagavelli, the report also contains superimposed scans for each API lot as tested both with and without (b) (4).

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The scans herein demonstrate the compliance of our drug substance with the identification test by <197K> in the USP monograph for Atorvastatin calcium. Further, the data show that it is necessary for Teva to (b) (4) and (b) (4) the API and USP reference standard in order to account for differences in polymorphic form, as directed by USP <197K>.

Additionally, please note that the requested API samples and USP reference standard were forwarded today to the St. Louis laboratory.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately two megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has also been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosures

Jean Zwicker/JP
Jean W. Zwicker
Senior Director, Regulatory Affairs

10/21/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson/gp

Philip Erickson, R.P.h.
Vice President, Regulatory Affairs

10/20/2011

Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 20, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/20/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/19/2011
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 19, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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JWZ/jbp
Enclosure

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Jean W. Zwicker
Senior Director, Regulatory Affairs

10/19/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/18/2011
Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 18, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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Jean W. Zwicker
Senior Director, Regulatory Affairs

10/18/2011
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 18, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
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Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO OCTOBER 17, 2011 INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending ANDA in response to an October 17, 2011 request for information from Dr. Paul Schwartz of the Office of Generic Drugs. Specifically, Teva was asked to demonstrate compliance with the current USP test for ID by IR for the drug substance.

Please find in **Attachment 1** a commitment that all API utilized under ANDA 078773 will comply with the identification test provided in the current USP monograph for the drug substance. Further, to demonstrate compliance of our drug substance with USP ID by IR, also provided in **Attachment 1** are comparative IR scans for three lots of Teva's API versus reference standard where each was tested in accord with the current USP monograph for Atorvastatin Calcium and the provisions of USP General Chapter <197>. Also provided are IR scans of USP standard alone, and USP standard versus our supplier's (Assia Chemical Industries/TAPI) in-house standard.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately two megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215)

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JWZ/jbp
Enclosures

Jean Zwicker /jg

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/18/2011

Date

TEVA PHARMACEUTICALS

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/17/2011
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 17, 2011

Keith Webber, Ph.D., Acting Director
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PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
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Dear Dr. Webber:

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This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/17/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/14/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 14, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/14/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

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Philip Erickson /pe

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/13/2011

Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax: 215 591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 13, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/31/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson /pe
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/12/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax: 215 591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 12, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/12/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson/gp
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/11/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 11, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean Zwicker/gp

Jean W. Zwicker
Senior Director, Regulatory Affairs

12/11/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson/JP
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/10/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 10, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/10/2011
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 10, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO AN OCTOBER 6, 2011 INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced, pending ANDA in response to an October 6, 2011 request from Leigh Ann Sears of the Office of Generic Drugs. Specifically, Teva was asked to provide an updated listing of sites on the Form 356h continued, with full contact information for all drug substance and drug product facilities referenced within ANDA 078773.

We have reviewed the listing of sites submitted to this ANDA via a September 28, 2011 telephone amendment, and found it to contain all applicable sites for both drug substance and drug product. However in **Attachment 1,** please find an updated list of sites that has been clarified to state the site of drug substance (b) (4) as submitted to this application in an April 22, 2011 amendment, as follows:

Assia Chemical Industries Ltd. (Teva API Division)
Teva-Tech Site
Ramat Hovav
P.O. Box 2049, Emek Sara
Be'er Sheva 84874, Israel
Tel: 972-8-6509555
Fax: 972-8-6509500
FEI no. 3004096736
DUNS no. 514678507

US Agent Contact Information:
Plantex-USA Inc.
US Agent for Assia Chemical
Industries, Ltd. (Teva API Division)
Mrs. Kerri McCullough Wood
400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677-7604
Phone: 201-307-6900
Fax: 201-307-6909
E-mail: bheil@plantexusa.com

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevapharm.com
www.tevausa.com

Regarding naming and references to the API site, please note that we may have referred to our supplier (Assia Chemical Industries, Ltd.) in various responses as simply "TAPI", and we apologize for any confusion this may have caused.

Please note that the supplier's DMF may allow for activities to occur at sites referred to as Plantex or Teva-India, which are all part of the Teva API Division. We have confirmed with Assia Chemical Industries, Ltd., that the Atorvastatin Calcium supplied to Teva for ANDA 078773 was manufactured, (b) (4), and tested for release and stability at the Assia/Teva Tech location only (see address on page one of this letter as well as in **Attachment 1**).

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/10/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/7/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 7, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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{see appended signature page}

JWZ/jbp
Enclosure

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Jean W. Zwicker
Senior Director, Regulatory Affairs

10/7/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/6/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 6, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/6/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson Jr
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/5/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 5, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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JWZ/jbp
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/5/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/4/11
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 4, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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{see appended signature page}

JWZ/jbp
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/4/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/3/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax. 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 3, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/31/2011
Date

TELEPHONE AMENDMENT FAX

ANDA 078773

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:
Teva Pharmaceuticals USA
ATTN: Philip Erickson, R. Ph., Senior Director, Regulatory Affairs

TEL: (215) 591-3141

FAX: (215) 591-8812

FROM: Haitao Li, PhD

FDA CONTACT PHONE: 240-276-8462

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg.

Reference is also made to the amendment dated August 04, 2011.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" with in ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of the Chemist at 240-276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

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.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10mg, 20mg,40 mg, and 80 mg

The deficiencies presented below represent Telephone Deficiencies.

(b) (4)

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

/s/

HAITAO LI
10/03/2011

LAXMA R NAGAVELLI
10/03/2011

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS, Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/30/2011
Date

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 30, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/30/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson/gs

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/29/2011

Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 29, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

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ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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www.tevausa.com

Jean W. Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/29/2011
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 29, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO INFORMATION REQUEST DATED SEPTEMBER 29, 2011

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending ANDA in response to a September 29, 2011 request for information from the Division of Chemistry III. For ease of review, a copy of the aforementioned request is provided in **Attachment 1**. We have addressed your comments in the order in which they were presented.

(b) (4)

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevapharm.com
www.tevausa.com

(b) (4)



This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /JWD

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/29/2011

Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

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Philip Erickson

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/28/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215 591 3000 Fax: 215 591.8600 www tevausa com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 28, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
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www.tevausa.com

Jean Zwicker/gp

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/28/2011
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 28, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO A SEPTEMBER 27, 2011 REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced, pending ANDA in response to requests made by Leigh Ann Sears, Haitao Li and Laxma Nagavelli of the Office of Generic Drugs in a conference call with Teva on September 27, 2011.

Regarding the limit for [redacted] (b) (4) in the drug substance, the limit has been tightened as requested. The proposed limit of NMT [redacted] (b) (4) % is based on batch data currently in this application (reference is made to Attachment 32 of Teva's February 15, 2010 minor amendment), as well as a review of all API lots obtained from our supplier thus far. Please find the revised drug substance specifications in **Attachment 1**.

Regarding the discussion about limits for [redacted] (b) (4) and [redacted] (b) (4) in the drug product release and stability specification, we hereby commit to place any drug product batch that is intended for commercial distribution, which has results greater than or equal to [redacted] (b) (4) % for either of these two impurities, on long-term stability.

In addition to the topics discussed in the September 27, 2011 teleconference, we hereby request withdrawal of two facilities which were previously proposed in this application. The sites being withdrawn (see below) were proposed as an alternate site of finished packaged product labeling [redacted] (b) (4), and a site of warehousing and distribution of drug product [redacted] (b) (4) These sites have not been used in support of this application.

[redacted] (b) (4)

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(b) (4)

Please find in **Attachment 2** a complete list of all sites referenced within ANDA 078773.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/28/2011
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 27, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT: CERTIFICATION TO U.S. PATENT NO. 8,026,376

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 8,026,376, which on its face, has been assigned to Pfizer, Inc. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide **certification** with regard to this patent. Please note that U.S. Patent No. 8,026,376 issued on September 27, 2011. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, and assignee of the '376 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately one megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/jbp
Enclosure

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Jean W. Zwicker
Senior Director, Regulatory Affairs

9/27/2011
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
8,026,376	May 23, 2027

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 8,026,376 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/27/2011
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.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

T-con report:	**Date:** 8/2/11
Participants: Keith Webber called and left voice message in response to a voice message from Debbie Jaskot of Teva. Minutes: Debbie Jaskot from Teva left me a voice message today asking about the status of their ANDAs for enoxaparin (76-726) and atorvastatin (78-773). I left her a voice message in return stating that the immunogenicity review was progressing and that we needed to wait until review of the whole amendment was complete before coming to a decision. I also said that I had no information on the atorvastatin ANDA to convey at this time and that I had not had a chance to talk to anyone about it.	**ANDA Number:** 76-726 78-773
	Product Name: Enoxaparin Atorvastatin
	Firm Name: TEVA
	Firm Representative: Debbie Jaskot
	Phone Number:
	FDA Representative: Keith Webber

CC: ANDA

V:\FIRMSAM\ \TELECONS\ .doc

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/s/

THOMAS O HINCHLIFFE
08/10/2011

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

August 4, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

QUALITY MINOR AMENDMENT - RESPONSE TO JULY 27, 2011 INFORMATION REQUEST
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a quality minor amendment to the above-referenced, pending ANDA in response to the July 27, 2011 request for information from the Division of Chemistry. Reference is also made to a teleconference communication with staff of Chemistry Division III on August 3, 2011. For ease of review, a copy of the aforementioned request is provided in **Attachment 1**. We have addressed your comments in the order in which they were presented.

1. As requested, the table below details the impurities observed at the (b) (4)-month stability station for Teva's 10 mg (b) (4) configuration.

(b) (4)

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Additionally, please find in **Attachment 2** the chromatogram from impurity analysis of the 10 mg (b) (4) configuration showing the Out of Specification (OOS) impurities observed at the (b) (4)-month CRT stability time station. When compared to the system suitability standard chromatogram (**Attachment 2**), it is apparent that peaks observed in the OOS sample are attributable to the known oxidative impurities of Atorvastatin (b) (4)

Knowing that oxidation was the cause of our OOS result for the 10 mg (b) (4) configuration, our investigative efforts focused on the packaging components of the product, with the most likely cause being the (b) (4) A risk assessment (**Attachment 3**) was performed to assess suitable and reproducible sealing of bottles. To this end, the parameters that were modified for suitable performance of the sealing unit wer (b) (4) Validation of all operational parameters of the (b) (4) ranges was performed (b) (4) As requested, please find in **Attachment 4** the revised performance qualification/validation protocol for the (b) (4) A table that summarizes the changes that were made is also provided herein (**Attachment 5**). A diagram of the sealing machine is included to visually show the components that were adjusted during the Performace Qualification study (**Attachment 6**) to improve performance. In addition, packaging instructions for the (b) (4) now require operators to document additional equipment controls (b) (4) machine set-up, performance and quality check form). Please refer to the form in **Attachment 7** where these controls will be documented for future commercial batches.

A 30-day in-use study was conducted for all strengths of Teva's drug product packaged in the proposed 30-count configurations and reports were provided in Teva's minor amendment dated August 18, 2010. However, due to a change of response factor for (b) (4) as discussed in Teva's telephone amendment dated April 22, 2011, results reported for (b) (4) have since been recalculated using the RRf value of (b) (4) Revised reports containing the recalculated results are provided in **Attachment 8**, and support the stability of the drug product under conditions which simulate anticipated consumer use for this configuration. In addition, the stability protocol which details how the in-use study was conducted is provided in **Attachment 9**. It is important to note that bottle seals were broken on Day 1 of the study and thus bottles remained unsealed for the duration of the 30-day study. Additionally, the study was conducted in our 30 count bottles as they are intended to be provided directly to consumers as unit of use container.

In the interest of expeditiously answering the current review letter and to enable the Agency to complete their review of the CMC portion of this application, we hereby request approval for only the 30-count configuration for each strength. While the (b) (4) (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, and the (b) (4)-month CRT stability study, we hereby withdraw them from this application. Teva will commercially launch this product in only the 30-count unit of use configurations, but will re-evaluate the (b) (4) (b) (4)

(b) (4)

Please refer to the revised package component summary in **Attachment 10** that reflects only the 30-count configurations. Revised labeling which reflects the removal of said configurations will be submitted to the Labeling Support Branch under separate cover.

2. Please find in **Attachment 11** a comprehensive toxicological assessment that is based on scientific arguments including QSAR predictions of genotoxicity using the DEREK application, results of mutagenicity studies conducted in Europe and results for brand product from the US and European markets. The attached qualification document was prepared by Teva's in-house toxicology experts and is supported by the expert opinion of (b) (6), a renowned toxicologist. The data in totality support the conclusion that these (b) (4) have no genotoxic potential based upon the following:

   - Negative Ames and mouse lymphoma cell assay results,
   - Discounting of the hindered (b) (4) as an alert for genotoxicity,
   - Lack of genotoxic alerts in DEREK,
   - Comparable levels of these impurities in the RLD, and
   - Experimental evidence of safety in 28-day toxicitiy studies provided to the EU MAA

   Therefore, Teva's limits for the (b) (4) and (b) (4) impurities are deemed justified as they are within the ICH Q3B qualification threshold, and are further justified and supported by levels of these impurities detected in RLD sourced from both the US and EU markets.

   In addition, it is important to note that sales of Lipitor in the US alone amounted to the equivalent of over (b) (4) administered in 2010 (over (b) (4) prescriptions). The billions of administered doses since the first approval of Lipitor in 1996 attest to the safety of these known impurities, as there are no known alerts or actions that have been taken to remove the RLD from the US market.

3. Atorvastatin Calcium (b) (4) is a (b) (4) material that is characterized unequivocally by its X-Ray diffraction pattern. Different crystalline forms of Atorvastatin Calcium, as well as the amorphous form, are described in the literature. The most common crystalline forms are Form I (US5969156), Form II (US5969156), Form III (US6121461), Form IV (US5969156), Form VIII (US20020183378) and amorphous form. Each crystalline form displays a characteristic and unique X-Ray diffraction pattern. Teva's (b) (4) shows (b) (4) that are specific to this form (b) (4) Please find the XRD diffraction pattern of (b) (4) in Table 1 in **Attachment 12**. Assia's manufacturing process and solvent system consistently produce (b) (4) (Table II in **Attachment 12**). Quantities of (b) (4) have been observed in Assia's (b) (4) material, but this form transforms completely to (b) (4). Nevertheless, the polymorphic specification is based on final (b) (4) material and the theoretical possibility that Assia's Atorvastatin Calcium (b) (4) may contain minimal quantities of (b) (4) due to the presence of (b) (4) in the system. Based on historical XRD

data obtained by Assia for this drug substance, we hereby propose revision of the drug substance XRD limit to NLT (b)(4)% (b)(4)

Test	Previous Acceptance Criterion	Proposed Acceptance Criterion
Identification by XRD	NLT (b)(4)% (b)(4)	NLT (b)(4)% (b)(4)

Please find herein the revised drug substance monograph (**Attachment 13**) and specification (**Attachment 14**), which demonstrates adherence to the revised limit. Teva will test all future lots in accord with the revised drug substance specification herein.

4. The (b)(4) (b)(4) specific to Teva's (b)(4) are not overlapped by excipient peaks in the drug product. As noted in Table 1 in **Attachment 15**, the ranges of (b)(4) are scanned for the presence of these (b)(4) peaks while also ensuring that no additional peaks from other polymorphic forms are detected. Please note, the scanning ranges between (b)(4) are not specific to our polymorphic measurements due to lower sensitivity and excipient interference in these areas. The XRD method for the drug product (**Attachment 16**) has since been revised to measure only the relevant ranges (b)(4) . The corresponding method validation report is provided herein (**Attachment 17**).

We have added acceptance criteria for the (b)(4) to the drug product polymorphism release and stability specifications (**Attachment 18**) in order to ensure polymorphic consistency from batch to batch and that it is maintained throughout the shelf life of the drug product.

Test	Previous Acceptance Criteria	Proposed Acceptance Criteria
Polymorphism	The Diffractogram of the tablet conforms to the diffractogram of Atorvastatin Calcium tablet reference standard	A. The Diffractogram of the tablet conforms to the diffractogram of Atorvastatin Calcium tablet reference standard
	-	B. Peak of Atorvastatin Calcium (b)(4) appears at about (b)(4)
	No (b)(4) are found in the diffractogram of the analyzed Atorvastatin Calcium tablets compared to the Atorvastatin Calcium tablet reference standard.	C. No (b)(4) of active ingredient are found in the diffractogram of the tablet in the range of (b)(4)

We have reviewed XRD results for product tested at the (b)(4)-month CRT stability station and found them to meet the revised specification stated above. The results are presented in Table II and Figure 1 & 2 in **Attachment 15**.

The revised analytical method is provided in **Attachment 16**. The (b) (4)-month CRT stability data have been re-evaluated and found to meet the revised criteria (please refer to a report in **Attachment 19**).

5. A production batch of Teva's Atorvastatin Calcium Tablets, Eq. to 80 mg base Lot # 72A001 is used as reference standard. This batch has been fully characterized via XRD and C13 SS-NMR analysis. The C13 SS-NMR overlay presented in Figure 1 below indicates that all peaks which were detected in the Atorvastatin Tablets reference standard were attributed to placebo or to Atorvastatin Calcium (b) (4)

   Figure 1. C13-SS NMR spectrum for tablet reference standard (red) compared to the NMR spectrum of the inactive ingredient (blue) and to the NMR spectrum of Atorvastatin (b) (4) (green)



6. Please refer to **Attachment 18** for Teva's revised drug product release and stability specifications, as discussed above in response # 4.

7. We acknowledge that Assia's July 12, 2011 amendment to DMF # 20069 will be reviewed concurrent with the Agency's review of this minor amendment. Please note that Assia further amended their DMF on August 4, 2011 to reflect changes related to the API as discussed herein. Please find in **Attachment 20**, a copy of the cover letter from Assia's US Regulatory Agent (Plantex USA, Inc.) that accompanied the August 4, 2011 submission.

8. Please note that (b) (4)-month controlled room temperature stability reports supporting Teva's proposed 30-count unit of use configurations were provided in a telephone amendment dated April 22, 2011. Subsequently, all earlier stability timepoints were recalculated using the corrected RRf value of (b) (4) Please find the revised complete shelf-life CRT stability reports in **Attachment 19**.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 37 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable district office of the FDA certifying that an electronic submission has been submitted to CDER.

Teva believes the information contained herein constitutes a complete response to the comments presented in the July 27, 2011 review letter, and submits this amendment toward the continued review and final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

8/4/11
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

August 4, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

LABELING AMENDMENT – REVISED FINAL PRINT LABELING
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a labeling amendment to the above-referenced pending Abbreviated New Drug Application to provide revised final print labeling. Specifically, Teva's package insert has been updated to reflect removal of the (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, and the (b) (4) configurations for the 80 mg strength. These package configurations were withdrawn via a minor amendment submitted by Teva on August 4, 2011. As a result, the "How Supplied" section of Teva's insert now reflects only a 30-count configuration for each strength.

Please find the following revised final print labeling in **Attachment 1**:

- Teva's final print package insert (Rev. B 2/2011). In addition, a comparison of Teva's current package insert (Rev. B 2/2011) to that which was last submitted (Iss. 4/2011) is provided in PDF format. Please note that no changes have been made to the patient package insert (Iss. 4/2011) since last submitted.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 3 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

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Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevapharm.com
www.tevausa.com

{see appended signature page}

JWZ/aw
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

8/4/11
Date

QUALITY DEFICIENCY - MINOR

ANDA 078773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, 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 June 20, 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 **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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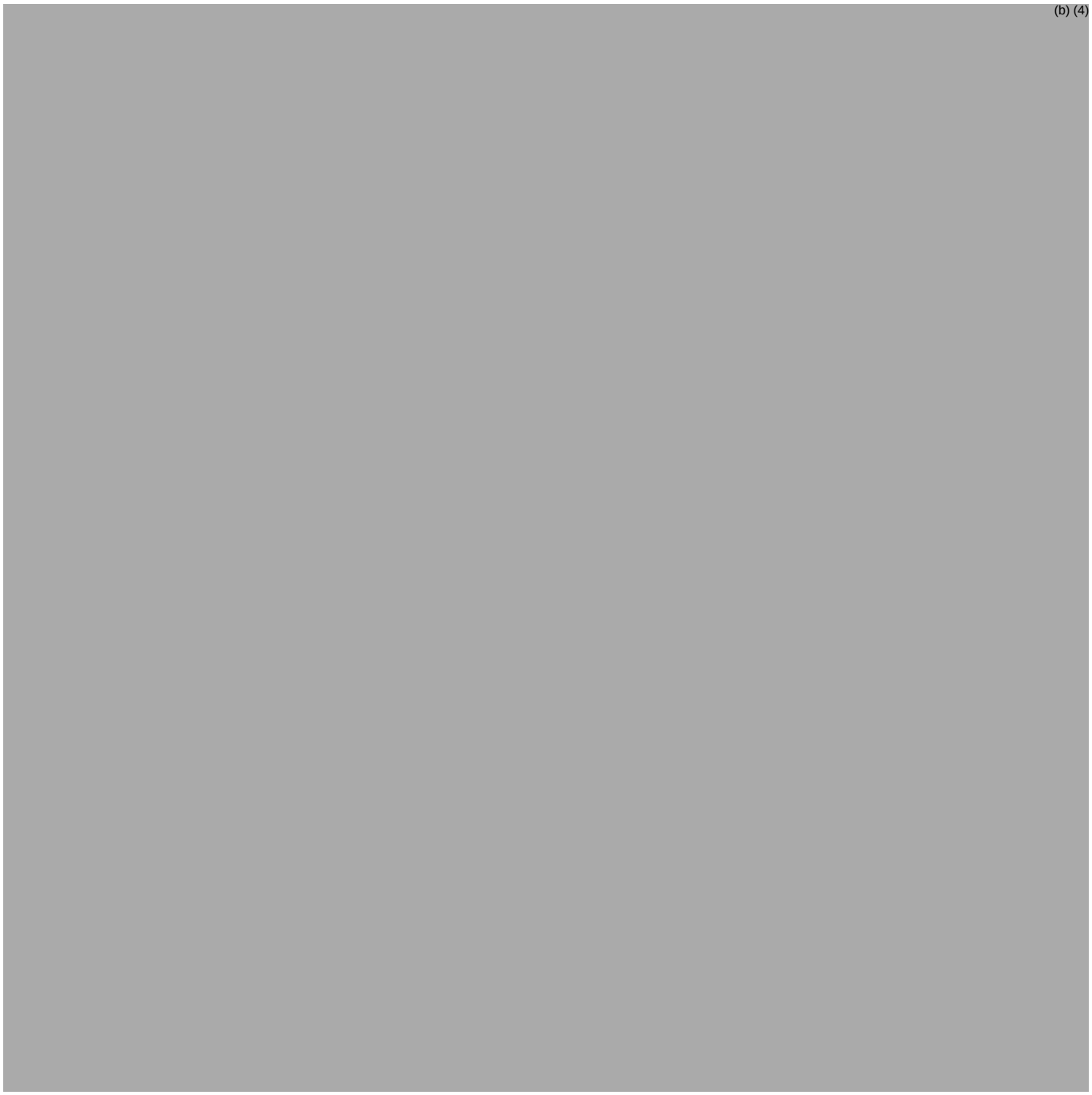
36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg, and
80 mg

The deficiencies presented below represent Minor Deficiencies.

(b) (4)





8. Please provide all available long term stability data for your drug product.

Sincerely yours,

{See appended electronic signature}

Vilayat 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/

LEIGH A SEARS
07/27/2011

LAXMA R NAGAVELLI
07/27/2011
Signed for Vilayat A Sayeed, PhD

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

June 20, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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QUALITY MINOR AMENDMENT - RESPONSE TO JUNE 9, 2011 INFORMATION REQUEST
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a quality minor amendment to the above-referenced, pending ANDA in response to the June 9, 2011 request for information from the Division of Chemistry. For ease of review, a copy of the aforementioned request is provided in **Attachment 1**. We have addressed your comments in the order in which they were presented.

1. Out of specification (OOS) results were observed at the (b) (4)-month stability station for Teva's 10 mg (b) (4) configuration for impurities (b) (4). An investigation was performed to identify the root cause of the stability failure. As part of the investigation of these results, the executed manufacturing record for the batch was examined, and no deviations from the manufacturing procedure that could affect the quality of the batch were noted. Further, the remaining package sizes for the 10 mg strength all yielded results that are within specification.

   The laboratory investigation involved a review of all analytical parameters which were found to be in accord with the analytical procedures. Samples were then re-run using the original bottle tested, and the OOS results were confirmed. The packaging for this sample was also assessed to ensure the results were not due to a defective container. The packaging was found to meet physical requirements (bottle was checked for height, body diameter, visual inspection of density, weight and finish), and the required quantity of (b) (4) and desiccants were present. A new bottle was then pulled from the stability chamber and analyzed. All results were found to be within specification.

   Based on the information above, we conclude that the OOS results were caused by a compromised seal on the original (b) (4) bottle that was tested at this stability time

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point. As Atorvastatin calcium is known to be sensitive to oxidation, and degrades to (b) (4) in the presence of oxygen, we believe that the improper seal allowed oxygen penetration of the bottle and thus the OOS results for these three impurities.

An evaluation of Teva's (b) (4) operation was performed in 2010 to ensure appropriate and reproducible sealing of all containers. As a result, the validation protocol for Teva's sealing operation was revised in 2010. This involved verification of proper functioning of the (b) (4) unit instrumentation (b) (4)). Also, re-validation of all operational parameter ranges (b) (4) was performed. All (b) (4) units at Teva's facility were revalidated accordingly between September 2010 and present (subsequent to the packaging of Lot K-41767, which was packaged in February 2009).

As a result of this re-validation, (b) (4) operating instructions were updated to include a more detailed set of instructions for the operation of the (b) (4) units. Updates include:

(b) (4)

We believe these revisions are appropriate to prevent issues with (b) (4) and will result in viable, protective seals for all future production batches.

As stated in our April 22, 2011 Telephone Amendment, all (b) (4) configurations were withdrawn from this application, and Teva commits that we will (b) (4) . All remaining package sizes for all strengths are within specification and support Teva's proposed (b) (4)-month shelf life for this product.

2. Please note that Teva has analyzed over twenty lots of brand product of varying ages to quantitate the (b) (4) impurity. This impurity was observed in the brand product at levels that exceed our proposed limit for this impurity. Specifically, results as high as (b) (4)% for (b) (4) were observed in RLD product that was tested at expiry. Please refer to a report presenting data for the lots of brand product tested in **Attachment 2**. Based on these results for RLD product, Teva's proposed release and

stability limits for this impurity are considered qualified based on the FDA Guidance for Industry *ANDAs: Impurities in Drug Products*, which states that a specified identified degradation product is considered qualified when "the observed level and proposed acceptance criterion for the degradation product do not exceed the level observed in the RLD". The guidance further notes that "A degradation product present in the generic drug product is considered qualified if the amount of identified degradation product in the generic drug product is similar to the levels observed in the RLD."

In conclusion, the results presented herein for Lipitor® Tablets support and qualify our proposed release and stability limits (NMT (b) (4) % for release and stability) for this impurity. As such, toxicology and genotoxicity studies are deemed unnecessary.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the continued review and approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker/JP

Jean W. Zwicker
Senior Director, Regulatory Affairs

6/20/2011
Date

QUALITY DEFICIENCY - MINOR

ANDA 078773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, 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 February 18, and April 22, 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/

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.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10mg, 20mg,40 mg and 80 mg Base

The deficiencies presented below represent Minor Deficiencies.

(b) (4)



Sincerely yours,

{See appended electronic signature}

Vilayat 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/

LEIGH A SEARS
06/08/2011

MOHAMMED K AHMED
06/09/2011

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

May 5, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

LABELING AMENDMENT – FINAL PRINT LABELING
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a labeling amendment to the above-referenced pending Abbreviated New Drug Application to provide revised final print labeling. Specifically, Teva's package insert has been updated to reflect the removal of the (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths, which were withdrawn via Teva's telephone amendment submitted on April 22, 2011. Therefore, the revised insert now reflects only those configurations for which stability data were provided in our April 22, 2011 chemistry amendment.

Please find the following revised final print labeling in **Attachment 1**:

- Teva's final print package insert (Iss. 4/2011). In addition, a comparison of Teva's current package insert (Iss. 4/2011) to that which was last submitted (Iss. 2/2011) is provided in PDF format. Please note, there were no changes to the patient package insert (Iss. 4/2010) since last submitted.

Please disregard the (b) (4) configuration bottle labels for the 10 mg, 20 mg and 40 mg strengths, which were provided in our February 23, 2011 amendment.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 3 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

05/05/11

Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

April 22, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT – RESPONSE TO INFORMATION REQUEST DATED MARCH 29, 2011

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a telephone amendment to the above-referenced, pending ANDA in response to a March 29, 2011 request for information from the Division of Chemistry. For ease of review, a copy of the aforementioned request is provided in **Attachment 1**. We have addressed your comments in the order in which they were presented. Please note that Dr. Leigh Ann Sears granted permission on April 11, 2011 for Teva to extend the 10-day response deadline.

(b) (4)

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

(b) (4)

2. Teva did utilize (b) (4) API to manufacture the ANDA batches and those submitted in our February 15, 2010 amendment. The API used for those batches was (b) (4) by our supplier, Assia Chemical Industries Ltd. Assia's DMF # 20069 for Atorvastatin Calcium details the (b) (4) processes that are followed for this drug substance.

Assia Chemical Industries Ltd. Teva-Tech Site Ramat Hovav P.O. Box 2049, Emek Sara Be'er Sheva 84874, Israel Tel: 972-8-6509555 Fax: 972-8-6509500 FEI no. 3004096736 DUNS no. 514678507	Contact: Mrs. Kerri McCullough Wood or associate Plantex-USA Inc. 400 Chestnut Ridge Road Woodcliff Lake, NJ 07677-7604 Phone: 201-3076914 Fax: 201-307-6909 E-mail: bheil@plantexusa.com

As per DMF # 20069. (b) (4) (b) (4) of the API prior to (b) (4) is performed with a (b) (4). It should be noted that the (b) (4) step has no effect on particle size. Following the (b) (4) (b) (4) step the material is (b) (4) with an (b) (4). Please refer to DMF # 20069 for details pertaining to the (b) (4) process and associated operating parameters.

Provided in **Attachment 4** is Teva's analytical method for the measurement of drug substance particle size distribution (b) (4) and the validation report for this method (b) (4)). Please note that method (b) (4) (R&D method: SI-100116) is suitable for both API grades (b) (4) and (b) (4). Grade (b) (4) is intended to be used for manufacture of commercial batches and pertains to API material that utilized the proposed alternate method for (b) (4) used in exhibit batches, as presented in a February 15, 2010 Minor Amendment to this application. An equivalency report is provided in **Attachment 5**.

3. The amendment to the validation report (VR-SI-19092 Amendment, Ed 03) for the drug product assay, impurities and degradation products determination method, which was provided in the February 18, 2011 Minor Amendment, incorrectly stated that (b) (4) cannot be synthesized. (b) (4) impurity standard was not available at the time of validation and a relative response factor (RRf) value of (b) (4) was assigned by default as in the case of unknown related impurities.

We have since obtained an (b) (4) impurity standard for validation. Please find in **Attachment 6** an amendment to the validation report (VR-SI-19092 Amendment 3, Ed. 01) which includes the quantitation limit, linearity and relative response factor for (b) (4) The RRf for (b) (4) was determined to be (b) (4), whereas the previous relative response factor for this peak was (b) (4) The proposed (b) (4) release and stability limit of NMT (b) (4)% remains unchanged based on the highest reported value of (b) (4)% at accelerated conditions using the old response factor of (b) (4) When recalculated using the new relative response factor of (b) (4), all stability results are still well within the proposed limit of NMT (b) (4)%. Consequently, all results reported for (b) (4) impurity at the (b) (4)-month time point (18-months for the 80 mg, (b) (4)) were recalculated using the RRf value of (b) (4) (**Attachment 7**). In support of the response factor change for (b) (4), the drug product method for Assay and Determination of Impurities and Degradation Products (SI-19092) has been updated and is provided in **Attachment 8**.

Please note that the RRf change for Impurity (b) (4) from (b) (4) was discussed previously in the August 18, 2010 Minor Amendment (comments # 15 and 19). As a result of improvements of the manufacturing process made by the supplier of the impurity, the RRf was reevaluated using freshly prepared standard to guarantee the accuracy of the results. The RRf was determined to be (b) (4) for the new lot of (b) (4) analytical standard and replaced the former value of (b) (4) in the analytical method. For ease of review, the method validation report (VR-SI-19092 Amendment 2, Ed.01) that supports this change (originally provided in an August 18, 2010 Minor Amendment) is provided herein (**Attachment 9**).

4. We hereby clarify that a (b) (4) configuration is not proposed for the 80 mg strength. Please note that the package insert most recently provided (in a March 1, 2011 Addendum to Labeling Amendment) correctly references only 30, (b) (4) bottle configurations for the 80 mg strength. Please find in **Attachment 10**, a summary of the proposed commercial packaging configurations for all strengths, for clarification. Stability data supporting all currently proposed configurations for each strength are provided in **Attachment 7**. Please refer to comment # 6 below which addresses the removal of the (b) (4) configurations for the 10 mg, 20 mg and 40 mg strengths.

5. The assay results obtained for the four strengths shows most values being in a (b) (4) range, with no apparent trend in any case. This distribution demonstrates good reproducibility of results, taking into consideration the intrinsic variability of any analytical procedure and/or production technology. Isolated results outside that range (such as batch K-41767 – 10 mg) are few, do not exceed the tight assay limits for the product ((b) (4)) and do not affect the overall assessment of stability for the particular configurations involved.

   We have reviewed the stability assay results and concluded that the observed fluctuations are in-line with the normal distribution of results that may be attributed to different analyst, dates of analysis and use of different HPLC instruments. The assay, impurities and degradation products method validation VR-SI-19092 and amendments demonstrate that the assay method is specific, linear, accurate, precise and robust for the analysis of Atorvastatin Calcium Tablets.

In accord with the ICH Q1E Guidance which states that "Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute...In general, the relationship between certain quantitative attributes and time is assumed to be linear", all long term stability study results were subjected to linear regression analysis. Slope and Y-intercept of the assay results versus time intervals were calculated by using the best-fit regression line for all packaging configurations for each strength, from time zero to (b) (4) months (18-months for the 80 mg (b) (4)) at (b) (4). In addition to average results, difference between average and intercept and relative standard deviation were calculated for each of the analyses. The results are summarized in **Attachment 11**.

6. Please find enclosed in **Attachment 7**, all available controlled room temperature stability data for batches K-41767 (10 mg), K-41769 (20 mg), K-41771 (40 mg) and K-41773 (80 mg). The (b) (4) package configuration for batch K-41773 (80 mg) was introduced into the stability program later than all other bottle configurations, therefore, 18-months shelf-life controlled room temperature stability data for the 80 mg (b) (4) bottle configurations are provided. For all other configurations, (b) (4)-month data are provided.

   Please be advised that out of specification results for three identified impurities were obtained at the (b) (4) month stability station for the 10 mg (b) (4) configuration. An investigation was opened, and testing was repeated on a separate 10 mg (b) (4) bottle. Results for that bottle were found to be within specification for these impurities. An investigation of the original results continues. However, because we have not defined an assignable cause at this time, we hereby withdraw all (b) (4) configurations (for the 10 mg, 20 mg and 40 mg strengths) and commit that we (b) (4). Therefore, updated stability data for these configurations are not provided. Revised labeling reflecting the removal of said configurations will be submitted under separate cover. Please refer to the updated package component summary in **Attachment 10** that reflects removal of the (b) (4) configurations.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 17 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /JWZ

Jean W. Zwicker
Senior Director, Regulatory Affairs

4/22/2011

Date

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.

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[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.

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[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

TELEPHONE CONFERENCE FAX

ANDA 78773

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: Teva Pharmaceuticals USA

TEL: (215) 591-3141
FAX: (215) 591-8812

ATTN: Philip Erickson

FDA CONTACT PHONE: 240-276-8462

FROM: Haitao Li, Ph.D

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg

Reference is also made to your amendment dated February 18, 2011

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of the Chemist at 240-276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

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.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10mg, 20mg,40 mg and 80 mg Base

The deficiencies presented below represent Telephone Deficiencies.



6. Please provide up to date stability studies for all strengths of drug product.

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

/s/

HAITAO LI
03/29/2011

LAXMA R NAGAVELLI
03/30/2011
Please change stability studies to stability data for deficiency 6. Thanks.

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 91226 and 78773
DRUG: Atorvastatin Calicum Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

APPLICANT: Matrix Laboratories Limited and TEVA Pharmaceuticals USA
DATE OF SUBMISSION:2/17/2011

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 180-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☐	L.Sears/3/2/2011
Chemistry Team Leader (sign as needed)	Grant☒	Deny☐	L.Nagavelli/3/2/2011
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☐	V.Sayeed/3/2/2011
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☒	Deny☐	B.West/2/17/2011-email concurrence below

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: Team 34
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE 3/2/2011
Paste Email Copy Below:

Reference ID: 2912719

From: West, Robert L
Sent: Thursday, February 17, 2011 7:50 AM
To: Sears, Leigh Ann; Gonitzke, Mark; Vu, Thuyanh (Ann); Chun, Nam
Cc: Li, Haitao; Sayeed, Vilayat A; Gill, Devinder; Jiang, Weiqin; Cuthbert, Gerrard D; Ya, Naiqi; Iser, Robert; Li, Bing; Sanchez, Aida L; Conner, Dale P; Webber, Keith; Hassall, Rita R; Ames, Timothy W; Nagavelli, Laxma; Zuk, Susan; Yu, Lawrence; Shimer, Martin; Rickman, William P; Golson, Lillie D; Grace, John F; Lee, Koung U
Subject: EXPEDITED REVIEW GRANTED FOR ANDA'S 78-773 (TEVA) AND 91-226 (MATRIX) FOR ATORVASTATIN CALCIUM TABLETS (LIPITOR/PFIZER) - CONFIDENTIAL

Atorvastatin Teams:

Both Teva (ANDA 78-773) and Matrix (ANDA 91-226) have submitted documentation to the office stating that each firm has settled its patent litigation for Atorvastatin Calcium Tablets with Pfizer. This has also been reported publically in the press (Pink Sheet - February 14, 2011). The settlements provide that the patent litigation will be dismissed on or about June 28, 2011, thereby making Matrix's ANDA eligible for final approval as of that date. (The '995 and '667 patents expire on that date as well).
Teva claims to have a Consent Order from the court in which Teva is not prohibited from launching their product after June 28, 2011. At present, we are not aware of any other ANDA applicants that have made similar settlements with Pfizer. (Note: As noted in the Pink Sheet, at least four other applicants, Apotex, Kudco, Dr. Reddy's and Actavis remain in litigation over various Lipitor patents).

To complicate the matter, we are aware that Ranbaxy currently appears to be eligible for 180-day generic drug exclusivity for Atorvastatin Calcium Tablets. However Ranbaxy's ANDA is currently subject to the Application Integrity Policy (AIP) and the (b) (4), (b) (5) We are uncertain as to the outcome of these negotiations. Nevertheless, due to the unique nature and medical necessity of Atorvastatin Calcium Tablets, I have discussed the issues with Keith Webber, and OGD counsel. Keith has also discussed the issues with OPS and the Center and we are in agreement that OGD needs to be prepared to take an action no matter what the outcome of the Ranbaxy 180-day eligibility decision.

At this time, the office is granting "expedited review" status to Teva's ANDA 78-773 and Matrix's ANDA 91-226 based upon their stated ability to be approved on or about June 28, 2011. DARRTS reveals the following with respect to these ANDAs:

	TEVA 78-773	Matrix 91-226
CMC Review Team	34	43
CMC	Pending with Teva	Pending
Bio	Acceptable	Pending (Bio Branch 6)
Labeling	Acceptable for T/A	Pending
EES	Withhold	Withhold

In the near future, we also expect to grant "expedited review" status to Ranbaxy's ANDA 76-477 (Team 34, CMC also assigned to Haitao Li) even though the firm is currently subject to the AIP policy. Keith Webber is currently briefing the Center and is expected to obtain its consent in the near future. It appears that Ranbaxy has also made a settlement with Pfizer allowing them to enter the market on November 30, 2011, provided they have obtained approval of their ANDA.

Thus, if the agency, OCC and the Justice Department conclude that Ranbaxy will retain its eligibility for 180-day generic drug exclusivity and that the ANDA can be approved, OGD will be ready. Alternatively, if the decision does not favor Ranbaxy, OGD will also be ready to approve alternate ANDAs in order to have a generic product in the marketplace as soon as possible.

Another issue is the presence of a Citizen Petition from Pfizer regarding the polymorph form

Reference ID: 2912719

present in the API. This is being actively addressed by the office, OCC and ORP and will need to be finalized prior to any OGD approval for Atorvastatin Calcium Tablets.

On a related note, it has been noted in the Pink Sheet that Watson has negotiated the exclusive right to market an authorized generic under Pfizer's NDA for 5 years and will launch in November 2011 or earlier should another applicant market prior to that date.

Thank you,

Bob

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
03/02/2011

VILAYAT A SAYEED
03/03/2011

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

March 1, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ADDENDUM TO LABELING AMENDMENT DATED FEBRUARY 23, 2011

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an addendum to our labeling amendment dated February 23, 2011 related to the above-referenced, pending Abbreviated New Drug Application. The referenced labeling amendment provided final print labeling and included revisions to support the removal of packaging configurations which were withdrawn via Teva's minor amendment submitted on February 18, 2011.

Please note that the insert provided in our February 23, 2011 inadvertently referenced a (b) (4) bottle configuration for the 80 mg strength. Therefore, please find herein a revised insert that now reflects only those configurations for which stability data were provided in our February 18, 2011 chemistry amendment. We apologize for the oversight, and request that the revised final print insert provided herein replace that provided in our February 23, 2011 submission.

Please find the following revised final print labeling provided in **Attachment 1**:

- Teva's final print package insert (Iss. 2/2011) and patient package insert (Iss. 4/2010) in Word and PDF formats. In addition, a comparison of Teva's current package insert (Iss. 2/2011) to that which was last submitted (Iss. 4/2010) is provided in PDF format. Please note, there were no changes to the patient package insert since last submitted.

Please disregard the bottle label for the 80 mg (b) (4) configuration which was provided in our February 23, 2011 amendment.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 4 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /bmo

Jean W. Zwicker
Senior Director, Regulatory Affairs

3/1/2011

Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

February 23, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

LABELING AMENDMENT – FINAL PRINT LABELING
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a labeling amendment to the above-referenced pending Abbreviated New Drug Application to provide final print labeling. Please note that Teva's labeling has been updated to support the removal of packaging configurations as presented in Teva's minor amendment submitted on February 18, 2011. Please find the following final print labeling provided in **Attachment 1**:

- Teva's final print package insert (Iss.1/2011) and patient package insert (Iss. 4/2010) in Word and PDF formats. In addition, a comparison of Teva's current package insert (Iss. 1/2011) to that which was last submitted (Iss. 4/2010) is provided in PDF format. Please note, there were no changes to the patient package insert since last submitted.

- Teva's final print container labels (Iss. 9/2010) in PDF format for intended marketing configurations. Please note, there were no changes to the container labels since they were last submitted.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 8 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the final approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /JWD

Jean W. Zwicker
Senior Director, Regulatory Affairs

2/23/2011

Date

Jean W. Zwicker
Senior Director, Regulatory Affairs

February 18, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

QUALITY MINOR AMENDMENT - RESPONSE TO JANUARY 13, 2011 INFORMATION REQUEST
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a quality minor amendment to the above-referenced, pending ANDA in response to the January 13, 2011 request for information from the Division of Chemistry. For ease of review, a copy of the aforementioned request is provided in **Attachment 1**. We have addressed your comments in the order in which they were presented.

A. Deficiencies:

(b) (4)

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

9 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

(b) (4)



This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission is presented in electronic format and is comprised of approximately 55 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the continued review and approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /JWD

Jean W. Zwicker
Senior Director, Regulatory Affairs

2/18/2011

Date

Gonitzke, Mark

From: West, Robert L
Sent: Thursday, February 17, 2011 7:50 AM
To: Sears, Leigh Ann; Gonitzke, Mark; Vu, Thuyanh (Ann); Chun, Nam
Cc: Li, Haitao; Sayeed, Vilayat A; Gill, Devinder; Jiang, Weiqin; Cuthbert, Gerrard D; Ya, Naiqi; Iser, Robert; Li, Bing; Sanchez, Aida L; Conner, Dale P; Webber, Keith; Hassall, Rita R; Ames, Timothy W; Nagavelli, Laxma; Zuk, Susan; Yu, Lawrence; Shimer, Martin; Rickman, William P; Golson, Lillie D; Grace, John F; Lee, Koung U
Subject: EXPEDITED REVIEW GRANTED FOR ANDA'S 78-773 (TEVA) AND 91-226 (MATRIX) FOR ATORVASTATIN CALCIUM TABLETS (LIPITOR/PFIZER) - CONFIDENTIAL

Atorvastatin Teams:

Both Teva (ANDA 78-773) and Matrix (ANDA 91-226) have submitted documentation to the office stating that each firm has settled its patent litigation for Atorvastatin Calcium Tablets with Pfizer. This has also been reported publically in the press (Pink Sheet - February 14, 2011). The settlements provide that the patent litigation will be dismissed on or about June 28, 2011, thereby making Matrix's ANDA eligible for final approval as of that date. (The '995 and '667 patents expire on that date as well).
Teva claims to have a Consent Order from the court in which Teva is not prohibited from launching their product after June 28, 2011. At present, we are not aware of any other ANDA applicants that have made similar settlements with Pfizer. (Note: As noted in the Pink Sheet, at least four other applicants, Apotex, Kudco, Dr. Reddy's and Actavis remain in litigation over various Lipitor patents).

To complicate the matter, we are aware that Ranbaxy currently appears to be eligible for 180-day generic drug exclusivity for Atorvastatin Calcium Tablets. However Ranbaxy's ANDA is currently subject to the Application Integrity Policy (AIP) and the [redacted] (b) (4), (b) (5) We are uncertain as to the outcome of these negotiations. Nevertheless, due to the unique nature and medical necessity of Atorvastatin Calcium Tablets, I have discussed the issues with Keith Webber, and OGD counsel. Keith has also discussed the issues with OPS and the Center and we are in agreement that OGD needs to be prepared to take an action no matter what the outcome of the Ranbaxy 180-day eligibility decision.

At this time, the office is granting "expedited review" status to Teva's ANDA 78-773 and Matrix's ANDA 91-226 based upon their stated ability to be approved on or about June 28, 2011. DARRTS reveals the following with respect to these ANDAs:

	TEVA 78-773	Matrix 91-226
CMC Review Team	34	43
CMC	Pending with Teva	Pending
Bio	Acceptable	Pending (Bio Branch 6)
Labeling	Acceptable for T/A	Pending
EES	Withhold	Withhold

In the near future, we also expect to grant "expedited review" status to Ranbaxy's ANDA 76-477 (Team 34, CMC also assigned to Haitao Li) even though the firm is currently subject to the AIP policy. Keith Webber is currently briefing the Center and is expected to obtain its consent in the near future. It appears that Ranbaxy has also made a settlement with Pfizer allowing them to enter the market on November 30, 2011, provided they have obtained approval of their ANDA.

Thus, if the agency, OCC and the Justice Department conclude that Ranbaxy will retain its eligibility for 180-day generic drug exclusivity and that the ANDA can be approved, OGD will be ready. Alternatively, if the decision does not favor Ranbaxy, OGD will also be ready to approve alternate ANDAs in order to have a generic product in the marketplace as soon as possible.

Another issue is the presence of a Citizen Petition from Pfizer regarding the polymorph form present in the API. This is

being actively addressed by the office, OCC and ORP and will need to be finalized prior to any OGD approval for Atorvastatin Calcium Tablets.

On a related note, it has been noted in the Pink Sheet that Watson has negotiated the exclusive right to market an authorized generic under Pfizer's NDA for 5 years and will launch in November 2011 or earlier should another applicant market prior to that date.

Thank you,

Bob

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

/s/

MARK A GONITZKE
02/17/2011

QUALITY DEFICIENCY - MINOR

ANDA 078773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Leigh Ann Bradford FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, 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 18, and August 24, 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.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals USA

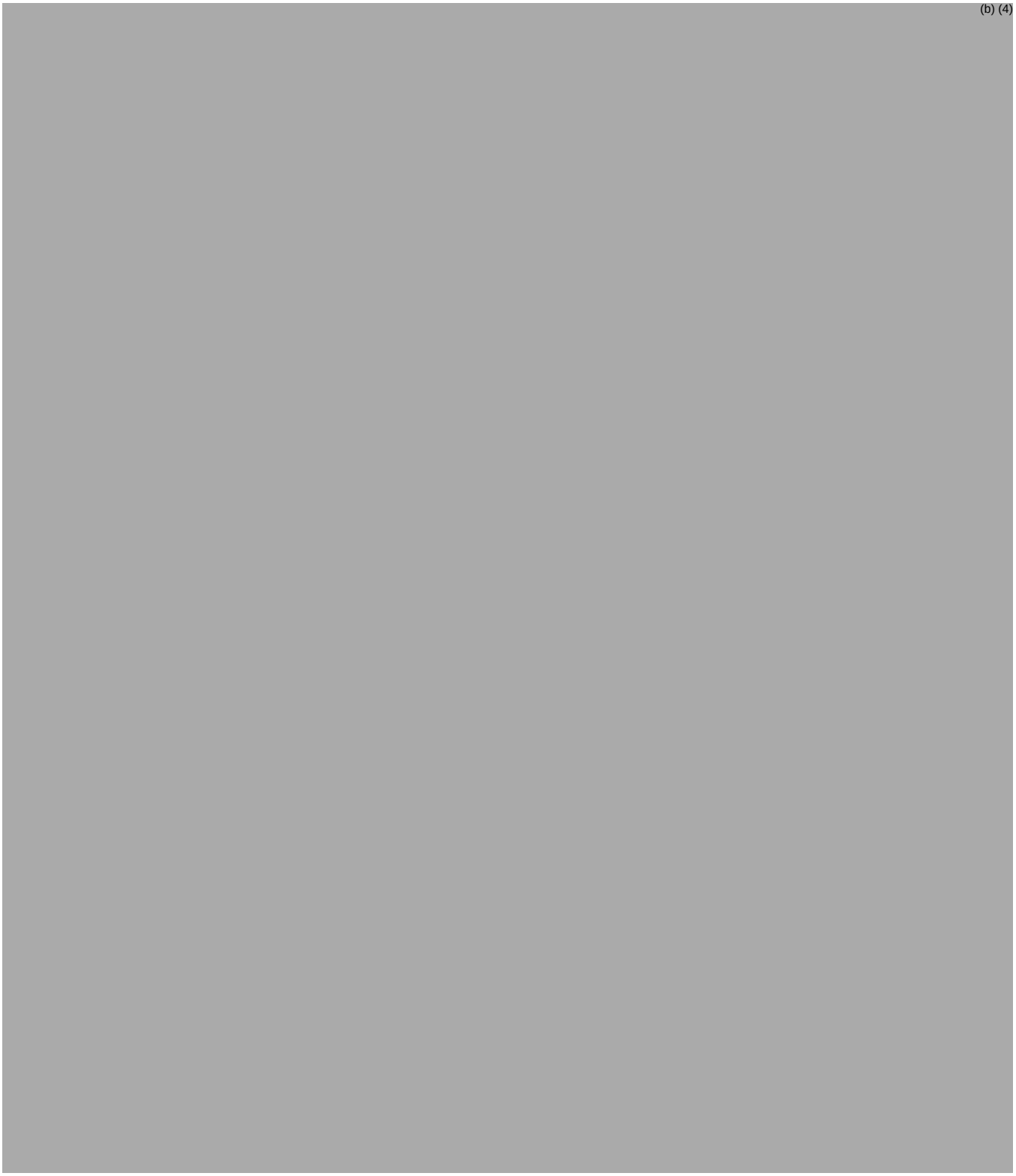
DRUG PRODUCT: Atorvastatin Calcium Tablets, 10mg, 20mg,40 mg and 80 mg Base

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)





B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.

2. 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}

Vilayat 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/

LEIGH A SEARS
01/13/2011

LAXMA R NAGAVELLI
01/13/2011
Signed for Vilayat A Sayeed, PhD

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

November 24, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

GRATUITOUS AMENDMENT – RESPONSE TO INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a Gratuitous Amendment to the above-referenced, pending ANDA in response to a November 17, 2010 request from Leigh Ann Bradford of your Office. Specifically, Teva was asked to clarify all sites applicable to this ANDA.

In accord with the November 17, 2010 request, please find in **Attachment 1** an updated list of all sites pertaining to this application. Further, please note that we hereby propose addition of (b) (4) and (b) (4)., as additional labeling facilities for the labeling of finished packaged drug product. The required cGMP and debarment certifications for these additional facilities are provided in **Attachment 2**. All required cGMP and debarment certifications for all other referenced facilities have previously been submitted to this application.

In addition, we hereby request withdrawal of the following contract labeling facility from this application:

(b) (4)

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 3 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

This information is submitted toward the continued review and approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker /JWZ

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/24/10

Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 28, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

UNSOLICITED LABELING AMENDMENT

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an unsolicited labeling amendment to the above-referenced pending Abbreviated New Drug Application to provide updated draft labeling. Our package insert and patient package insert have been revised in accord with the most recent labeling for the reference listed drug, Lipitor®, approved on June 17, 2009. Additionally, the labeling has been updated to support the additional packaging configurations presented in the minor amendment submitted on February 15, 2010. Please find the following revised labeling provided in **Attachment 1**:

- Teva's draft package insert (Iss. 4/2010) and patient package insert (Iss. 4/2010) in Word and PDF formats. Due to extensive changes in the RLD insert, which is now in PLR format, a comparison of Teva's revised insert to the RLD insert is provided in PDF format. In addition, a comparison of Teva's current patient package insert (Iss. 4/2010) to that which was last submitted (Iss. 1/2008) is provided in PDF format. Please also note that the revised package insert and patient package insert are provided in SPL format in accord with the SPL Implementation Guide for FDA Content of Labeling Submissions, Version 2a and Docket 92S-0251, Memorandum 32.

- Teva's draft container labels (Iss. 9/2010), [redacted] (b) (4) and container labels (Iss. 4/2010) in Word and PDF formats. Also provided in PDF format are the corresponding annotated comparisons of Teva's current container labels and [redacted] (b) (4) to those which were last submitted.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Please be informed that a sufficient quantity of patient package inserts will be provided to accompany each configuration to allow distribution of one with each prescription of thirty tablets:

Bottles
30 count – 1 ppi



The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 4 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

This information is submitted toward the continued review and approval of this ANDA. Should you have any questions on the information contained herein, please do not hesitate to contact me by phone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/28/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Date 10/7/10

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 7, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/7/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/6/10
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 6, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

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Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/6/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/5/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 5, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker
Senior Director, Regulatory Affairs

10/5/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/4/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 4, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

10/4/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

10/1/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

October 1, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker
Senior Director, Regulatory Affairs

10/1/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Date 9/30/10

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 30, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

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ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/30/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Vice President, Regulatory Affairs

9/29/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 29, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/29/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/28/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 28, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

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Jean Zwicker/gp

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/28/10
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TEVA PHARMACEUTICALS

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9/27/10
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TEVA PHARMACEUTICALS

Jean W. Zwicker
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September 27, 2010

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/24/10
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 24, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

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JWZ/dl
Enclosures

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www.tevausa.com

Jean W. Zwicker

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/24/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/23/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 23, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/23/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/22/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 22, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/22/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Date 9/21/10

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 21, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean Zwicker /gp
Jean W. Zwicker
Senior Director, Regulatory Affairs

9/21/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Date 9/20/10

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 20, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/20/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Vice President, Regulatory Affairs

9/17/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 17, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker
Senior Director, Regulatory Affairs

9/17/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/16/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 16, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

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Jean W. Zwicker
Senior Director, Regulatory Affairs

9/16/10
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TEVA PHARMACEUTICALS

PATENT CERTIFICATION

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/15/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 15, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
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www.tevausa.com

Jean Zwicker / JP
Jean W. Zwicker
Senior Director, Regulatory Affairs

9/15/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/14/10
Date

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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 14, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

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www.tevausa.com

Jean Zwicker Jr

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/14/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/13/10
Date

Administrative Offices:
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Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 13, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 1 megabyte. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/dl
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/3/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

Teva Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA 020702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/10/10
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 10, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

{see appended signature page}

JWZ/dl
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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/10/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent 7,790,197 which has been filed for Lipitor® Tablets is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

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Philip Erickson/gp

Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/9/10

Date

Administrative Offices:
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TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 9, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

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Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/9/10
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

Date 9/8/10

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 8, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

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www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/8/2010
Date

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date
7,790,197	October 14, 2025

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Philip Erickson/93
Philip Erickson, R.Ph.
Vice President, Regulatory Affairs

9/7/2010
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

September 7, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT NO. 7,790,197

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has become aware of the existence of U.S. Patent No. 7,790,197, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, Teva wishes to provide certification with regard to this patent. Please note that U.S. Patent No. 7,790,197 issued on September 7, 2010. Therefore, Teva anticipates that Pfizer, Inc., as owner of NDA 020702 for Lipitor® Tablets, or Warner-Lambert Company, as the assignee of the '197 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/dl
Enclosures

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

Jean W. Zwicker
Senior Director, Regulatory Affairs

9/7/2010
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

August 24, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ADDENDUM TO QUALITY MINOR AMENDMENT DATED AUGUST 18, 2010
ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Regarding the above-referenced pending ANDA, Teva Pharmaceuticals USA submits herewith an addendum to our quality minor amendment dated August 18, 2010.

Please note that a typographical error was found on one in-use stability report provided in Attachment 31 of the August 18, 2010 quality minor amendment. Specifically, (b) (4) impurity result for the 20 mg (b) (4) study at time zero should read (b) (4) %. The corrected in-use stability report is provided in **Attachment 1**. We apologize for any confusion caused by this error.

The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 2 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.8725 Fax: 215.591.8812 Email: jean.zwicker@tevausa.com
www.tevausa.com

This information is submitted toward the continued review and approval of this ANDA. If there are any questions on the information contained herein, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean W. Zwicker
Senior Director, Regulatory Affairs

8/24/10
Date

TEVA PHARMACEUTICALS

Jean W. Zwicker
Senior Director, Regulatory Affairs

August 18, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs, HFD-600
CDER / FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

QUALITY MINOR AMENDMENT - RESPONSE TO MAY 17, 2010 INFORMATION REQUEST

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base

Dear Dr. Webber:

Teva Pharmaceuticals USA submits herewith a quality minor amendment to the above-referenced, pending ANDA in response to the May 17, 2010 request for information from the Division of Chemistry. For ease of review, a copy of the aforementioned request is provided in **Attachment 1**. We have addressed your comments in the order in which they were presented.

A. Deficiencies:

(b) (4)



1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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10 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

(b) (4)



The entire submission is presented in electronic format. An originally signed paper certification or declaration accompanies this submission wherever a handwritten signature is currently provided. The electronic submission is provided on one CDROM comprised of approximately 100 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry, Manufacturing, and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic submission has been submitted to CDER.

It is Teva Pharmaceuticals USA's belief that the information provided herein represents a complete response to the comments presented in the May 17, 2010 review letter. This information is submitted toward the continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me via telephone at (215) 591-8725 or via facsimile at (215) 591-8812.

Sincerely,

{see appended signature page}

JWZ/aw
Enclosures

Jean Zwicker for JWZ

Jean W. Zwicker
Senior Director, Regulatory Affairs

8/18/10
Date

QUALITY DEFICIENCY - MINOR

ANDA 078773

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: Teva Pharmaceuticals USA TEL: (215) 591-3141

ATTN: Philip Erickson FAX: (215) 591-8812

FROM: Leigh Ann Bradford FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, 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 March 12, 2008 and February 15, 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 **5** 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
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** 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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36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10mg, 20mg,40 mg and 80 mg Base

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

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

1. Please provide all available long-term stability data.

(b) (4)

Sincerely yours,

{See appended electronic signature}

Vilayat Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78773	ORIG-1	TEVA PHARMACEUTICALS USA	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/

ROBERT L ISER
05/17/2010
signed for V. Sayeed

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

February 15, 2010

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT
(ELECTRONIC FORMAT)

ANDA # 078773
ATORVASTATIN CALCIUM TABLETS, Eq. to 10 mg, 20 mg, 40 mg and 80 mg base
MINOR AMENDMENT - RESPONSE TO AUGUST 1, 2007 REVIEW LETTER

Dear Mr. Buehler:

Teva Pharmaceuticals USA submits herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to an August 1, 2007 review letter applicable to the 80 mg base strength. Subsequent to receipt of the review letter, Teva amended this application with a proposal to include the 10 mg, 20 mg and 40 mg strengths of drug product. Comments in the August 1, 2007 letter, which relate to the drug product, have been addressed with respect to all four strengths of drug product. For ease of review, please find enclosed a copy of the aforementioned letter in **Attachment 1**.

A. Deficiencies

(b) (4)



1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

13 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE



In accord with the Agency's request to provide our response in electronic format, the entire submission is presented electronically on the enclosed disk. Please note that an originally signed paper certification or declaration accompanies this submission wherever an original handwritten signature is currently provided. The electronic minor amendment is provided on one CDROM comprised of approximately 280 megabytes. The submission is virus free, per our server protection (ServerProtect, Version 8.7.1.0, by Trend Micro) and client protection (OfficeScan, Version 8.0, by Trend Micro).

It is our understanding that sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room. Therefore, Teva Pharmaceuticals USA hereby certifies that a letter has been forwarded to the applicable office of the FDA certifying that an electronic quality minor amendment has been submitted to CDER.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the August 1, 2007 review letter. We look forward to your review and comment. Please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812 with any further questions.

Sincerely,

Philip Erickson /93

PE/aw
Enclosures

TEVA PHARMACEUTICALS

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

July 17, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 10 mg, 20 mg, 40 mg and 80 mg base
PATENT AMENDMENT – REVISED PATENT CERTIFICATION TO U.S. PATENTS 5273995 and RE40667

Dear Mr. Buehler:

We submit herewith a Patent Amendment to the above-referenced pending ANDA for the purpose of providing a revised patent certification statement. Specifically, the enclosed patent certification statement reflects a change from Paragraph IV certification to Paragraph III with regard to U.S. Patents 5,273,995 and RE40667, listed for the reference-listed drug, Lipitor® Tablets.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/jp

PE/dl
Enclosure

RECEIVED
JUL 17 2009
OGD

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3141 Fax: 215.591.8812 Email: philip.erickson@tevausa.com
www.tevausa.com

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

(Revised certification from Paragraph PIV to Paragraph III for U.S. Patents 5273995 and RE40667)

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg, 20 mg, 40 mg and 80 mg Base

The undersigned certifies that to the best of our knowledge and in TEVA Pharmaceuticals USA's opinion there are six listed patents which claim the reference drug Lipitor® Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

U.S. Patent #	Expiration Date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	November 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013
RE40667	December 28, 2010	June 28, 2011

Paragraph IV Certification

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patents 5686104, 5969156, and 6126971 which have been filed for Lipitor® are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, has given notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA # 20-702 for Lipitor® Tablets and to the patent assignees. This notice included a detailed statement of the factual and legal basis of the applicant's opinion that the patents are invalid, unenforceable, or will not be infringed.

Paragraph III Certification

The undersigned further certifies pursuant to Section 505(j)(2)(A)(vii)(III) of the Act, as amended, that U.S. Patent 4681893 will expire on September 24, 2009 and its associated pediatric exclusivity will expire on March 24, 2010. Additionally, U.S. Patents 5273995 and RE40667 will expire on December 28, 2010 and their associated pediatric exclusivities will expire on June 28, 2011. TEVA Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to June 28, 2011.

Philip Erickson /jr

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

7/17/09
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

Authorized to use FedEx Tracking 21 April 2009

TEVA FACSIMILE

TEVA PHARMACEUTICALS USA
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454
Phone: (215) 591-3000
FAX: (215) 591-8812

TO: Martin Shimer	**DATE:** March 17, 2009
COMPANY: FDA	
FAX NUMBER: 240-276-8428	**FROM:** Jill Pastore, R.Ph.
NO. OF PAGES: 1	**DIRECT LINE:** 215-591-3150

ANDA # 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 10 mg, 20 mg, 40 mg and 80 mg base
RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) and 21 CFR 314.95

Dear Mr. Shimer:

In the very near future, TEVA will submit a patent amendment to ANDA # 78-773 for the above-referenced product to provide certification to U.S. Patent No. RE40667. Simultaneously, TEVA will provide a Notice of Certification regarding this patent to Pfizer, Inc., as the holder of NDA 20-702 for Lipitor® Tablets and to the patent assignee in accord with 21 CFR 314.95(b).

The purpose of this communication is to inform you of our intent to utilize Federal Express Tracking Documentation as evidence of receipt of Notice of Certification by Pfizer, Inc., and the patent assignee in lieu of a United States Postal Service return receipt, in accord with 21 CFR 314.95(e).

Response to this correspondence may be made to my attention by telephone at (215) 591-3150 or via facsimile at (215) 591-8812.

Sincerely,

Jill Pastore

Jill Pastore
Director, Regulatory Affairs

PROMPT DELIVERY IS APPRECIATED

NOTICE: The documents accompanying this telecopy transmission from TEVA Pharmaceuticals USA contains information belonging to the sender. The information is intended only for the use of the individual or entity named above. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify the sender by telephone to arrange for the return of the original document.

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
6/26/2009 11:10:05 AM
CSO

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

March 18, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

N/XP

ANDA # 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 10 mg, 20 mg, 40 mg and 80 mg base
PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT RE40667

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. TEVA has recently become aware of the existence of U.S. Patent No. RE40667, which on its face, has been assigned to Warner-Lambert Company. On information and belief that the aforementioned patent is sought to be listed in FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* for the reference listed drug Lipitor® Tablets, TEVA wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. RE40667 issued on March 17, 2009. Therefore, TEVA anticipates that Pfizer, Inc., as owner of NDA 20-702 for Lipitor® Tablets, or Warner-Lambert Company, as assignee of the '667 patent, would take steps to list the patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosure

RECEIVED
MAR 19 2009
OGD

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

U.S. Patent No.	Expiration Date	Pediatric Exclusivity Expiry
RE40667	December 28, 2010	June 28, 2011

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent RE40667, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i), (ii) and (iii) to Pfizer, Inc., as the holder of NDA #20-702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

3/18/09
Date

Administrative Offices:
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Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

Administrative Offices:
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Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

March 17, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

N-000- XP

ANDA # 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 10 mg, 20 mg, 40 mg and 80 mg base
PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT RE40667

Dear Mr. Buehler:

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosure

RECEIVED
MAR 17 2009
OGD

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

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On information and belief that a new patent which claims the reference listed drug, Lipitor® Tablets, has been submitted for listing in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations,* the undersigned provides certification with respect to said patent.

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Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

3/17/09
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
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Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

March 17, 2009

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

N/MC

ANDA # 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 10 mg, 20 mg, 40 mg and 80 mg base
PATENT AMENDMENT – CERTIFICATION TO U.S. PATENT RE40667

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosure

FedEx

MAR 18 2009

OGD

TEVA PHARMACEUTICALS

PATENT CERTIFICATION

ATORVASTATIN CALCIUM TABLETS,
Eq. 10 mg base, 20 mg base, 40 mg base, and 80 mg base

Paragraph IV Certification

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U.S. Patent No.	Expiration Date	Pediatric Exclusivity Expiry
RE40667	December 28, 2010	June 28, 2011

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patent RE40667, which has been filed for Lipitor® Tablets, is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i), (ii) and (iii) to Pfizer, Inc., as the holder of NDA #20-702 for Lipitor® Tablets and to the assignee of the patent. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed.

Philip Brickson, R.Ph.
Senior Director, Regulatory Affairs

3/17/09
Date

Administrative Offices:
1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090
Phone: 215.591.3000 Fax: 215.591.8600 www.tevausa.com

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-773 **FIRM NAME**: TEVA PHARMACEUCTICALS USA

RELATED APPLICATION(S): NA

First Generic Product Received? NO

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DRUG NAME: ATORVASTATIN CALCIUM

DOSAGE FORM: TABLETS, EQ. 10 MG, 20 MG, 40 MG AND 80 MG BASE (NEW STRENGTH 10 MG, 20 MG AND 40 MG)

Random Queue: 12

Chem Team Leader: Iser, Robert PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Beth Fabian-Fritsch

Letter Date: MARCH 12, 2008 **Received Date**: MARCH 13, 2008

Comments: EC -1 + 3 = 4 YES **On Cards:** YES

Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)**

Review copy: YES E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

Field Copy Certification (Original Signature) YES p. 1741

Methods Validation Package (3 copies PAPER archive)
(Required for Non-USP drugs)

Cover Letter YES | **Table of Contents** YES

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 Susan E. Pellock	**Recommendation:**
Date May 8, 2008	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Philip Erickson
215.591.3141 (P)
215.591.8812 (F)

Form 3674 is provided on page 3 of the ANDA

QOS/QbR provided in PDF and Word Files

Lot #:
10 mg: K-38319 and R: 10605V
20 mg: K-38320 and R: 0508055
40 mg: K-38321 and R: 0324075

Top 200 Drug Product:

(b) (4)

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 20-702** Ref Listed Drug: LIPITOR Firm: PFIZER ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: IV '995, '104, '156, '971 PIII '893 expire 3/24/2010 2. Expiration of Patent: 7/19/2013 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES I-471 (exp. 9/21/08) and I-523 (exp. 3/2/2010) expire prior to '893 patent and M-36 and I-434 have already expired	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Atorvastatin Calcium 3. Route of administration Oral 4. Dosage Form Tablet 5. Strength NS 10 mg, 20 mg and 40 mg - Original Submission 80 mg Base	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL x 2. 1 RLD label and 1 RLD container label x - RLD PI located in original submission 3. 1 side by side labeling comparison with all differences annotated and explained x 4. Was a proprietary name request submitted? No (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NA Original submission **2. Request for Waiver of In-Vivo Study(ies): YES ON 10 MG, 20 MG AND 40 MG p. 74** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) Proportional **4. Lot Numbers of Products used in BE Study(ies):** Original Submission **5. Study Type:** (Continue with the appropriate study type box below)	☒

Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 80 MG DATED ON ORIGINAL DATE 12/29/06 a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES x	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation All justified please see below 2. Inactive ingredients as appropriate	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers x b. Type II DMF authorization letters or synthesis #20069 c. COA(s) specifications and test results from drug substance mfgr(s) x d. Applicant certificate of analysis x e. Testing specifications and data from drug product manufacturer(s) x f. Spectra and chromatograms for reference standards and test samples x g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified p. 208 b. Testing specifications (including identification and characterization) x c. Suppliers' COA (specifications and test results) x d. Applicant certificate of analysis x	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES x 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address x 2. Functions x 3. CGMP Certification/GLP x 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 10 mg: (b) (4) / 20 mg: (b) (4) / 40 mg: (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization n/a 4.Filter validation (if aseptic fill) n/a 5. Reprocessing Statement p. 658	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation See below for summary 2. In-process Controls - Specifications and data	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data (Type III DMF References) (b) (4) 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing x 5. Source of supply and suppliers address x	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data x 2. Certificate of Analysis for Finished Dosage Form x	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted x 2. Post Approval Commitments x 3. Expiration Dating Period (b)(4) months 4. Stability Data Submitted x a. 3 month accelerated stability data x b. Batch numbers on stability records the same as the test batch x	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) No US Agent 2. Debarment Certification (original signature): YES x 3. List of Convictions statement (original signature)	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

Table 2.3.P.1-1 Unit Composition for Atorvastatin Calcium Tablets Eq. To 10, 20 & 40 mg base

Ingredient	Quality standard	Function	Amount (mg) / Tablet				Amount (%) / Tablet			
			10mg	20mg	40mg	80 mg†	10mg	20mg	40mg	80 mg†
(b) (4)										
Atorvastatin Calcium (b) (4)										
Lactose Monohydrate (b) (4)										
Crospovidone (b) (4)										
Magnesium Carbonate (b) (4)										
Colloidal Silicon Dioxide (b) (4)										
Magnesium Stearate										
(b) (4)										
(b) (4)										

† Bio-strength from the original ANDA for Atorvastatin Calcium Eq. to 80 mg base

(b) (4)

Table 2.3.P.1-2 Unit Composition for Atorvastatin Calcium Tablets Eq. to 10, 20 & 40 mg base (b) (4)

Ingredient*	Amount (mg) / Tablet	Amount (%) / Tablet
Hypromellose (b) (4)	(b) (4)	(b) (4)
Polydextrose (b) (4)		
Titanium Dioxide (b) (4)		
Polyethylene Glyco (b) (4)		
Total		

† Bio-strength from the original ANDA for Atorvastatin Calcium Eq. to 80 mg base

* Please see vendor's quantitative statement in section VIII

(b) (4)

Inactive Ingredients Search for ANDA 78773

TEVA Pharmaceuticals USA – Atorvastatin Calcium Tablets, 80 mg

LACTOSE MONOHYDRATE CROSPOVIDONE MAGNESIUM CARBONATE SILICON DIOXIDE, COLLOIDAL MAGNESIUM STEARATE	ORAL; TABLET	(b) (4)	(b) (4) N021443 5/10/2004 (b) (4) (b) (4) (b) (4)

Components of [redacted]

[redacted]	[redacted]	[redacted]
TITANIUM DIOXIDE	[redacted]	[redacted]
POLYETHYLENE GLYCOL [redacted]	[redacted]	[redacted]
POLYDEXTROSE	[redacted]	[redacted]

PACKAGING AND DISBURSEMENT

ATORVASTATIN CALCIUM TABLETS Eq. to 10 mg base

(b) (4)

11 pages have been withheld 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/

Martin Shimer

5/19/2008 02:36:09 PM

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

March 12, 2008

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE
UNSOLICITED AMENDMENT – ADDITION OF Eq. 10 mg BASE, Eq. 20 mg BASE and Eq. 40 mg BASE STRENGTHS

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced pending ANDA to propose addition of the 10 mg, 20 mg and 40 mg (Eq. Base) strengths of Atorvastatin Calcium Tablets. This submission is presented in the basic format of an ANDA in accord with the format of the original application.

Copies are presented in a total of 13 volumes; 6 for the archival copy and 7 for the review copy. The application contains a request for waiver of *in vivo* bioavailability study for the 10 mg, 20 mg and 40 mg strengths.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141, or by facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

November 15, 2007

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 78-773
ATORVASTATIN TABLETS, Eq. 80 mg base
PATENT AMENDMENT – RECEIPT OF NOTICE OF CERTIFICATION/ END OF 45-DAY CLOCK/ LEGAL STATUS

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that Notice of Certification for U.S. Patent Nos. 6,126,971, 5,969,156, 5,686,104 and 5,273,995 was provided to Pfizer, Inc., as the holder of NDA # 20-702 for Lipitor® Tablets and to Warner-Lambert Company, as the assignee of the patents. Please be informed that the Notice, dated April 24, 2007, contained the information required under 21 CFR 314.95(c).

Please note that the original ANDA contained a Paragraph III certification to all of the above-referenced patents, however, TEVA Pharmaceuticals USA revised its certification to a Paragraph IV in our January 30, 2007 New Correspondence to this ANDA.

In accord with requirements set forth in the Medicare Prescription Drug & Modernization Act of 2003, Notice was sent to the necessary parties within twenty days of the postmark date of FDA's correspondence acknowledging filing of TEVA's ANDA for Atorvastatin Tablets. Documentation of the date of acknowledgement, which was received via facsimile on April 19, 2007, is provided in **Attachment 1** for your reference.

In accord with 21 CFR 314.95(e), TEVA Pharmaceuticals USA is hereby providing documentation in **Attachment 2** of the receipt of the above-referenced April 24, 2007 Notice. As evidenced by the enclosed documentation, Notice was received by both Pfizer, Inc. and Warner-Lambert Company on April 25, 2007. In accord with 21 CFR 314.95(f), the first day of the 45-day period provided for in Section 505(j)(4)(B)(iii) of the Act was April 26, 2007, the first day after the receipt of Notice. Therefore, the 45-day period ended on June 9, 2007.

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NOV 16 2007
OGD

Please note that on March 8, 2007, Teva received approval from the Regulatory Support Branch to use Federal Express delivery documentation in lieu of U.S. Postal Service certified delivery in accord with 21 CFR 314.95(e). Therefore, the documentation of receipt of Notice provided herein is in the form of Federal Express delivery tracking.

We hereby inform the Agency of a suit filed by Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export Ltd. against TEVA Pharmaceuticals USA concerning U.S. Patent No. 5,273,995. The suit, Civil Action No. 07-360 was filed on June 7, 2007 in the United States District Court for the District of Delaware. The aforementioned suit was filed within the 45-day period. Teva hereby commits to provide the Agency notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 3** for your records.

No suit was brought against TEVA regarding U.S. Patent Nos. 6,126,971, 5,969,156 and 5,686,104 within the 45 day period. Resultant from the failure of Pfizer, Inc. and Warner-Lambert Company to undertake legal action within the 45-day period, they have waived their right to pursue future legal action under the scope of Waxman-Hatch with respect to these patents.

This information is submitted for your continued review of ANDA 78-773. If there are any questions on the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosures

ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

September 14, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT
(CONTAINS CMC)

ORIG AMENDMENT
N/AB

ANDA 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE
BIOEQUIVALENCY AMENDMENT – RESPONSE TO JULY 30, 2007 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced pending ANDA in response to a July 30, 2007 review letter from the Division of Bioequivalence. For ease of your review, a copy of the letter is provided in **Attachment 1**.

We acknowledge the Agency's acceptance of the following proposed Dissolution test method:

Equipment:	Apparatus 2 (paddle)
Medium:	0.05 M Phosphate buffer at pH 6.8
Volume:	900 mL
Stirring rate:	75 rpm
Temperature:	37 °C ± 0.5 °C

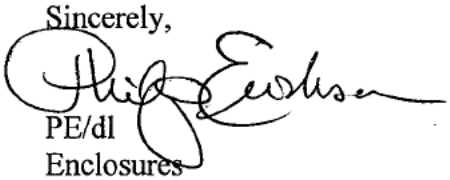
Per your request, the dissolution specification has been revised from NLT (b)(4)% (Q) in (b)(4) minutes to NLT (b)(4)% (Q) in 15 minutes. The revised specification is reflected in the updated Shelf Life Specifications and Finished Product Stability Protocol, enclosed in **Attachment 2.** Additionally, an updated Dissolution Test method, SI-19091, which reflects the revised sampling time, is provided in **Attachment 3**.

Please be informed that all dissolution test results obtained during the accelerated and room-temperature stability studies meet the tightened specification.

RECEIVED
SEP 17 2007
OGD

We believe this constitutes a complete response to your July 30, 2007 review letter. Should you have any further questions, please feel free to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/dl
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA 78-773

ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE

BIOEQUIVALENCY AMENDMENT –
RESPONSE TO JULY 30, 2007 REVIEW LETTER

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and is provided to the Office of Generic Drugs to be forwarded as appropriate.

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

9/14/07
Date

MINOR AMENDMENT

ANDA 78-773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Jeanne Skanchy PROJECT MANAGER: (301) 827-5719

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 29, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

Reference is also made to your amendment dated May 15, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the 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. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

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.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

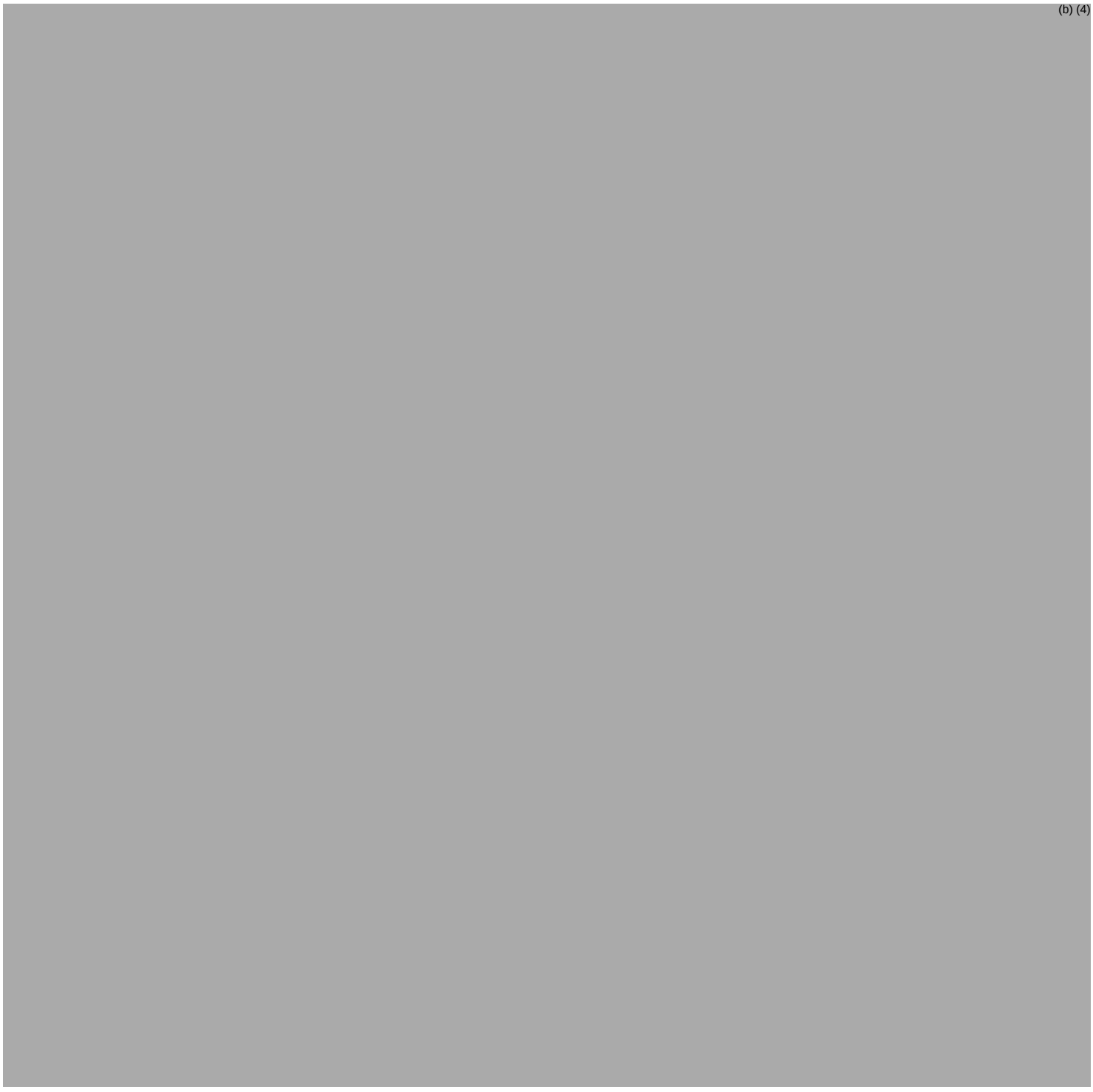
ANDA: 78-773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg (Base)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)





B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available drug product room temperature stability data.

2. Bioequivalence and labeling information you have provided is pending review. After the reviews are completed, any deficiencies found will be communicated to you separately.

3. Please be advised that acceptance of your proposed drug product release and stability dissolution specifications will be based on the recommendation of the office of Generic Drug's Division of Bioequivalence.

4. OGD is changing its CMC review process through our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

   OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

   Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

Sincerely yours,

(See appended electronic signature page)

Vilayat 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/

Hossein Khorshidi
8/1/2007 02:08:28 PM
For Vilayat Sayeed, Ph.D.,

BIOEQUIVALENCY AMENDMENT

ANDA 78-773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

FROM: Beth Fabian-Fritsch PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 29, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 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 **1** 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 "Bioequivalency 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:

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: 78-773 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Atorvastatin Calcium Tablets, Eq. 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 and has the following comment presented below. The review of the bioequivalence studies will be conducted later.

1. Your dissolution testing is acceptable. However, your proposed dissolution specification (NLT (b)(4)% (Q) in (b)(4) minutes) is not acceptable. Please acknowledge the following FDA-recommended method and specification:

The dissolution testing should be conducted in 900 mL of 0.05M Phosphate buffer at pH 6.8 using Paddle at 75 rpm. The test product should meet the following specification:

Not less than (b)(4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

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

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

/s/

Barbara Davit
7/27/2007 02:24:49 PM
Signing for Dale P Conner

Telephone Fax

ANDA 78-773

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986

TO: TEVA Pharmaceuticals USA TEL: 215-591-3141

ATTN: Philip Erickson FAX: 215-591-8812

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 Tablets, 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: 78-773 Dates of Submission: December 29, 2006

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Atorvastatin Calcium Tablets, 80 mg

Labeling Deficiencies:

1. CONTAINER ((b) (4))

   Add a statement to the pharmacist to dispense patient leaflet with medication.

2. INSERT:

   A. Your product uses the (b) (4) while the reference listed drug uses trihydrate. Please comment on your product and why you consider it to be the same as the reference listed drug.

   B. Revise your product to be in accord with the recent supplement approval for the reference listed drug; as of this review the NDA/20-702/S-047 approved 3/2/2007. Please visit www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm site for the most recent approved labeling.

3. PATIENT INFORMATION SHEET:

   Please submit the patient information sheet. Also state the number of sheets you intend on providing with your bottles of (b) (4) and (b) (4)

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://www.fda.gov/cder/cdernew/listserv.html

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
7/2/2007 09:52:11 AM
for Wm Peter Rickman

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

May 15, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT

ORIG AMENDMENT
N/AA

ANDA 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE
UNSOLICITED AMENDMENT – UPDATED DMF AUTHORIZATION LETTER

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced pending ANDA for the purpose of providing additional information. Please note that at the time of submission of the original ANDA, a Drug Master File number for the drug substance, Atorvastatin Calcium, was not available. Please be informed that DMF No. 20069 has now been assigned to Assia Chemical Industries Ltd., the manufacturer of Atorvastatin Calcium. Enclosed herein, please find an updated DMF authorization letter from Assia Chemical Industries Ltd. – Teva-Tech Site.

We look forward to your review and approval of ANDA # 78-773. Should you have any questions, please feel free to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/dl
Enclosures

RECEIVED
MAY 16 2007
OGD

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-773 **FIRM NAME**: TEVA PHARMACEUTICALS USA

RELATED APPLICATION(S):

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM
DOSAGE FORM: TABLETS, 80 MG

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Random Queue: 12
Chem Team Leader: Khorshidi, Hossein PM: Jeanne Skanchy Labeling Reviewer: Ann Vu

Letter Date: DECEMBER 29, 2006 **Received Date**: JANUARY 3, 2007

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)**
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections
Field Copy Certification (Original Signature) YES – Page 1054

Methods Validation Package (3 copies PAPER archive) **YES**
(Required for Non-USP drugs)

Cover Letter YES | **Table of Contents** YES

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 Rebekah Granger

Date 04/10/2007

Recommendation:

☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
Philip Erickson (TEVA) was contacted on April 11 regarding the Protocol for Stability of Finished Dosage Form. Requested submission of protocol for Drug Product.

The firm was contacted again on 4/12 to address the I-523 Exclusivity.

Per correspondence submitted by sponsor dated 4/12/2007 the above is adequate for filing.

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES – Page 15	☒
Sec. II	**Basis for Submission** **NDA# : 20-702** Ref Listed Drug: LIPITOR Firm: PFIZER ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒

Sec. III

Patent Certification

1. Paragraph: III YES – Page
2. Expiration of Patent: 1/08/17

A. Pediatric Exclusivity Submitted?

B. Pediatric Exclusivity Tracking System checked?

Exclusivity Statement: YES – Page 13

Patent and Exclusivity Search Results from query on Appl No 020702 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020702	004	4681893	SEP 24,2009	Y	Y	U-161
020702	004	4681893*PED	MAR 24,2010			U-161
020702	004	5273995	DEC 28,2010	Y	Y	U-162
020702	004	5273995*PED	JUN 28,2011			U-162
020702	004	5686104	NOV 11,2014		Y	U-213
020702	004	5686104*PED	MAY 11,2015			U-213
020702	004	5969156	JUL 08,2016	Y		
020702	004	5969156*PED	JAN 08,2017			
020702	004	6126971	JAN 19,2013		Y	
020702	004	6126971*PED	JUL 19,2013			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020702	004	I-523	MAR 02,2010
020702	004	M-36	JUL 30,2007
020702	004	I-471	SEP 21,2008
020702	004	I-434	JUL 30,2007

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
I-523	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
M-36	ADDITION OF INFORMATION TO CLINICAL STUDIES REGARDING PREVENTION OF CARDIOVASCULAR DISEASE
I-471	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
I-434	PREVENTION OF CARDIOVASCULAR DISEASE IN ADULT PATIENTS WITHOUT CLINICALLY EVIDENT HEART DISEASE, BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE TO REDUCE RISK OF MI AND RISK FOR REVASCULARIZATION PROCEDURES AND ANGINA

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Route of administration SAME 4. Dosage Form SAME 5. Strength SAME	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL YES 2. 1 RLD label and 1 RLD container label YES 3. 1 side by side labeling comparison with all differences annotated and explained YES 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies): NO** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** K-37191 **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 80 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) YES b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation YES 2. Inactive ingredients as appropriate YES	☒
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers YES b. Type II DMF authorization letters or synthesis YES – DMF #20069 c. COA(s) specifications and test results from drug substance mfgr(s) YES d. Applicant certificate of analysis YES e. Testing specifications and data from drug product manufacturer(s) YES f. Spectra and chromatograms for reference standards and test samples YES g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified YES – Page 137 b. Testing specifications (including identification and characterization) YES c. Suppliers' COA (specifications and test results) YES d. Applicant certificate of analysis YES	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒

Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address YES 2. Functions YES 3. CGMP Certification/GLP YES 4. CFN numbers YES	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement YES – Page 458 Proposed Commercial Batch Size: (b) (4)	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES 2. In-process Controls - Specifications and data YES Exhibit Made Packaged K-37191 (b) (4) (b) (4) (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data (Type III DMF References) YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data YES 2. Certificate of Analysis for Finished Dosage Form YES – Page 702	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted YES 2. Post Approval Commitments YES 3. Expiration Dating Period YES – (b) (4) Months 4. Stability Data Submitted a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch YES	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance YES 2. Finished Dosage Form YES 3. Same lot numbers YES	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒

Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES – Page 1052 3. List of Convictions statement (original signature)	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

(b) (4)



Table 2. Statistical Summary of the Comparative Bioavailability Data

Atorvastatin

Atorvastatin Calcium 1 x 80 mg Tablet Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}	164.629	150.634	109	105; 114
AUC_{∞}	167.503	153.457	109	105; 114
C_{max}	38.657	34.695	111	101; 122
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}	154.268	155.052	99.5	96.1; 103
AUC_{∞}	158.083	158.804	99.5	96.2; 103
C_{max}	29.221	31.519	92.7	83.4; 103

Table 5. Formulation Data Summary Table

ATORVASTATIN CALCIUM TABLETS Eq. to 80 mg base

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet
[redacted]		(b) (4)
Atorvastatin Calcium (b) (4)	(b) (4)	
Lactose Monohydrate (b) (4)		
Crospovidone (b) (4)		
Magnesium Carbonate (b) (4)		
Colloidal Silicon Dioxide (b) (4)		
Magnesium Stearate (b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Total		

1. (b) (4) (b) (4) is equivalent to 80.0 mg of Atorvastatin base

Table 5. Formulation Data Summary Table (*continued*)

(b) (4)

Ingredient	Amount (mg) / tablet	Amount (%)/ tablet
Hypromellose (b) (4) (b) (4)	(b) (4)	
Polydextrose (b) (4)		
Titanium Dioxide (b) (4)		
Polyethylene Glycol (b) (4)		
Total		



Inactive Ingredients Search for ANDA 78773

TEVA Pharmaceuticals USA – Atorvastatin Calcium Tablets, 80 mg

LACTOSE MONOHYDRATE	ORAL; TABLET	(b) (4)	N021443 5/10/2004	(b) (4)
CROSPOVIDONE		(b) (4)		(b) (4)
MAGNESIUM CARBONATE				
SILICON DIOXIDE, COLLOIDAL				
MAGNESIUM STEARATE				

Components of [redacted]

[redacted]	[redacted]	[redacted]
TITANIUM DIOXIDE		
POLYETHYLENE GLYCOL [redacted]		
POLYDEXTROSE		

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

4/13/2007 11:01:26 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-773

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

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 also made to the telephone conversation dated April 11, 2007 and your correspondence dated April 12, 2007.

NAME OF DRUG: Atorvastatin Calcium Tablets, 80 mg

DATE OF APPLICATION: December 29, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 3, 2007

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
301-827-5719

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
4/13/2007 11:02:34 AM
Signing for Wm Peter Rickman

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

April 12, 2007

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

Me

ANDA 78-773
ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE
NEW CORRESPONDENCE TO ORIGINAL ANDA: RESPONSE TO APRIL 12, 2007 REQUEST

Dear Mr. Buehler:

In response to an April 12, 2007 request made by Rebekah Granger of the Office of Generic Drugs, TEVA Pharmaceuticals USA submits herewith new correspondence to the above-referenced ANDA for Atorvastatin Calcium Tablets, eq. 80 mg base which was submitted on December 29, 2006. Specifically, TEVA has been asked to provide a copy of pages 972- 974 which contain the finished product stability protocol. In addition, Ms. Granger noted that a new exclusivity posted for the reference listed drug since our original ANDA submission and asked that we address this exclusivity.

Please find in **Attachment 1** copies of the pages from TEVA's original ANDA that contain the finished product stability protocol, and an updated exclusivity statement in **Attachment 2** which addresses exclusivity I-523. Relevant printouts from the electronic Orange Book are also provided in **Attachment 2** for ease of reference.

We look forward to your acceptance of this application. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
APR 13 2007
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA 78-773

ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg base

NEW CORRESPONDENCE TO ORIGINAL ABBREVIATED NEW DRUG APPLICATION- RESPONSE TO 4/12/07 REQUEST

In accord with the 21 CFR 314.94(d)(5), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and is provided to the Office of Generic Drugs to be forwarded as appropriate.

Philip Erickson, R.Ph.
Senior Director, Regulatory Affairs

4/12/07
Date

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

78773

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

January 30, 2007

ORIGINAL
MC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE:
REVISED PATENT CERTIFICATION

NEW CORRESPONDENCE TO ORIGINAL ANDA SUBMITTED 12/29/06
ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE

Dear Mr. Buehler:

TEVA Pharmaceuticals USA submits herewith new correspondence to an abbreviated new drug application for Atorvastatin Calcium Tablets, eq. 80 mg base which was submitted on December 29, 2006, to provide a revised patent certification statement for this drug product. Specifically, the patent certification statement provided herein contains a Paragraph IV certification to four of the patents listed for the reference drug product for which TEVA provided a Paragraph III certification in the original ANDA. Please note that the NDA holder and patent assignee(s) will be provided Notice of said certification upon acknowledgement of acceptance of this ANDA for filing by the Office of Generic Drugs.

We look forward to your acceptance of this application. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
JAN 31 2007
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

PATENT CERTIFICATION

(Revised certification from Paragraph III to Paragraph IV for U.S. Patents 5273995, 5686104, 5969156 and 6126971)

ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg Base

The undersigned certifies that to the best of our knowledge and in TEVA Pharmaceuticals USA's opinion there are five listed patents which claim the reference drug Lipitor® Tablets, 80 mg.

U.S. Patent #	Expiration Date	Pediatric Exclusivity
4681893	September 24, 2009	March 24, 2010
5273995	December 28, 2010	June 28, 2011
5686104	November 11, 2014	May 11, 2015
5969156	July 8, 2016	January 8, 2017
6126971	January 19, 2013	July 19, 2013

Paragraph IV Certification

The undersigned hereby certifies, pursuant to Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act as amended, that U.S. Patents 5273995, 5686104, 5969156, and 6126971 which have been filed for Lipitor® are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted. TEVA Pharmaceuticals USA, the applicant, will give notice as required by 505(j)(2)(B)(i) and (ii) to Pfizer as the holder of NDA # 20-702 for Lipitor® Tablets and to the patent assignees. This notice will include a detailed statement of the factual and legal basis of the applicant's opinion that the patents are invalid, unenforceable, or will not be infringed.

Paragraph III Certification

The undersigned further certifies pursuant to Section 505(j)(2)(A)(vii)(III) of the Act, as amended, that U.S. Patent 4681893 will expire on September 24, 2009 and its associated pediatric exclusivity will expire on March 24, 2010. TEVA Pharmaceuticals USA will not engage in the commercial distribution of Atorvastatin Calcium Tablets prior to the expiration of this patent and its pediatric extension.

Deborah Jaskot

Deborah A. Jaskot
Vice President, Regulatory Affairs

Jan. 30, 2007
Date

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Sr. Director, Regulatory Affairs

Direct Dial: (215) 591-3141
Direct FAX: (215) 591-8812
philip.erickson@tevausa.com

December 29, 2006

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
ATORVASTATIN CALCIUM TABLETS, Eq. 80 mg BASE

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Atorvastatin Calcium Tablets, eq. 80 mg base.

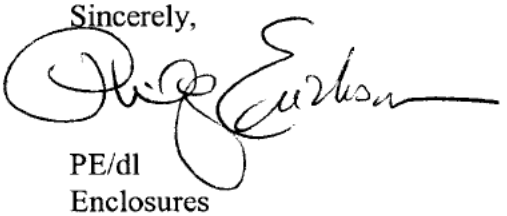
Enclosed are archival and review copies assembled in accord with the Office of Generic Drugs' February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of **9** volumes; **4** for the archival copy and **5** for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Atorvastatin Calcium Tablets, eq. 80 mg base manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Lipitor® Tablets, Eq. 80 mg under both fasting and post-prandial conditions.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,



PE/dl
Enclosures