CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 091226

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

Sponsor: Mylan Pharmaceuticals Inc.

Approval Date: May 29, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091226

Mylan Pharmaceuticals Inc.
U.S. Agent for: Mylan Laboratories Limited
Attention: Shane Shupe
Senior Manager, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 30, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base).

Reference is also made to the tentative approval letter issued by this office on February 1, 2012, and to your amendments dated March 13, and May 15, 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 Mylan Laboratories Limited, formerly Matrix Laboratories Limited (Matrix), complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '156 patent was brought against Matrix within the statutory 45-day period in the United States District Court for the District of Delaware [Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner Lambert Company LLC v. Mylan Inc., Mylan Laboratories Limited and Matrix Laboratories Inc., Civil Action No. 09-CV-0441]. You notified the agency that the case was dismissed with prejudice.

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 091226

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091226

Mylan Pharmaceuticals Inc.
U.S. Agent for: Matrix Laboratories Limited
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 30, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base).

Reference is also made to your amendments dated September 30, and October 20, 2009; April 8, August 12, September 14, November 9, November 18, December 6, and December 14, 2010; and March 1, March 7, March 31, May 26, June 28, October 24, November 21, November 22, November 23, December 1, December 2, (2 submissions), and December 27, 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 patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), under this ANDA. You have notified the agency that Matrix Laboratories Limited. (Matrix) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '156 patent was brought against Matrix within the statutory 45-day period in the United States District Court for the District of Delaware [Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner Lambert Company LLC v. Mylan Inc., Mylan Laboratories Limited and Matrix Laboratories Inc., Civil Action No. 09-441]. The 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your ANDA, has expired.[1]

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 1)on May 28, 2012, the date that is 180 days after the date the agency received 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.[2] In addition, your ANDA will be

[1] On June 30, 2011, you notified us that on June 28, 2011, the parties filed with the court a joint motion to dismiss the case pursuant to a January 24, 2011 settlement agreement. We have not, however, received notification that the court dismissed the case.

[2] 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).

eligible for final approval if, prior to those dates, the other applicant's exclusivity ceases to be a barrier to subsequent ANDA approval for any reason.

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

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 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

02/01/2012

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

LABELING

ATORVASTATIN CALCIUM TABLETS
10 mg, 20 mg, 40 mg and 80 mg
75005297
MX:ATOR:R5ppt

ATORVASTATIN CALCIUM TABLETS
10 mg, 20 mg, 40 mg and 80 mg
75005297
MX:ATOR:R5ppt

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.

Atorvastatin Calcium Tablets for Oral Administration

Initial U.S. Approval: 1996

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

Drug Interactions (7) 02/2012

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

Atorvastatin is 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 nonfatal MI, fatal and nonfatal 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 mg to 80 mg once daily (2.1).

Recommended start dose: 10 mg 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 mg, 20 mg, 40 mg 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 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 Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX (1-877-446-3679) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION

REVISED MARCH 2012

MX:ATOR:R5ppt/MX:PL:ATOR:R4p/MX:PL:ATOR:R4pt

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Prevention of Cardiovascular Disease

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

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

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

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

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

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of fatal and nonfatal 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 mg 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 mg 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 mg 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 oval, film-coated tablets containing 10 mg, 20 mg, 40 mg or 80 mg atorvastatin calcium, USP.

4 CONTRAINDICATIONS

4.1 Active Liver Disease, which may include Unexplained Persistent Elevations in Hepatic Transaminase Levels

4.2 Hypersensitivity to any Component of this Medication.

4.3 Pregnancy

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

4.4 Nursing Mothers

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

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

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

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

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

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

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

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

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

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

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

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

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on two 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 mg, 20 mg, 40 mg and 80 mg, respectively.**

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

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

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

5.3 Endocrine Function

Increases in HbA_{1c} and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

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

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of two 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 placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin vs. 7,311 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 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 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 in placebo controlled trials (n = 8,755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6%) 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 (n = 8,755), from 17 placebo-controlled trials.

Table 2. Clinical Adverse Reactions Occurring in ≥ 2% in Patients Treated with Any Dose of Atorvastatin and at an Incidence Greater Than Placebo Regardless of Causality (% of Patients).

Adverse Reaction*	Any Dose N = 8,755	10 mg N = 3,908	20 mg N = 188	40 mg N = 604	80 mg N = 4,055	Placebo N = 7,311
Nasopharyngitis	8.3	12.9	5.3	7	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	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6	3.3	4.3
Nausea	4	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
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

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

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

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin 10 mg daily (n = 5,168) or placebo (n = 5,137), the safety and tolerability profile of the group treated with atorvastatin 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% 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% Asians, 2% other) with clinically evident CHD treated with atorvastatin 10 mg daily (n = 5,006) or atorvastatin 80 mg daily (n = 4,995), 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 = 4,439) or simvastatin 20 mg to 40 mg daily (n = 4,449), 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 4,731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3% 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 = 2,365) or placebo (n = 2,366) 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%). 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 (218/2,365, 9.2% vs. 274/2,366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). The incidence of nonfatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 nonfatal hemorrhagic strokes) as compared to the placebo group (16 nonfatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin 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%) than in the placebo group (4%).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of atorvastatin. 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 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 nonfatal hepatic failure, dizziness, depression, peripheral neuropathy and pancreatitis.

There have been rare post-marketing 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 (one 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 mg to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

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

7.1 Strong Inhibitors of Cytochrome P450 3A4

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

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

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

nonfamilial forms of hypercholesterolemia and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG and non-HDL-C and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin 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, 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 dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

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

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following 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 and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

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

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

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

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

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

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

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

Coadministered Drug and Dosing Regimen	Atorvastatin		
	Dose (mg)	Change in AUC[k]	Change in C_{max}[k]
[d]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[d]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg SD	↑ 9.4 fold	↑ 8.6 fold
[d]Telaprevir 750 mg q8h, 10 days	20 mg SD	↑ 7.88 fold	↑ 10.6 fold
[d, i]Saquinavir 400 mg BID/ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[d]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[d]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[d]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[d]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[d]Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
[d]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
[d]Grapefruit Juice, 240 mL QD*	40 mg SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg SD	↑ 15%	↓ 12%
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[d]Rifampin 600 mg QD, 7 days (coadministered)†	40 mg SD	↑ 30%	↑ 2.7 fold
[d]Rifampin 600 mg QD, 5 days (doses separated)†	40 mg SD	↓ 80%	↓ 40 %
[d]Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less than 1%
[d]Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%

[k] 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).

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

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

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

† Due to the dual interaction mechanism of rifampin, simultaneous 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.

‡ 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	[d]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

[d] 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, two 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 two of ten 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 2 years.

14 CLINICAL STUDIES

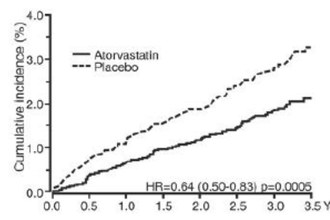
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and nonfatal 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 three 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 = 5,168) or placebo (n = 5,137), 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 significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs. 60 events in the atorvastatin group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin vs. 3% 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 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 Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and nonfatal 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 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 on cardiovascular disease (CVD) endpoints was assessed in 2,838 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 one 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 (1,429) or placebo (1,411) 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.

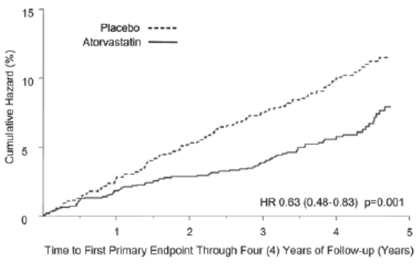
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin 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 was seen regardless of age, sex or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin 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 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, nonfatal myocardial infarction, resuscitated cardiac arrest and fatal and nonfatal 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)

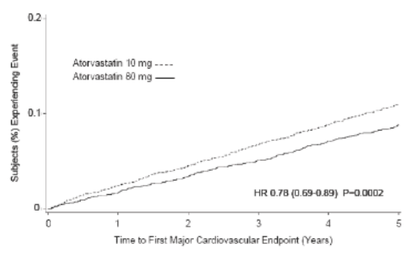


Table 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N = 5,006)		Atorvastatin 80 mg (N = 4,995)		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)	0.8 (0.61, 1.03)
Nonfatal, 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 nonfatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First 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, 0.8)
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)
Suicide, homicide and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

[a] Atorvastatin 80 mg; atorvastatin 10 mg

[b] Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint

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

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

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day significantly reduced the rate of nonfatal, non-procedure related MI and fatal and nonfatal 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 mg 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, nonfatal 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 mg to 40 mg group.

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

Atorvastatin 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 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 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 two 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 mg, 20 mg, 40 mg 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 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[1]		-9.2, -6.5	-10.7, -7.1	-10, -6.5	-15.2, -7.1	-1.7, 2	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

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

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

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

[c] 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 in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the atorvastatin-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 (-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 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30)	-33 (-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 mg 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 four patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, two patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining three 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 (n = 140) or placebo (n = 47) for 26 weeks and then all received atorvastatin 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 mg/dL) in the atorvastatin group compared to 230 mg/dL (range: 160.0–324.5 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 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 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	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12	-34

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 to 242 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152 to 385 mg/dL) in the placebo group during the 26-week double-blind phase.

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

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 Tablets are available containing atorvastatin calcium, USP equivalent to 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin.

The 10 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **A15** on the other side. They are available as follows:

NDC 0378-2015-77
bottles of 90 tablets

NDC 0378-2015-05
bottles of 500 tablets

The 20 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **A17** on the other side. They are available as follows:

NDC 0378-2017-77
bottles of 90 tablets

NDC 0378-2017-05
bottles of 500 tablets

The 40 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **121** on the other side. They are available as follows:

NDC 0378-2121-77
bottles of 90 tablets

NDC 0378-2121-05
bottles of 500 tablets

The 80 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **122** on the other side. They are available as follows:

NDC 0378-2122-77
bottles of 90 tablets

NDC 0378-2122-05
bottles of 500 tablets

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 using a child-resistant closure.

PHARMACIST: Dispense a Patient Information Leaflet with each prescription.

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 coun

PATIENT INFORMATION LEAFLET
ATORVASTATIN CALCIUM TABLETS
(a tor′′ va stat′ in kal′ see um)
10 mg, 20 mg, 40 mg and 80 mg

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

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

What is atorvastatin?

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

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery and chest pain in patients who have 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 may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast-feeding. Atorvastatin can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

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

What should I avoid while taking atorvastatin calcium tablets?

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

What are the possible side effects of atorvastatin calcium tablets?

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

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

Call your doctor right away if you have:

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

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

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

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store atorvastatin calcium tablets?

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

General information about atorvastatin calcium tablets:

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

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

What are the ingredients in atorvastatin calcium tablets?

Active Ingredient: atorvastatin calcium, USP

Inactive Ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-Arginine, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum.

Manufactured in India by:
Mylan Laboratories Limited
Hyderabad — 500 034, India
Code No.: MH/DRUGS/25/NKD/89

Manufactured for:

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED MARCH 2012
75005296 MX:PL:ATOR:R4pt

MXPLATORR4pt

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

LABELING REVIEWS

****LABELING APPROVAL SUMMARY #3****
(SUPERCEDES AP SUM #2 DATED 12/29/10)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091226 Dates of Submission: March 13, 2012

Applicant's Name: Mylan Laboratories Limited (formerly Matrix)

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 SPL: e-submission

BASIS OF APPROVAL:

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (all strengths in bottles of 90s and 500s):
Final printed labels acceptable in March 13, 2012 e-submission

Professional Package Insert Labeling: Final printed labeling acceptable in March 13, 2012 e-submission

Patient Information Sheet: Final printed labeling acceptable in March 13, 2012 e-submission

Revisions needed post-approval: Yes

INSERT:

FULL PRESCRIBING INFORMATION: CONTENTS*

7 DRUG INTERACTIONS:

- Revise the subheading 7.1 to read “7.1 Strong Inhibitors of CYP 3A4”.
- Delete the following subtitles located under subheading 7.1

Clarithromycin
Combination of Protease Inhibitors
Itraconazole

The above post-approval comments will be communicated to the firm to Shane Shupe at (304) 554-4148, once the review has been signed off.

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: None

FOR THE RECORD: Please note that the previous review cycles were completed by Thuyanh Vu, labeling reviewer. Portions of this review were taken from the TA Summary signed off in DARRTS 12/29/2010.

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

   In addition to updating their labeling to be in accord with the labeling approved for the RLD, Mylan revised the labeling as requested by the Agency in the email correspondence dated 2/1/2012 in DARRTS.

   From: "Vu, Thuyanh (Ann)" <Thuyanh.Vu@fda.hhs.gov>
   To: "'Wayne.Talton@mylanlabs.com'" <Wayne.Talton@mylanlabs.com>
   Date: 02/01/2012 12:43 PM
   Subject: 91226 (Matrix's atorvastatin) labeling revision before full approval
   Wayne,
   Please make the following labeling revision prior to full approval of the drug product.
   11 DESCRIPTION
   Revise "(b) (4).." to "Atorvastatin calcium is a white to offwhite powder..[delete (b) (4)]"
   Please acknowledge this email.
   Thanks
   Ann

   Supplement 056, approved 6/17/2009, and provides for changes to the format of the labeling in accordance to the PLR.

   Matrix submitted a gratuitous amendment 9/14/10 to add "(b) (4)" in the drug substance description to be consistent with the Chemistry, Manufacturing and Controls section of the application.

RLD Container



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	III	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	III	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011 ped	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	III	Same As

Note that Lipitor is granted another patent: 7,790,197 on September 7, 2010, thus the patent will expire on September 7, 2017. This patent is NOT listed in the OB yet, but it is listed in the OB. In the patent amendment dated 12/28/10- Matrix filed a patent cert IV to the '197 patent.

PATENT AMENDMENT UPDATE (dated 5/4/12)

Please note that in the amendment dated 5/4/12, Mylan submitted an update to their Patent amendment. The patents are not listed in the OB, therefore the firm does not have to certify to the patents.

Mylan Laboratories Limited ("Mylan") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Mylan's certifications were and remain correct. This current amendment is submitted to address new patent filings (U.S. Patent Nos. 7,790,197 and 8,026,376) by the holder of the referenced drug (Lipitor®), which were filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent Nos. 7,790,197 and 8,026,376 are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Current PATENT DATA taken from Orange Book (checked May 9, 2012)

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020702	001	5686104	Nov 11, 2014		Y	U - 213	
N020702	001	5686104*PED	May 11, 2015			U - 213	
N020702	001	5969156	Jul 8, 2016	Y			
N020702	001	5969156*PED	Jan 8, 2017				
N020702	001	6126971	Jan 19, 2013		Y		
N020702	001	6126971*PED	Jul 19, 2013				

Previous reviews

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

Exclusivity Data (checked 5/7/12)

There is no unexpired exclusivity for this product.

[original submission]

3. INACTIVE INGREDIENTS:

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-arginine,lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum

[2.3.P.1-original submission]

Note that Matrix uses the (b) (4) form of atorvastatin- there are several other generic companies such as (b) (4) that use the (b) (4) form also and from chemistry's point of view, the use is acceptable.

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

Matrix Laboratories Ltd.
F04 & F-12, Malegaon MIDC, Sinnar
Nashik-422 113, Maharashtra, India

5. FINISHED DOSAGE FORM:

The HOW SUPPLIED section of the insert matches the 2.3.P.5 of the original submission.

RLD:

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

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

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

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

ANDA:

10 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A15" on the other side

20 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A17" on the other side

40 mg: white, oval (b) (4) film-coated tablets. Debossed with "MX" on one side and "121" on the other side

80 mg: white, oval (b) (4) film-coated tablets. Debossed with "MX" on one side and "122" on the other side

5. CONTAINER/CLOSURE [2.3.P.7- original submission]

Bottle packs

Configuration	Container	Closure	Desiccant
Atorvastatin Calcium Tablets, 10 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 20 mg			
90's Bottle STB	(b) (4) HDPE bottl (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 40 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 80 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)

In the amendment dated 3/13/2012, Mylan's bottle labels were revised in accordance with Mylan's current standard formatting.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:

USP: DS is 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 label: 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 using a child-resistant closure.

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is adequate. (taken from CMC Review dated 1/26/12)

9. SCORING:

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION:

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

ANDA: All strengths in bottles of 90s and 500s.

11. SPL:

The DLDE section of the SPL is acceptable as of March 13, 2012.

12. PATIENT INFORMATION SHEETS:

From AF 10/20/09:

(b) (4)

13. REMS:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Date of Review: May 9, 2012 Dates of Submission: March 13, 2012

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

Mylan

Atorvastatin Calcium
Tablets

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan | www.mylan.com

RMX2015MM3

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

This container is not intended for dispensing for household use.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

RMX2015B3

Mylan | www.mylan.com

Mylan®

Atorvastatin Calcium Tablets



PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

N 3 0378-2015-05 8

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

75005289

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan® | www.mylan.com

RMX2017MM3

Mylan®

Atorvastatin Calcium
Tablets

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Code No.: MHDRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

N 3 0378-2017-77 9

75005290

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

This container is not intended for dispensing for household use.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

RMX2017B3

Mylan® | www.mylan.com

Mylan®

Atorvastatin Calcium Tablets



PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

N 3 0378-2017-05 2

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

75005291

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan® | www.mylan.com

RMX2121MM3

Mylan®

Atorvastatin Calcium Tablets



PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

N 3 0378-2121-77 3

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

75005292

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

This container is not intended for dispensing for household use.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

RMX2121B3

Mylan® | www.mylan.com

Mylan®

Atorvastatin Calcium Tablets



PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

N 3 0378-2121-05 6

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

75005293

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Mylan® | www.mylan.com

RMX2122MM3

Mylan®

Atorvastatin Calcium Tablets



PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

N 3 0378-2122-77 0

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

7500 5294

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

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

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

This container is not intended for dispensing for household use.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

RMX2122B3

Mylan® | www.mylan.com

Mylan®

Atorvastatin Calcium Tablets



PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

N
3 0378-2122-05 3

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Lot

Exp.

NO VARNISH ZONE

75005295

ATORVASTATIN CALCIUM TABLETS
10 mg, 20 mg, 40 mg and 80 mg
75005297
MX:ATOR:R5ppt

ATORVASTATIN CALCIUM TABLETS
10 mg, 20 mg, 40 mg and 80 mg
75005297
MX:ATOR:R5ppt

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.

Atorvastatin Calcium Tablets for Oral Administration

Initial U.S. Approval: 1996

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

Drug Interactions (7) 02/2012

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

Atorvastatin is 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 nonfatal MI, fatal and nonfatal 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 mg to 80 mg once daily (2.1).

Recommended start dose: 10 mg 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 mg, 20 mg, 40 mg 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 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 Mylan Pharmaceuticals Inc. at 1-877-4-INFO-RX (1-877-446-3679) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION

REVISED MARCH 2012

MX:ATOR:R5ppt/MX:PL:ATOR:R4p/MX:PL:ATOR:R4pt

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Prevention of Cardiovascular Disease

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

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

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

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

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

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of fatal and nonfatal 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 mg 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 mg 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 mg 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 oval, film-coated tablets containing 10 mg, 20 mg, 40 mg or 80 mg atorvastatin calcium, USP.

4 CONTRAINDICATIONS

4.1 Active Liver Disease, which may include Unexplained Persistent Elevations in Hepatic Transaminase Levels

4.2 Hypersensitivity to any Component of this Medication.

4.3 Pregnancy

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

4.4 Nursing Mothers

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

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

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

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

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

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

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

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

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

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

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

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

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on two 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 mg, 20 mg, 40 mg and 80 mg, respectively.**

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

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

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

5.3 Endocrine Function

Increases in HbA_{1c} and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

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

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of two 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 placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin vs. 7,311 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 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 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 in placebo controlled trials (n = 8,755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6%) 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 (n = 8,755), from 17 placebo-controlled trials.

Table 2. Clinical Adverse Reactions Occurring in ≥ 2% in Patients Treated with Any Dose of Atorvastatin and at an Incidence Greater Than Placebo Regardless of Causality (% of Patients).

Adverse Reaction*	Any Dose N = 8,755	10 mg N = 3,908	20 mg N = 188	40 mg N = 604	80 mg N = 4,055	Placebo N = 7,311
Nasopharyngitis	8.3	12.9	5.3	7	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	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6	3.3	4.3
Nausea	4	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
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

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

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

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin 10 mg daily (n = 5,168) or placebo (n = 5,137), the safety and tolerability profile of the group treated with atorvastatin 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% 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% Asians, 2% other) with clinically evident CHD treated with atorvastatin 10 mg daily (n = 5,006) or atorvastatin 80 mg daily (n = 4,995), 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 = 4,439) or simvastatin 20 mg to 40 mg daily (n = 4,449), 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 4,731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3% 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 = 2,365) or placebo (n = 2,366) 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%). 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 (218/2,365, 9.2% vs. 274/2,366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). The incidence of nonfatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 nonfatal hemorrhagic strokes) as compared to the placebo group (16 nonfatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin 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%) than in the placebo group (4%).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of atorvastatin. 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 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 nonfatal hepatic failure, dizziness, depression, peripheral neuropathy and pancreatitis.

There have been rare post-marketing 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 (one 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 mg to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

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

7.1 Strong Inhibitors of Cytochrome P450 3A4

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

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

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

nonfamilial forms of hypercholesterolemia and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG and non-HDL-C and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin 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, 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 dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

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

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following 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 and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

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

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

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

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

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

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

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

Coadministered Drug and Dosing Regimen	Atorvastatin		
	Dose (mg)	Change in AUC[k]	Change in C_{max}[k]
[d]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
[d]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg SD	↑ 9.4 fold	↑ 8.6 fold
[d]Telaprevir 750 mg q8h, 10 days	20 mg SD	↑ 7.88 fold	↑ 10.6 fold
[d, i]Saquinavir 400 mg BID/ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
[d]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[d]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
[d]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
[d]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
[d]Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
[d]Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
[d]Grapefruit Juice, 240 mL QD*	40 mg SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg SD	↑ 15%	↓ 12%
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[d]Rifampin 600 mg QD, 7 days (coadministered)†	40 mg SD	↑ 30%	↑ 2.7 fold
[d]Rifampin 600 mg QD, 5 days (doses separated)†	40 mg SD	↓ 80%	↓ 40 %
[d]Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less than 1%
[d]Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%

[k] 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).

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

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

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

† Due to the dual interaction mechanism of rifampin, simultaneous 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.

‡ 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	[d]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

[d] 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, two 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 two of ten 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 2 years.

14 CLINICAL STUDIES

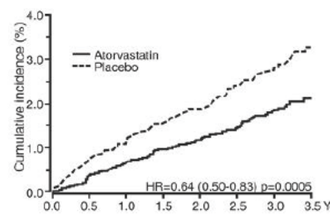
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and nonfatal 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 three 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 = 5,168) or placebo (n = 5,137), 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 significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs. 60 events in the atorvastatin group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin vs. 3% 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 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 Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and nonfatal 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 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 on cardiovascular disease (CVD) endpoints was assessed in 2,838 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 one 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 (1,429) or placebo (1,411) 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.

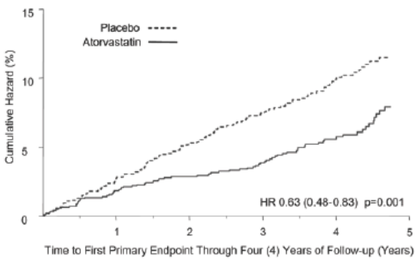
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin 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 was seen regardless of age, sex or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin 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 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, nonfatal myocardial infarction, resuscitated cardiac arrest and fatal and nonfatal 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)

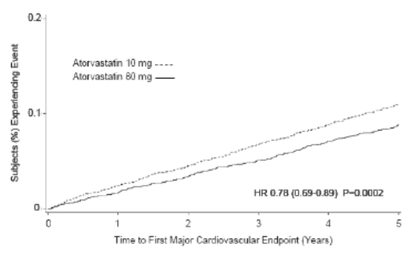


Table 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N = 5,006)		Atorvastatin 80 mg (N = 4,995)		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)	0.8 (0.61, 1.03)
Nonfatal, 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 nonfatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First 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, 0.8)
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)
Suicide, homicide and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

[a] Atorvastatin 80 mg; atorvastatin 10 mg

[b] Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint

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

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

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day significantly reduced the rate of nonfatal, non-procedure related MI and fatal and nonfatal 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 mg 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, nonfatal 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 mg to 40 mg group.

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

Atorvastatin 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 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 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 two 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 mg, 20 mg, 40 mg 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 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[1]		-9.2, -6.5	-10.7, -7.1	-10, -6.5	-15.2, -7.1	-1.7, 2	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

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

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

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

[c] 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 in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the atorvastatin-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 (-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 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30)	-33 (-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 mg 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 four patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, two patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining three 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 (n = 140) or placebo (n = 47) for 26 weeks and then all received atorvastatin 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 mg/dL) in the atorvastatin group compared to 230 mg/dL (range: 160.0–324.5 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 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 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	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12	-34

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 to 242 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152 to 385 mg/dL) in the placebo group during the 26-week double-blind phase.

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

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 Tablets are available containing atorvastatin calcium, USP equivalent to 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin.

The 10 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **A15** on the other side. They are available as follows:

NDC 0378-2015-77
bottles of 90 tablets

NDC 0378-2015-05
bottles of 500 tablets

The 20 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **A17** on the other side. They are available as follows:

NDC 0378-2017-77
bottles of 90 tablets

NDC 0378-2017-05
bottles of 500 tablets

The 40 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **121** on the other side. They are available as follows:

NDC 0378-2121-77
bottles of 90 tablets

NDC 0378-2121-05
bottles of 500 tablets

The 80 mg tablets are white to off-white film-coated, oval, unscored tablets debossed with **MX** on one side of the tablet and **122** on the other side. They are available as follows:

NDC 0378-2122-77
bottles of 90 tablets

NDC 0378-2122-05
bottles of 500 tablets

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 using a child-resistant closure.

PHARMACIST: Dispense a Patient Information Leaflet with each prescription.

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 coun

PATIENT INFORMATION LEAFLET
ATORVASTATIN CALCIUM TABLETS
(a tor′′ va stat′ in kal′ see um)
10 mg, 20 mg, 40 mg and 80 mg

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

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

What is atorvastatin?

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

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery and chest pain in patients who have 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 may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast-feeding. Atorvastatin can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

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

What should I avoid while taking atorvastatin calcium tablets?

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

What are the possible side effects of atorvastatin calcium tablets?

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

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

Call your doctor right away if you have:

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

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

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

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store atorvastatin calcium tablets?

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

General information about atorvastatin calcium tablets:

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

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

What are the ingredients in atorvastatin calcium tablets?

Active Ingredient: atorvastatin calcium, USP

Inactive Ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-Arginine, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum.

Manufactured in India by:
Mylan Laboratories Limited
Hyderabad — 500 034, India
Code No.: MH/DRUGS/25/NKD/89

Manufactured for:

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED MARCH 2012
75005296 MX:PL:ATOR:R4pt

MXPLATORR4pt

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

LABELING APPROVAL SUMMARY
(SUPERCEDES AP SUM #1 DATED 3/11/10)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91226 Dates of Submission: September 14 and December 6, 2010

Applicant's Name: Matrix Laboratories Ltd.

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

---

BASIS OF APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? No

Container Labels (all strengths in bottles of 90s and 500s):
Final printed labels acceptable in 8/12/10 e-submission.

Professional Package Insert Labeling: Final printed labeling acceptable in 9/14/10 e-submission

Patient Information Sheet: Final printed labeling acceptable in 9/14/10 e-submission

Revisions needed before full approval:

PPI: What is Atorvastatin Calcium tablets?: last bullet, please separate “atorvastatin calcium tablets start to work in about 2 weeks” from this bullet. The phrase should stand alone.

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:

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. Supplement provides changes to the format of the labeling in accordance to the PLR.

   Matrix submitted a gratuitious amendment 9/14/10 to add "(b) (4)" in the drug substance description to be consistent with the Chemistry, Manufacturing and Controls section of the application.

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	III	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	III	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011 ped	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	III	Same As

Note that Lipitor is granted another patent: 7,790,197 on September 7, 2010, thus the patent will expire on September 7, 2017. This patent is NOT listed in the OB yet, but it is listed in the OB. In the patent amendment dated 12/28/10- Matrix filed a patent cert IV to the '197 patent.

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

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-arginine,lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum

[2.3.P.1-original submission]

Note that Matrix uses the (b) (4) form of atorvastatin- there are several other generic companies such as (b) (4) that use the (b) (4) form also and from chemistry's point of view, the use is acceptable.

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

Matrix Laboratories Ltd.
F04 & F-12, Malegaon MIDC, Sinnar
Nashik-422 113, Maharashtra, India

5. FINISHED DOSAGE FORM

The HOW SUPPLIED section of the insert matches the 2.3.P.5 of the original submission.

RLD:

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

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

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

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

ANDA:

10 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A15" on the

other side

20 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A17" on the other side

40 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "121" on the other side

80 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "122" on the other side

5. CONTAINER/CLOSURE [2.3.P.7- original submission]

Bottle packs

Configuration	Container	Closure	Desiccant
Atorvastatin Calcium Tablets, 10 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	HDPE bottle (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 20 mg			
90's Bottle STB	HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	HDPE bottl (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 40 mg			
90's Bottle STB	HDPE bottl (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	HDPE bottle (b) (4)	(b) (4)	(b) (4) (b) (4)
Atorvastatin Calcium Tablets, 80 mg			

90's Bottle STB	HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	HDPE bottle (b) (4)	(b) (4)	(b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: DS is 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 label: 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 using a child-resistant closure.

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is pending as of May 11, 2009.

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

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

ANDA: All strengths in bottles of 90s and 500s.

11. SPL

The DLDE section of the SPL is acceptable as of May 11, 2009.

12. PATIENT INFORMATION SHEETS

From AF 10/20/09:

[redacted] (b) (4)

Date of Review: December 28, 2010 Dates of Submission: September 14 and December 6, 2010

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Reference ID: 2884140
10 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

THUYANH VU
12/28/2010

JOHN F GRACE
12/29/2010

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

ANDA Number: 91226 Date of Submission: August 12, 2010

Applicant's Name: Matrix Laboratories Ltd.

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

---

Labeling Deficiencies:

1. CONTAINER (all strengths in bottles of 90s and 500s):

   Acceptable in final print

2. INSERT

   FULL PRESCRIBING INFORMATION: CONTENTS

   Revise to read:

   2.1 Hyperlipidemia [delete “Heterozygous...IIb]

   2.2 Heterozygous Familial...Patients [delete “10 to 17....Age]

   6.3 Postintroduction Reports

   14.2 Hyperlipidemia and Mixed Dyslipidemia [delete “Heterozygous Familial...Nonfamilial” and “Frederickson Types... IIb]

   14.3 Hypertriglyceridemia [delete “Fredrickson Type IV]

   14.4 Dysbetalipoproteinemia [delete Fredrickson Type III]

   We refer you to the reference listed drug’s labeling.

3. PATIENT INFORMATION SHEET:

   What is Atorvastatin Calcium tablets?: last bullet, please separate “atorvastatin calcium tablets start to work in about 2 weeks” from this bullet. The phrase should stand alone.

Submit labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? No

Container Labels (all strengths in bottles of 90s and 500s)
Final printed labels acceptable in 8/12/10 e-submission.

Professional Package Insert Labeling: No

Patient Information Sheet: No

Revisions needed before full approval: Was this approval based upon a petition? No

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

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

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

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

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. Supplement provides changes to the format of the labeling in accordance to the PLR.

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	III	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	III	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011 ped	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	III	Same As

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

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-arginine,lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum

[2.3.P.1-original submission]

Note that Matrix uses the (b) (4) form of atorvastatin- there are several other generic companies such as (b) (4) that use the (b) (4) form also and from chemistry's point of view, the use is acceptable.

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

Matrix Laboratories Ltd.
F04 & F-12, Malegaon MIDC, Sinnar
Nashik-422 113, Maharashtra, India

5. FINISHED DOSAGE FORM

The HOW SUPPLIED section of the insert matches the 2.3.P.5 of the original submission.

RLD:

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

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

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

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

ANDA:

10 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A15" on the other side

20 mg: white, oval (b) (4) film-coated tablets. Debossed with "MX" on one side and "A17" on the other side

40 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "121" on the other side

80 mg: white, oval (b) (4) film-coated tablets. Debossed with "MX" on one side and "122" on the other side

5. CONTAINER/CLOSURE [2.3.P.7- original submission]

Bottle packs

Configuration	Container	Closure	Desiccant
Atorvastatin Calcium Tablets, 10 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottl (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 20 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 40 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
Atorvastatin Calcium Tablets, 80 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)
500's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not USP
RLD: store at CRT 20-25°C (68-77°F) [see USP].

ANDA label: Store at 20° to 25°C (68° to 77°F) [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 using a child-resistant closure.

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is pending as of May 11, 2009.

9. SCORING

   RLD: Not scored
   ANDA: Not scored

10. PACKAGE CONFIGURATION

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

   ANDA: All strengths in bottles of 90s and 500s.

11. SPL

   The DLDE section of the SPL is acceptable as of May 11, 2009.

12. PATIENT INFORMATION SHEETS

   From AF 10/20/09:

(b) (4)

[redacted]

Date of Review: September 10, 2010 Date of Submission: August 12, 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
09/10/2010

JOHN F GRACE
09/20/2010

LABELING APPROVAL SUMMARY

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

ANDA Number: 91226 Date of Submission: October 20, 2009

Applicant's Name: Matrix Laboratories Ltd.

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

---

BASIS OF APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (all strengths in bottles of 90s and 500s):

Final printed labels submitted in 10/20/09 e-submission.

Professional Package Insert Labeling: Final printed labels submitted in 10/20/09 e-submission.

Patient Information Sheet: Final printed labels submitted in 10/20/09 e-submission.

Revisions needed before full approval: Yes

PPI: What is Atorvastatin Calcium tablets?: last bullet, please separate “atorvastatin calcium tablets start to work in about 2 weeks” from this bullet. The phrase should stand alone.

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:

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. Supplement provided labeling in the PLR format. S-046 approved 6/23/06 provided the patient package insert.

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	III	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	III	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011 ped	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	III	Same As

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***

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

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: anhydrous lactose, anhydrous sodium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-arginine,lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum

[2.3.P.1-original submission]

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

Matrix Laboratories Ltd.
F04 & F-12, Malegaon MIDC, Sinnar
Nashik-422 113, Maharashtra, India

5. FINISHED DOSAGE FORM

The HOW SUPPLIED section of the insert matches the 2.3.P.5 of the original submission.

RLD:

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

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

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

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

ANDA:

10 mg: white, oval, (b) (4) film-coated tablets. Debossed with “MX” on one side and “A15” on the other side

20 mg: white, oval, (b) (4) film-coated tablets. Debossed with “MX” on one side and “A17” on the other side

40 mg: white, oval, (b) (4) film-coated tablets. Debossed with “MX” on one side and “121” on the other side

80 mg: white, oval, [redacted] film-coated tablets. Debossed with “MX” on one side and “122” on the other side

5. CONTAINER/CLOSURE [2.3.P.7- original submission]

Bottle packs

Configuration	Container	Closure	Desiccant
Atorvastatin Calcium Tablets, 10 mg			
90’s Bottle STB	[redacted] HDPE bottle [redacted]	[redacted]	[redacted]
500’s Bottle STB	[redacted] HDPE bottle [redacted]	[redacted]	[redacted]
Atorvastatin Calcium Tablets, 20 mg			
90’s Bottle STB	[redacted] HDPE bottle [redacted]	[redacted]	[redacted]
500’s Bottle STB	[redacted] HDPE bottle [redacted]	[redacted]	[redacted]
Atorvastatin Calcium Tablets, 40 mg			
90’s Bottle STB	[redacted] HDPE bottle [redacted]	[redacted]	[redacted]
500’s Bottle STB	[redacted] HDPE bottle [redacted]	[redacted]	[redacted]
Atorvastatin Calcium Tablets, 80 mg			
90’s Bottle STB	[redacted] HDPE bottl [redacted]	[redacted]	[redacted]

500's Bottle STB	HDPE bottle (b) (4)	(b) (4)	(b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: Not USP
   RLD: store at CRT 20-25°C (68-77°F) [see USP].
   ANDA label: Store at 20° to 25°C (68° to 77°F) [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 using a child-resistant closure.

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is pending as of May 11, 2009.

9. SCORING

   RLD: Not scored
   ANDA: Not scored

10. PACKAGE CONFIGURATION

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

    ANDA: All strengths in bottles of 90s and 500s.

11. SPL

    The DLDE section of the SPL is acceptable as of May 11, 2009.

12. Container Color Differentation:

    10 mg= Both the established name and strength are red against a white background

    20 mg= Both the established name and strength are green against a white background

    40 mg= Both the established name and strength are purple against a white background

    80 mg= Both the established name and strength are yellowish orange against a white background

13. PPI

    From AF 10/20/09:

(b) (4)

[redacted]

Date of Review: March 11, 2010 Date of Submission: October 20, 2009

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	ATORVASTATIN CALCIUM

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

/s/

THUYANH VU
03/11/2010

JOHN F GRACE
03/11/2010

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

ANDA Number: 91-226 Date of Submission: December 30, 2008

Applicant's Name: Matrix Laboratories Ltd.

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

---

Labeling Deficiencies:

1. CONTAINER (all strengths in bottles of 90s and 500s):

   a. Storage temperature statement- please relocate the period between the two phrases to the end of the bracket, e.g. “Store at 20 to 25C (68 to 77F) [See USP for Controlled Room Temperature].”

   b. Since this drug product is associated with a patient package insert, we encourage you to add to the principal display panel: “Pharmacist: please dispense with patient package insert”.

2. INSERT

   ADVERSE REACTIONS, Postintroduction Reports- add “and hepatic failure” after “tendon rupture”.

3. PATIENT INFORMATION SHEET:

   a. Please submit the patient package insert. We refer you to 20-702/S-046 approved on 6/23/06 at the Drugs@FDA website.

   b. Please state the number of sheets you intend on providing in order for each patient to receive one.

Submit labels and labeling electronically. We refer you to the website http://www.fda.gov/oc/datacouncil/spl.html for further guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF TENTATIVE APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? No

Container Labels (all strengths in bottles of 90s and 500s)
No, see comments above.

Professional Package Insert Labeling: No

Patient Information Sheet: No

Revisions needed before full approval: Was this approval based upon a petition? No

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

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-057; approved 3/27/09.

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:

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-057; approved 3/27/09. Supplement provided changes to the ADVERSE REACTIONS, Postintroduction, addition of "hepatic failure". S-046 approved 6/23/06 provided the patient package insert.

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	III	Same As

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5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	Same As
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6126971	Jan 19, 2013 ped July 19, 2013	—		IV	Same As
RE40667	Jun 28, 2011 ped	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	III	Same As

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

[original submission]

3. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: anhydrous lactose, anhydrous sodium

carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, L-arginine,lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide and xanthan gum

[2.3.P.1-original submission]

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

Matrix Laboratories Ltd.
F04 & F-12, Malegaon MIDC, Sinnar
Nashik-422 113, Maharashtra, India

5. FINISHED DOSAGE FORM

The HOW SUPPLIED section of the insert matches the 2.3.P.5 of the original submission.

RLD:

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

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

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

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

ANDA:

10 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A15" on the other side

20 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "A17" on the other side

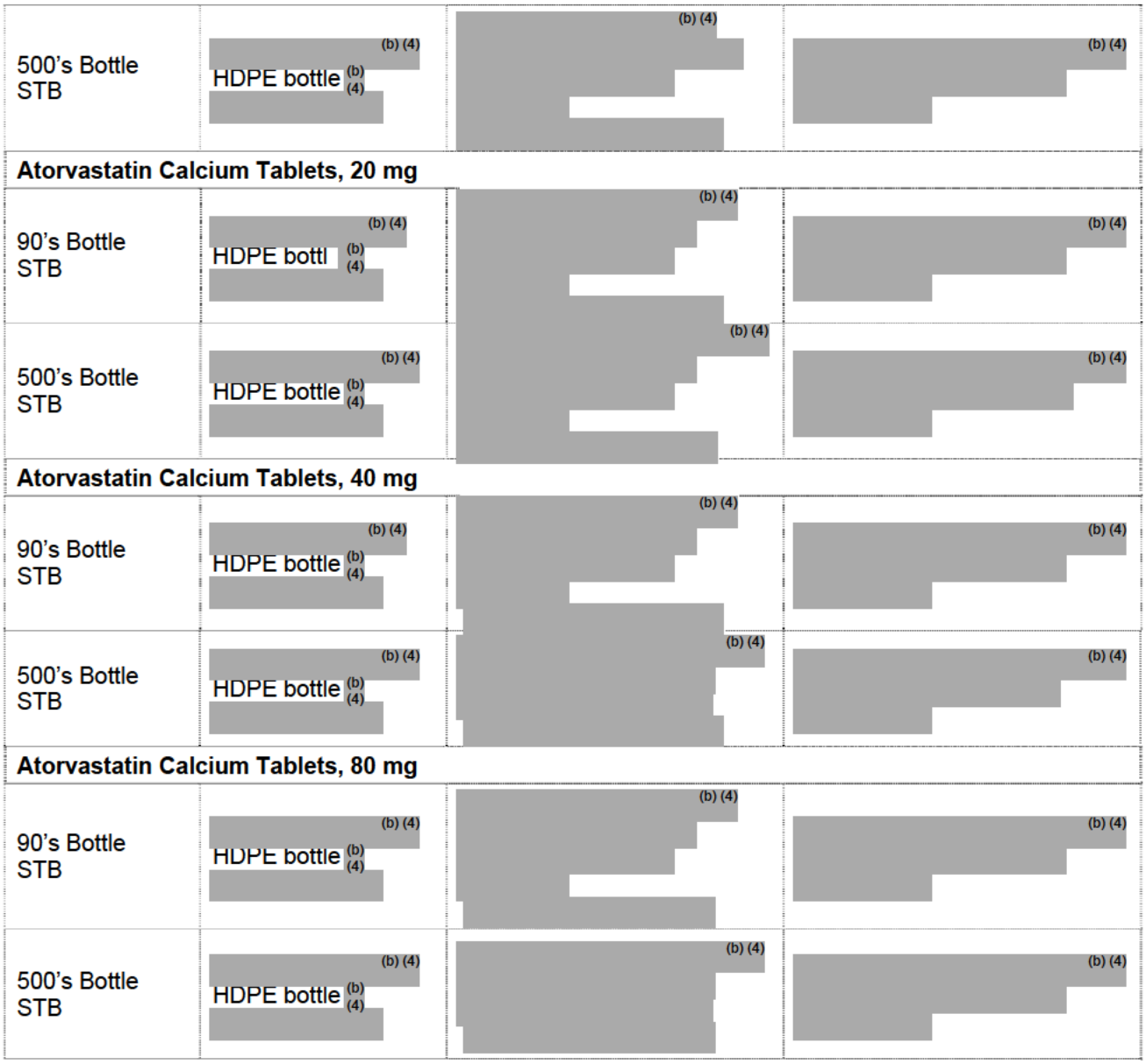
40 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "121" on the other side

80 mg: white, oval, (b) (4) film-coated tablets. Debossed with "MX" on one side and "122" on the other side

5. CONTAINER/CLOSURE [2.3.P.7- original submission]

Bottle packs

Configuration	Container	Closure	Desiccant
Atorvastatin Calcium Tablets, 10 mg			
90's Bottle STB	(b) (4) HDPE bottle (b) (4)	(b) (4)	(b) (4)



6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: Not USP
   RLD: store at CRT 20-25°C (68-77°F) [see USP].
   ANDA label: Store at 20° to 25°C (68° to 77°F) [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 using a child-resistant closure.

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is pending as of May 11, 2009.

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

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

ANDA: All strengths in bottles of 90s and 500s.

11. SPL

The DLDE section of the SPL is acceptable as of May 11, 2009.

Date of Review: May 11, 2009 Date of Submission: December 30, 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
5/11/2009 04:35:41 PM
LABELING REVIEWER

John Grace
5/14/2009 11:04:20 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

CHEMISTRY REVIEWS

Addendum # 1

ANDA 091226

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

Mylan Laboratories Limited (Matrix)

Haitao Li, Ph.D.
Chemistry Division III

The addendum #1 is generated for ANDA 091226 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg in response to the firm's gratuitous Amendment on May 15, 2012 and their final approval request dated March 13, 2012. The applicant requested their full approval to be granted on May 28, 2012 concurrent with the expiration of the 180-day exclusivity by the first to file applicant.

The firm revised their outside testing plan per gratuitous amendment dated May 15, 2012.
In response to an Agency request, Mylan submitted a Gratuitous amendment dated June 28, 2011 wherein Mylan provided details of all facilities used in manufacturing or testing activities related to subject product. The June 28th amendment provided for partial testing of the drug substance, Atorvastatin calcium and excipient Magnesium Stearate at different contract testing labs. Since Mylan, Nashik is now equipped to conduct all testing related to drug substance, Atorvastatin calcium within its quality control set-up, Mylan is accordingly providing a revised outside testing plan. Also, Mylan laboratories limited, Unit-1/Unit-2 is being proposed for the partial testing of excipient (Magnesium Stearate) instead of earlier proposed (b) (4). A copy of the revised outside testing plan and cGMP certificate for Mylan laboratories limited, Unit-1/Unit-2 is enclosed in Section 3.2.P.3.1.A
Summary of all the manufacturing and testing establishments associated with this application (ANDA 091226) is provided as an attachment to FDA Form 356h including details about the facility, address, contact person, phone, fax, email and FEI number. The information is also shown below.

DRUG SUBSTANCE:
(Activities related to Drug Substance manufacturing by the DMF holder)

Address of the manufacturing facility	Mylan Laboratories Limited (Unit-3) Plot No. 35, 36, 38 to 40, 49 to 51, Phase IV, IDA, Jeedimetla, Hyderabad- 500055 Andhra Pradesh, INDIA
Establishment registration #	3003937580
DUNS #	916568827
Contact person (facility)	Mr. Imtiyaz Basade Tel: 0091.40.30492413 Fax: 0091.8458279305 Email: imtiyaz.basade@mylan.in
US Agent for Mylan Laboratories Limited **(For drug substance submissions)**	Mylan Laboratories Inc. 76, South Orange Ave, Suite 301 South Orange, NJ 07079, USA Contact: Sree Malepati Phone : 973 761 1600 Fax: 973 761 1680 Email: sree.malepati@mylan.in

Chemistry Assessment Section

DRUG PRODUCT:
(Testing, Manufacturing, Holding, Packaging, Release and Stability testing of Drug Product)

Address of the manufacturing facility	Mylan Laboratories Ltd., Plot # F/4, F/12, Malegaon M.I.D.C. Sinnar, Nashik District - 422113 Maharashtra State, India.
Establishment Registration #	3005587313
DUNS #	725584960
Contact person	Mr. Pramod Kumar Singh, Site-Head Phone : 0091.2551.230092; Fax : 0091.2551.230924 Email: pramodkumar.singh@mylan.in

DRUG PRODUCT- *OUTSIDE TESTING FACILITIES:*

Mylan Laboratories Limited (Unit-1/Unit-2) – ((b) (4) testing of Magnesium Stearate)

Address of the manufacturing facility	Mylan Laboratories Limited (Unit-1/Unit-2) Survey No.10/42, Gaddapotharam, Kazipally Industrial Area, Medak District – 502319, Andhra Pradesh, INDIA
Establishment registration #	3004713397
DUNS #	918608878
Contact person	Mr. Imtiyaz Basade Tel: 0091.40.30492413 Fax: 0091.8458279305 Email: imtiyaz.basade@mylan.in

Outside Laboratories Testing Plan

Product Name : Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, 80 mg	OTP No. : OTP-11-0046-02
	Type - API/Excipients ✓ (b) (4)

S.No.	Material Name	Tests	Name of outside Laboratory
01	Magnesium stearate	a. Specific surface area	Mylan Laboratories Ltd, Unit-I / II

The facility information has been updated in EES.

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

1. Satisfactory EES
2. DMF is adequate as of 1/13/2012
3. DS meets the current USP monograph

4. No CMC changes since TA per applicant letter dated Mar 13, 2012

30. MICROBIOLOGY
NA

31. SAMPLES AND RESULTS/METHODS VALIDATIONs·
NA

32. LABELING
Acceptable on 5/10/2012

33. ESTABLISHMENT INSPECTION
Acceptable 5/21/2012

34. BIOEQUIV ALENCE
Acceptable 02/17/2011.

Endorsement
HFD-630/H. Li /Reviewer /5/23/2012
HFD-630/L. Nagavelli/5/24/2012
HFD-617/L. Sears/5/24/2012

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TYPE OF LETTER: APPROVABLE

Reference ID: 3135755

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
05/24/2012

LAXMA R NAGAVELLI
05/24/2012

LEIGH A SEARS
05/24/2012

ANDA 091226
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Mylan Laboratories Limited (Matrix)
Haitao Li, PhD
Office of Generic Drugs
Division of Chemistry III

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List of Deficiencies To Be Communicated	

(b) (4)

Reference ID: 3077549

CMC REVIEW DATA SHEET

1. ANDA #: 091226 2. REVIEW #: 5
3. REVIEW DATE: July 7, 2011; revised January 24, 2012
4. REVIEWER: Haitao Li, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents: None	Document Date
Original	December 30, 2008 (Rev.#1)
CMC Amendment	April 8, 2010 (Rev.#2)
CMC Amendment	DEC. 14, 2010 (Rev.#3)
Gratuitous Amendment	NOV. 18, 2010 (Rev.#3)
CMC Amendment	March 7, 2011 (Rev.#4)
CMC Amendment	March 1, 2011 (Rev.#4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Gratuitous Amendment	March 31, 2011
CMC Amendment	May 26, 2011
CMC Amendment	June 28, 2011
CMC Amendment	October 24, 2011
CMC Amendment	November 21, 2011
CMC Amendment	November 22, 2011
CMC Amendment	November 23, 2011
CMC Amendment	December 1, 2011
CMC Amendment (two amendments)	December 2, 2011
CMC Amendment	December 27, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Laboratories Limited (formerly Matrix)
Address:	Plot No. 564/A/22, Road No. 92 Jubilee Hills Hyderabad 500 034 Andhra Pradesh (AP) India
U.S. Representative:	Keith Giunta Mylan Pharmaceuticals. Inc. 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-554-5899, 800-848-0461, ext. 5899
Fax:	304-285-6407

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702

Reference ID: 3077549

The applicant filed paragraph IV certifications for 7,790,197.
Original ANDA was submitted under a paragraph IV.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
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 8, 2016	Y			
020702	004	5969156*PED	Jan 8, 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-471	Sep 21, 2008
020702	004	I-523	Mar 2, 2010

10. PHARMACOL. CATEGORY: Lipid Lowering Agent/Inhibitor of HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis in liver.

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

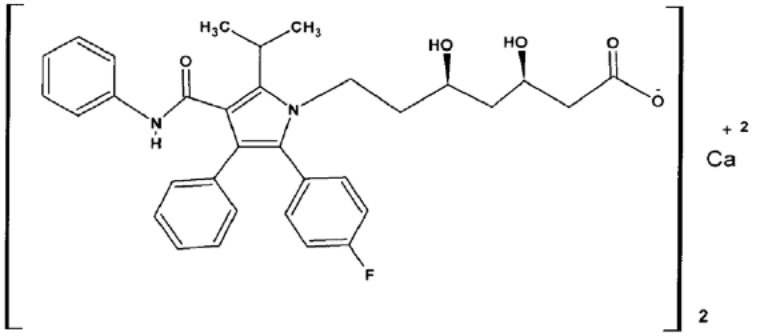
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed
_X___Not a SPOTS product

15b. NANO TECHNOLOGY PRODUCTS TRACKING SYSTEM:
NANO product – Form Completed
_X___Not a NANP product

Reference ID: 3077549

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:



[R-(R,R)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino) carbonyl]- 1H-pyrrole-1-heptanoic acid hemi calcium salt
$(C_{33}H_{34}FN_2O_5)_2Ca$
MW: 1155.36

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21477	II	Matrix Laboratories Ltd.	Atorvastatin Calcium	1	Adequate	1/13/2012	by H. Li
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

(b) (4)	III	(b) (4)	4	N/A	

Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	12/15/2011	
Methods Validation	NA		
Labeling	Acceptable*	3/11/2010	A. Vu
Bioequivalence	Adequate	2/17/2011	H. Zhang
EA	NA		
Radiopharmaceutical	NA		

* label indicates API as (b) (4) material.

19. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt.
_____ Yes __X__ No If no, explain reason(s) below:
The application is expedited by Office.

Reference ID: 3077549

The Executive Summary

Recommendation and Conclusion on Approvability:
CMC Approvable (Review #5)

Summary of Chemistry Assessments
A. Description of the Drug Product(s) and Drug Substance(s)
NDA 20702 for RLD Lipitor® from Pfizer uses crystalline Atorvastatin Calcium trihydrate as drug substance. ANDA firm uses [redacted] (b) (4) API. The impurities in the ANDA drug product are at higher levels than the observed for the NDA product, however, the impurity levels in the ANDA product are found acceptable by our in-house toxicology division based on the pharm-tox information provided by the ANDA holder.

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablet. It is indicated for lipid regulation. 10 mg strength is a white, oval, [redacted] (b) (4) film-coated tablets: White to off-white, oval, [redacted] (b) (4), film coated tablet debossed with "MX" on one side, "A15" on the other side. 20 mg strength is a White to off white, oval, [redacted] (b) (4), film-coated tablet: debossed with "MX" on one side, "A17" on the other side. 40 mg strength is a White to off white, oval, [redacted] (b) (4) film-coated tablets, debossed with "MX" on one side, "121" on the other side. 80 mg strength is a White to off-white, oval [redacted] (b) (4) film coated tablet debossed with "MX" on one side and "122" on the other side.

Critical Attributes of the Formulation: The manufacturing process is a [redacted] (b) (4) The unit operations are [redacted] (b) (4)

The DS is about [redacted] (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities, including the epoxide impurities and lactone impurity (which is also a metabolite).

Mechanism of Drug Release: The dosage form consists of [redacted] (b) (4)% of [redacted] (b) (4), croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously.

Drug Substance: The DS is atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. Based on the 3-month ACC and [redacted] (b) (4)-month long-term studies, the firm has requested an expiration period of [redacted] (b) (4) months at room conditions in original submission. They revised to 18 month expiry date in Amendment dated 3/7/2011.

The MDD for adults is 80 mg.
ICHQ3A: IT: 0.10%, QT: 0.15%
ICHQ3B: IT: 0.20%, QT: [redacted] (b) (4)%.

USP Status

Reference ID: 3077549

The DS was not compendial per USP, BP or EP in Rev.#1. PF35(1) In-Process Revision for Atorvastatin Calcium drug substance came out in Rev.#2. USP monograph for Atorvastatin Calcium is official in Rev.#3. The USP specifies the trihydrate both in chemical structure and in water content criteria. Also the description and solubility reference chapter indicates that Atorvastatin Calcium is crystalline.

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 Mylan'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 memorandum in DARRTS dated Jan 26, 2012.

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

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 90 counts, 500 counts (b) (4) and in bulk packages for pharmacy. Dosing is once a day. MDD is 80 mg.

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: 3077549
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/s/

HAITAO LI
01/26/2012

LAXMA R NAGAVELLI
01/26/2012

LEIGH A SEARS
01/26/2012

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: 3047049

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: 3047049

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: 3047049

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: 3047049

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

/s/

JAMES F ALLGIRE
11/18/2011

ANDA 091226
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Matrix Laboratories Ltd.
Haitao Li, PhD
Office of Generic Drugs
Division of Chemistry III

Table of Contents — Page #

Executive Summary 6
Chemistry, Manufacturing and Controls Assessments 8
Updated Review of CTD - Quality Module 2: QOS and Module 3.2: Body of Data
Drug Substance Specification
Drug Product Description and Composition
Drug Product In Process Control
Drug Product Specification (Release)
Drug Product Specification (Stability)
List of Deficiencies To Be Communicated

(b) (4)

Reference ID: 2945206

REVIEW OF CHEMISTRY, MANUFACTURING & CONTROLS
OFFICE OF GENERIC DRUGS

CMC REVIEW DATA SHEET

1. ANDA #: 091226
2. REVIEW #: 4
3. REVIEW DATE: March 28, 2011
4. REVIEWER: Haitao Li, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents: None	Document Date
Original	December 30, 2008 (Rev.#1)
CMC Amendment	April 8, 2010 (Rev.#2)
CMC Amendment	DEC. 14, 2010 (Rev.#3)
Gratuitous Amendment	NOV. 18, 2010 (Rev.#3)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CMC Amendment	March 7, 2011 (Rev.#4)
CMC Amendment	March 1, 2011 (Rev.#4)

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Labororatories Ltd.
Address:	1-1-151/1,4th Floor Sairam Towers, Alexander Road Secunderabad – 500 003 Andhra Pradesh (AP) India
U.S. Representative:	Keith Giunta Mylan Pharmaceuticals. Inc. 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-554-5899, 800-848-0461, ext. 5899
Fax:	304-285-6407

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The applicant filed paragraph IV certifications for 7,790,197.
Original ANDA was submitted under a paragraph IV.

Reference ID: 2945206

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
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 8, 2016	Y			
020702	004	5969156*PED	Jan 8, 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-471	Sep 21, 2008
020702	004	I-523	Mar 2, 2010

10. PHARMACOL. CATEGORY: Lipid Lowering Agent/Inhibitor of HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis in liver.

11. DOSAGE FORM: Tablets

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

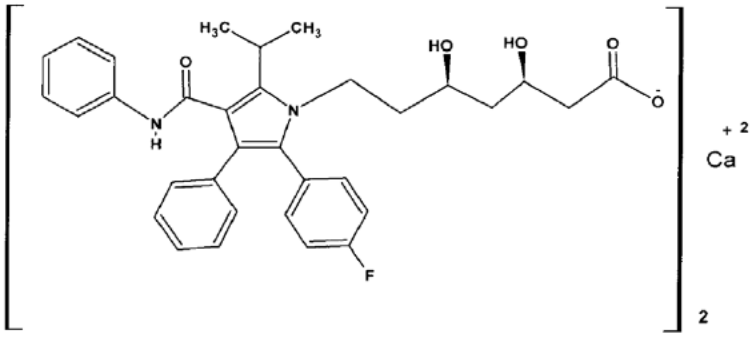
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed
_X___Not a SPOTS product

15b. NANO TECHNOLOGY PRODUCTS TRACKING SYSTEM:
NANO product – Form Completed
_X___Not a NANP product

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:



[R-(R,R)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino) carbonyl]- 1H-pyrrole-1-heptanoic acid hemi calcium salt
$(C_{33}H_{34}FN_2O_5)_2Ca$
MW: 1155.36

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21477	II	Matrix Laboratories Ltd.	Atorvastatin Calcium	1	Inadequate	3-30-2011	CR5by H. Li
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			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	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable		AS of 12/29/10 – WITHHOLD – A.Inyard
Methods Validation	NA		
Labeling	Acceptable*	3/11/2010	A. Vu
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		
Pharm/Tox	None		

* label now indicates (b) (4) powder and shows structure as (b) (4) molecule.

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: 2945206

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #4)

Summary of Chemistry Assessments

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

NDA 20702 for RLD Lipitor® from Pfizer uses crystalline Atorvastatin Calcium trihydrate as drug substance. ANDA firm uses [redacted] API. ANDA drug product contains more impurities at higher levels due to the different stability of different polymorphs of API. Pharm-Tox consults have been sent out and review results are pending.

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablet. It is indicated for lipid regulation. 10 mg strength is a white, oval, [redacted] film-coated tablets: White to off-white, oval, [redacted] film coated tablet debossed with "MX" on one side, "A15" on the other side. 20 mg strength is a White to off white, oval, [redacted], film-coated tablet: debossed with "MX" on one side, "A17" on the other side. 40 mg strength is a White to off white, oval. [redacted] film-coated tablets, debossed with "MX" on one side, "121" on the other side. 80 mg strength is a White to off-white, oval [redacted], film coated tablet debossed with "MX" on one side and "122" on the other side.

Critical Attributes of the Formulation: The manufacturing process is a [redacted]. The unit operations are [redacted]

The DS is about [redacted]% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is [redacted] metabolite). There are 2 impurities which are only reported for DP, not for DS. Mechanism of

Drug Release: The dosage form consists of [redacted]% of [redacted], croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers.

Based on the 3-month ACC and [redacted] month long-term studies, the firm has requested an expiration period of [redacted] months at room conditions in original submission. They revised to 18 month expiry date in Amendment dated 3/7/2011.

The MDD for adults is 80 mg.

ICHQ3A: IT: 0.10%, QT: 0.15%

ICHQ3B: IT: 0.20%, QT: [redacted]%.

USP Status

Was not compendial per USP, BP or EP in Rev.#1. PF35(1) In-Process Revision for Atorvastatin Calcium drug substance came out in Rev.#2. USP monograph for Atorvastatin Calcium is official in Rev.#3. The USP specifies the trihydrate both in chemical structure and in water content criteria. Also the description and solubility reference chapter indicates that

Atorvastatin Calcium is crystalline. USP pending monograph for Atorvastatin came out in review #4 (b) (4)

B. Description of How the Drug Product is Intended to be Used
The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 90 counts, 500 counts (b) (4) and in bulk packages for pharmacy. Dosing is once a day. MDD is 80 mg.

C. Basis for Approvability or Not-Approval Recommendation
The application is not approvable due to drug product stability related minor deficiencies and pending pharm-tox consults.

Reference ID: 2945206
63 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
05/11/2011

LEIGH A SEARS
05/11/2011

MOHAMMED K AHMED
05/12/2011

ANDA 091226

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

Matrix Laboratories Ltd.
Weiqin Jiang, PhD

Office of Generic Drugs
Division of Chemistry III

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List of Deficiencies To Be Communicated	

(b) (4)

CMC REVIEW DATA SHEET

1. ANDA #: 091226
2. REVIEW #: 3
3. REVIEW DATE: 10-JAN-2011
4. REVIEWER: W. Jiang, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents: None	Document Date
Original	December 30, 2008 (Rev.#1)
CMC Amendment	April 8, 2010 (Rev.#2)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CMC Amendment	DEC. 14, 2010
Gratuitous Amendment	NOV. 18, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Labororatories Ltd.
Address:	1-1-151/1,4th Floor Sairam Towers, Alexander Road Secunderabad – 500 003 Andhra Pradesh (AP) India
U.S. Representative:	Keith Giunta Mylan Pharmaceuticals. Inc. 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-554-5899, 800-848-0461, ext. 5899
Fax:	304-285-6407

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
   Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
   The applicant filed paragraph IV certifications for 7,790,197.
   Original ANDA was submitted under a paragraph IV.

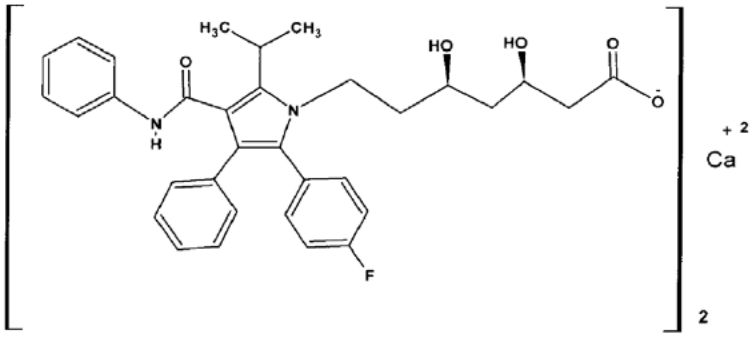
Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
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 8, 2016	Y			
020702	004	5969156*PED	Jan 8, 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-471	Sep 21, 2008
020702	004	I-523	Mar 2, 2010

10. PHARMACOL. CATEGORY: Lipid Lowering Agent/Inhibitor of HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis in liver.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    SPOTS product – Form Completed __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:



[R-(R,R)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino) carbonyl]- 1H-pyrrole-1-heptanoic acid hemi calcium salt

$(C_{33}H_{34}FN_2O_5)_2Ca$
MW: 1155.36

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21477	II	Matrix Laboratories Ltd.	Atorvastatin Calcium Tablets	1	Inadequate	12-20-2010	CR04 by W. Jiang
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			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	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable		AS of 12/29/10 – WITHHOLD – A.Inyard
Methods Validation	NA		
Labeling	Acceptable*	3/11/2010	A. Vu
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		
Pharm/Tox	None		

* label now indicates (b) (4) powder and shows structure as (b) (4) molecule.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. x_ Yes ____ No If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #3)

Summary of Chemistry Assessments

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

NDA 20702 for RLD Lipitor® from Pfizer uses crystalline Atorvastatin Calcium trihydrate as drug substance. ANDA firm uses [redacted] API. ANDA drug product contains more impurities at higher levels due to the different stability of different polymorphs of API. Pharm-Tox consults have been sent out and review results are pending.

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablet. It is indicated for lipid regulation. 10 mg strength is a white, oval, [redacted] film-coated tablets: White to off-white, oval, [redacted] film coated tablet debossed with "MX" on one side, "A15" on the other side. 20 mg strength is a White to off white, oval, [redacted], film-coated tablet: debossed with "MX" on one side, "A17" on the other side. 40 mg strength is a White to off white, oval, [redacted] film-coated tablets, debossed with "MX" on one side, "121" on the other side. 80 mg strength is a White to off-white, oval [redacted], film coated tablet debossed with "MX" on one side and "122" on the other side. Critical Attributes of the Formulation: The manufacturing process is a [redacted]. The unit operations are [redacted]

The DS is about [redacted]% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). There are 2 impurities which are only reported for DP, not for DS. Mechanism of Drug Release: The dosage form consists of [redacted]% of [redacted], croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers.

Based on the 3-month ACC and [redacted]-month long-term studies, the firm has requested an expiration period of [redacted] months at room conditions.

The MDD for adults is 80 mg.

ICHQ3A: IT: 0.10%, QT: 0.15%

ICHQ3B: IT: 0.20%, QT: [redacted]%.

USP Status

Was not compendial per USP, BP or EP in Rev.#1. PF35(1) In-Process Revision for Atorvastatin Calcium drug substance came out in Rev.#2. USP monograph for Atorvastatin Calcium is official in Rev.#3. The USP specifies the trihydrate both in chemical structure and in water content criteria. Also the description and solubility reference chapter indicates that Atorvastatin Calcium is crystalline.

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

The DP is intended for long term use. Thus, it is packaged in bottles, with [redacted], in 90 counts, 500 counts [redacted] and in bulk packages for pharmacy. Dosing is once a day. MDD is 80 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to drug product stability related minor deficiencies and pending pharm-tox consults.

40 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

WEIQIN JIANG
02/25/2011

MARK A GONITZKE
02/25/2011

SUSAN ZUK
02/25/2011

ANDA 091226

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

Matrix Laboratories Ltd.
Weiqin Jiang, PhD

Office of Generic Drugs
Division of Chemistry III

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(b) (4)

CMC REVIEW DATA SHEET

1. ANDA #: 091226
2. REVIEW #: 2
3. REVIEW DATE: 27-MAY-2010
4. REVIEWER: W. Jiang, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents: None	Document Date
Original	December 30, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	April 8, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Labororatories Ltd.
Address:	1-1-151/1,4th Floor Sairam Towers, Alexander Road Secunderabad – 500 003 Andhra Pradesh (AP) India
U.S. Representative:	Keith Giunta Mylan Pharmaceuticals. Inc. 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-554-5899, 800-848-0461, ext. 5899
Fax:	304-285-6407

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702

10. PHARMACOL. CATEGORY: Lipid Lowering Agent/Inhibitor of HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis in liver.

11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed __X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:
Please see 2.3.S

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21477	II	Matrix Laboratories Ltd.	Atorvastatin Calcium Tablets	1	Inadequate	05-28-2010	CR03 by W. Jiang
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable		
Methods Validation	Not Applicable		
Labeling	Acceptable	3/11/2010	A. Vu
Bioequivalence	Dissolution-deficient	6/16/2009	Z. Williams
EA	Satisfactory	8/28/2009	W. Jiang
Radiopharmaceutical	Not Applicable		
Pharm/Tox	None		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. x_ Yes ____ No If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #2)

Summary of Chemistry Assessments

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

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, (b) (4) film-coated tablets: White to off-white, oval, (b) (4), film coated tablet debossed with "MX" on one side, "A15" on the other side. 20 mg strength is a White to off white, oval, (b) (4) film-coated tablet: debossed with "MX" on one side, "A17" on the other side. 40 mg strength is a White to off white, oval, (b) (4) film-coated tablets, debossed with "MX" on one side, "121" on the other side. 80 mg strength is a White to off-white, oval (b) (4), film coated tablet debossed with "MX" on one side and "122" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4) . The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4), croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers.

The MDD for adults is 80 mg.
ICHQ3A: IT: 0.10%, QT: 0.15%
ICHQ3B: IT: 0.20%, QT: (b) (4)%.

Not compendial per USP, BP or EP. There is PF35(1) In-Process Revision for Atorvastatin Calcium drug substance.

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

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 90 counts, 500 (b) (4) and in bulk packages for pharmacy. The DP is manufactured by (b) (4) . The unit operations are (b) (4) Based on the 3-month accelerated studies, the firm has requested an expiration period of (b) (4) months at room conditions

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to a few CMC related minor deficiencies and pharm-tox consult pending.

72 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

WEIQIN JIANG
07/30/2010

SARAH K NGUYEN on behalf of LEIGH A BRADFORD
08/02/2010

SUHAS J PATANKAR on behalf of LAXMA R NAGAVELLI
08/03/2010

ANDA 91-226

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

Matrix Laboratories Ltd.
Weiqin Jiang, PhD

Office of Generic Drugs
Division of Chemistry III

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II. Review of CTD - Quality Module 2: QOS and Module 3.2: Body of Data	6
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(b) (4)

CMC REVIEW DATA SHEET

1. ANDA #: 91-226
2. REVIEW #: 01
3. REVIEW DATE: 07-09-09
4. REVIEWER: W. Jiang, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents: None	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	December 30, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Matrix Labororatories Ltd.
Address:	1-1-151/1,4th Floor Sairam Towers, Alexander Road Secunderabad – 500 003 Andhra Pradesh (AP) India
U.S. Representative:	Ronald T. Groman Mylan Pharmaceuticals. Inc. 781 Chestnut Ridge Road, P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-554-5899, 800-848-0461, ext. 5899
Fax:	304-285-6407

8. DRUG PRODUCT NAME: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets
9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
10. PHARMACOL. CATEGORY: Lipid Lowering Agent/Inhibitor of HMG-CoA reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis in liver.

11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg and 80 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed __X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.:
Please see 2.3.S

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
21477	II	Matrix Laboratories Ltd.	Atorvastatin Calcium Tablets	1	Not Adequate	07-10-2009	by W. Jiang
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF	5 – Authority to reference not granted
3 – Reviewed previously and no revision since last review	6 – DMF not available
4 – Sufficient information in application	7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending		
Methods Validation	Not Applicable		
Labeling	Pending		
Bioequivalence	Pending		
EA	Adequate		
Radiopharmaceutical	Not Applicable		
Pharm/Tox	None		

19. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No
If no, explain reason(s) below:

The Executive Summary

Recommendation and Conclusion on Approvability: Not Approvable. Minor (Review #1)

Summary of Chemistry Assessments

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

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release coated tablets. It is indicated for lipid regulation. 10 mg strength is a white, oval, (b) (4) film-coated tablets: debossed with "MX" on one side, "A15" on the other side. 20 mg strength is a White to off white, oval, (b) (4) film-coated tablet: debossed with "MX" on one side, "A17" on the other side. 40 mg strength is a White to off white, oval, (b) (4) film-coated tablets: debossed with "MX" on one side, "121" on the other side. 80 mg strength is a White, oval, (b) (4) film-coated tablets: Engraved (b) (4) on one side, (b) (4)" on the other side. Critical Attributes of the Formulation: The manufacturing process is a (b) (4). The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite). Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4), croscarmellose sodium. The dosage form disintegrates and releases the drug simultaneously. Drug Substance: The DS is atorvastatin calcium. The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The MDD for adults is 80 mg. ICHQ3A: IT: 0.10%, QT: 0.15% ICHQ3B: IT: 0.2%, QT: (b) (4)%. Not compendial per USP, BP or EP.

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

The DP is intended for long term use. Thus, it is packaged in bottles, with (b) (4), in 90 counts, 500 (b) (4) and in bulk packages for pharmacy. The DP is manufactured by (b) (4). The unit operations are (b) (4) Based on the 3-month accelerated studies, the firm has requested an expiration period of (b) (4) months at room conditions

C. Basis for Approvability or Not-Approval Recommendation

The application is not yet approved due to a few CMC related minor deficiencies and a pharm/tox consult response.

78 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 91226	ORIG 1	MATRIX LABORATORIES LTD	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/

WEIQIN JIANG
08/27/2009

JEANNE SKANCHY
08/28/2009

ROBERT L ISER
08/28/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091226
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg
Applicant Name	Matrix Laboratories Limited, India
Address	Matrix Laboratories Limited. 4th Floor, Sairam Towers, Alexander Road, Secunderabad 500 003 INDIA
Authorized US Agent	Keith J. Giunta, Director
Contact's Telephone Number	(304) 554-5899 (800) 848-0461, Ext. 5899
Contact's Fax Number	(304)-285-6407
Original Submission Date(s)	12/30/2008
Submission Date(s) of Amendment(s) Under Review	11/09/2010
Reviewer	Hongling Zhang, Ph.D.

Study Number (s)	022-08	162-08	023-08
Study Type (s)	Fasting	Fed	Fed (failed study)
Strength (s)	80 mg	80 mg	80 mg
Clinical Site	GVK Biosciences Pvt Limited		
Clinical Site Address	7th Floor Swarna jayanthi Commercial Complex, Ameerpet, Hyderabad-500037, India Tel: +91-40-66275566, Fax: +91-40-66275599		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE pending DSI inspection only**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI INSPECTION RESULT	**INADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
#1, #7	**Dissolution**	**10 mg, 20 mg, 40 mg and 80 mg**	**ADEQUATE**
#1	**Fasting Study**	**80 mg**	**ADEQUATE**
#1	**Fed Study**	**80 mg**	**ADEQUATE**

Review of a Study Amendment

1 EXECUTIVE SUMMARY

This is the review of a bioequivalence amendment for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The firm, Matrix Laboratories Limited, India, is responding to the deficiency letter received from the Division of Bioequivalence (DBE) on 9/7/2010[1]. The original submission, dated 12/30/2008, contained fasting and fed bioequivalence (BE) studies comparing Matrix Laboratories Limit's test product, Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfzier's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg. However, the studies were incomplete due to the deficiencies.

In this amendment, the firm responded to the above mentioned deficiencies. The firm's responses are adequate. The fasting and fed BE studies are considered tentatively complete and adequate.

The dissolution testing has been found acceptable previously.

The waiver requests for *in vivo* BE study requirements for the firm's lower strengths of the test product, 10 mg, 20 mg and 40 mg, is tentatively granted.

The Division of Scientific Investigations (DSI) inspection for the clinical site is pending. No DSI inspection for the analytical site is pending or necessary[2].

The application is **inadequate** pending the outcome of the DSI inspection for the clinical site**.**

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[1] DARRTS, ANDA 091226, COR-ANDADE-01(Bio Incomplete Deficiencies), check in date: 9/7/2010

[2] The routine DSI inspection of the clinical site was requested on (b) (4) and it is still pending (Ref. (b) (4)). The last routine DSI inspection of the analytical site was completed on (b) (4) and the outcome was NAI (no action indicated) (Ref (b) (4)).

2 REVIEW OF SUBMISSION

Deficiency 1:

For your pre-study method validation, please specify the salt form of the Ethylenediaminetetraacetic Acid (EDTA), the anticoagulant used in the blank human plasma of the method validation samples.

Firm's Response:

We confirm that potassium salt of the Ethylene diamine tetra acetic Acid (EDTA) i.e. K3 EDTA has been used for the pre-study method validation and also during fasting study (022-08) and fed bio study (162-08). A copy of the anticoagulant preparation record indicating the use of K3 EDTA as the anticoagulant is enclosed as Attachment# 1.

Reviewer's Comment:

The firm indicated that K_3EDTA was used as the anticoagulant in the blank human plasma for the preparations of the samples during the pre-study validation. The same anticoagulant was used for the collections of the clinical samples.

The firm's response to deficiency 1 is acceptable.

Deficiency 2:

Your repeat analysis for both fasting and fed study is incomplete. Please provide the followings:

1) *For the fasting study (study No. 022-08), please provide the quality control (QC) data of the run for the samples of subject No. 09 to show clearly that the batch was rejected due to the QC data not meeting the acceptance criteria.*

Firm's Response:

The analytical batch of Subject No # 09 from study No. 022-08 was not accepted for Atorvastatin while it was accepted for 2-hydroxy and 4-hydroxy metabolites as the calibration curve did not meet the run acceptance criteria (3 out of (b) (4) *calibration standards were outside the acceptance range) as per the criteria outlined in the SOP No.* (b) (4) *enclosed as Attachment # 2. In addition, both the LQCs did not meet the acceptance criteria, hence batch was rejected. Please find the attached result table of rejected batch for Subject no # 09 as Attachment # 3.*

Reviewer's Comment:

The firm provided the original raw data of the failed run which contained the sample analysis of subject #9. The data showed that there were 3 out of (b) (4) calibration standard

samples outside the acceptance range and according to the firm's SOP, (b) (4) % of the CS samples should be within the acceptance range for the run to be accepted. In addition, the data showed that both LQC were out of the acceptable range. Therefore, the run was rejected according to the SOP.

The firm's response to deficiency 2.1 is acceptable.

2) *For the fed study (study No. 162-08), please provide the original concentrations of atorvastin of subject No. 25 for further evaluation.*

Firm's Response:

The analytical batch of Subject No # 25 from study No. 162-08 failed to meet set criteria for Atorvastatin since both the replicate samples of "Plasma blank+ISTD (Zero Standard)" of calibration curve showed measurable peak area at the analyte RT (More than 20% of the CS-1 analyte response). On investigation, it was observed that the interference area was limited to zero standard replicates and did not carry forward or contribute to the quantification of rest of other calibration standard /QC's concentration (The Accuracy was well within the acceptable limit). The analytical batch of Subject No. 25 was not accepted for atorvastatin as per criteria defined in the Section 5.1.9 of SOP No. (b) (4) *" i.e. "At least 50% of blank matrix and 50% of the zero standard samples should not have more than 20% and 5% interference at analyte and Internal standard RT respectively". Please find the attached result table of rejected batch for Subject No # 25 enclosed as Attachment # 4.*

The back calculated concentrations from subject samples in the original run and repeat run were tabulated to demonstrate that the results were not significantly different from their original values and are provided as Attachment # 5.

Reviewer's Comments:

The firm's original raw data showed that there was significant interference for both the 'zero standard' samples (the peak area of the interference was over 20% of the LLOQ). Therefore, according to the firm's SOP, the run was rejected. The firm also provided the concentrations of the study samples (for subject #25) obtained from the failed run, as compared with the concentrations after repeats. Except one sample, the differences of the original concentrations and the repeated concentrations were all less than 10%. The difference of one sample was more than 20%. Since the concentration of this sample was not Cmax, it is not expected to influence the study outcome.

3) *Please provide the Standard Operation Procedures (SOP) for the re-integration of the chromatograms. In addition, please provide the concentrations of the three analytes of subject No. 42 and No. 43 in fasting study and subject No. 01 and No. 02 in fed study, obtained using the original integration parameters that were used for other batches in the fasting and fed study, respectively.*

Firm's Response:

The SOP No. [redacted] *entitled "Integration and Evaluation of chromatogram" was referred for reintegration of Chromatograms for subject no # 42 and 43 in fasting study (Study # 022-08) and Subject # 01 and 02 in Fed study (Study # 162-08). A copy of SOP is enclosed as Attachment # 6.*

The Result table of Subject No.: 42 & 43 (ATR, O-ATR, P-ATR) in Study No. 022-08 (Fasting) and Subject No. 01 & 02 (ATR, O-ATR, P-ATR) in Study No. 162-08 (Fed) are provided as Attachment # 7.

The reason for reintegration of these subjects has been described as below:

Due to possible decrease in the instrument sensitivity, the analyte area response was found substantially low for all three analytes resulting CS-1 peak not integrated properly. During the review of the data the group leader and the project manager concluded that optimization of integration parameters is necessary for the selected batches for an accurate measurement. According to our procedure on reintegration, entire batch, rather than individual or selected chromatograms need to be reintegrated when justified, and the same was considered for reintegration using modified integration parameters, as given below. Refer a copy of representative chromatograms of CS-1 as given in Attachment # 8.

Additionally, a side-by-side comparative evaluation of the data from the original integration and the data after reintegration for all three analytes was performed and which in turn showed no significant difference between original and reintegrated values. The comparison table is provided as Attachment # 9.

The Following Integration parameter was modified in order to integrate the chromatograms and applied to entire sample data for Study No. 022-08 and 162-08:

Study #	Subject #	Integration parameters	Atorvastatin	O-hydroxy-Atorvastatin	p-hydroxy-Atorvastatin
022-08	42 & 43	Noise Threshold	Changed from 100 to 20	Changed from 50 to 20	Changed from 20 to 3
162-08	01 & 02	Noise Threshold	Changed from 100 to 10	Changed from 50 to 10	Changed from 20 to 10

Reviewer's Comments:

- The firm provided the SOP for integration and evaluation of chromatograms (SOP [redacted]). The effective date of the SOP is 3/10/2010. However, both studies were conducted in 2008.

- The firm indicated that the reintegration of some samples were due to the reason that the peak of calibration standard 1 was not integrated properly, as shown in the chromatograms that they provided. The new integration

parameters were used for all samples in the same run. The reintegration was conducted according to the firm's SOP.

- The firm provided the comparisons between the concentrations obtained using original integration parameters and concentrations obtained using the new integration parameters. For the very low concentrations, such as samples for the first two sampling time points or samples for the later sampling points, the concentrations after reintegration were different significantly from the original concentrations. For other samples, there were no significant differences (most were less than 5%). In addition, the exclusion of the data of these subjects did not change the outcome of the studies, as shown in the DBE's original review. Therefore, the reintegration of the study samples is not expected to change the outcome of the study.

Deficiency 3:

For the clinical report of the fed study, please explain why some elevated creatine phosphokinase (CPK) levels obtained in some subjects during the post-study lab assessment were listed as adverse events (For example, increased CPK levels of 310 U/L in Subject #3), while some other similar increased CPK levels obtained during the washout period were not listed as adverse events (For example, the CPK level of 410 U/L in Subject #16 and the CPK level of 342 U/L in Subject #49). Please provide a complete list of abnormal laboratory results obtained during the washout and post-study assessment even if the results were not considered clinically significant.

Firm's Response:

According to Section 8.2 of the protocol, about 0.5 ml of blood was collected from all the subjects who had reported for period-02 of the study for biochemistry analysis as an additional safety monitoring measure, and the reports were evaluated on the same day (period-01 wash-out value). Though the values were outside the normal acceptable range, they were not documented as adverse events and the subjects were dosed in period-02. The clinical decision was made by the Investigator from the inferences taken from the product monograph which suggest that treatment with subject drug need not be discontinued unless there is significant increase in CPK (CPK more than 10 times of reference range). A copy of the product monograph is enclosed as Attachment #10 and the justification for continuing the subjects in the study is documented in a 'memo to file' dated 10 Oct 2008 enclosed as Attachment # 11.

However, as per the product monograph, the subjects with abnormal values of certain parameters (serum CPK, SGOT, SGPT) who require withdrawal of the treatment were withdrawn from the study and only those were documented as adverse events and were followed-up. Accordingly, subject nos. 14 (due to high CPK-2137 U/L) and Subject No 56 (due to increased Total bilirubin-1.38 mg/dL) were withdrawn from the study before period-02 dosing (period-01 washout) and they were documented as adverse events and were followed up. In the table below in column "period-1 washout value", marked in

bold are values outside normal range and marked with "underline" are documented adverse events.

All the post study (period-02) abnormal values (outside the Acceptable range) were only documented as adverse events and were followed up as per our SOP (b) (4) *(effective at that time) enclosed in Attachment # 12.*

Following is the tabulated abnormal values in period-01 wash out with pre-study and post study values:

#	Subject #	Abnormal lab parameter	Pre-study value	Period-01 washout value	Post study value	Treatment sequence
1	02	Serum Triglycerides	191 mg/dl	359 mg/dl	122 mg/dl	TR
2	03	Serum CPK	160 U/L	285 U/L	**310 U/L** (lost to follow up)	TR
3	04	Serum Triglycerides	136 mg/dl	342 mg/dl	201 mg/dl	RT
4	07	Serum CPK	91 U/L	288 U/L	**244 U/L** →198 U/L (resolved)	RT
5	10	Serum Triglycerides	86 mg/dl	321 mg/dl	107 mg/dl	RT
6	14	SGPT	27 IU/L	50 IU/L	27 IU/L	TR
		Serum CPK	178 U/L	**2137 U/L**	**257 U/L** Lost to follow-up	
7	16	Serum CPK	115 U/L	410 U/L	155 U/L	RT
8	17	Serum Triglycerides	149 mg/dl	291 mg/dl	243 mg/dl	TR
		Serum CPK	143 U/L	351 U/L	130 U/L	
9	19	Serum CPK	106 U/L	505 U/L	156 U/L	TR
10	20	Serum Triglycerides	192 mg/dl	328 mg/dl	154 mg/dl	RT
11	22	Serum CPK	93 U/L	413 U/L	**282 U/L** Lost to follow up	TR
12	23	Serum Triglycerides	149 mg/dl	309 mg/dl	174 mg/dl	TR
13	28	SGPT	27 IU/L	49 IU/L	40 IU/L	RT
14	29	Serum CPK	115 U/L	502 U/L	115 U/L	TR
15	30	Serum CPK	170 U/L	303 U/L	155 U/L	RT
16	34	SGPT	28 IU/L	66 IU/L	**56 IU/L**→ 37 U/L (resolved)	RT
		Serum Triglycerides	128 mg/dl	428 mg/dl	146 mg/dl	
17	35	Serum Triglycerides	196 mg/dl	398 mg/dl	72 mg/dl	TR
18	37	SGPT	40 IU/L	51 IU/L	40 IU/L	TR
19	38	Serum Amylase	111 U/L	124 U/L	**267 U/L** Lost to follow up	RT
20	41	Serum CPK	110 U/L	290 U/L	108 U/L	TR
21	42	Serum Triglycerides	121 mg/dl	147 mg/dl	**304 mg/dl** Lost to follow up	RT
22	45	SGPT	28 IU/L	40 IU/L	65 IU/L	RT
23	49	Serum CPK	129 U/L	342 U/L	103 U/L	TR
24	52	SGPT	14 IU/L	39 IU/L	**212 IU/L** (lost to follow up)	RT
		SGOT	19 IU/L	33 IU/L	**164 IU/L** (lost to follow up)	
25	53	Serum CPK	218 U/L	448 U/L	**335 U/L** (lost to follow up)	TR
26	54	Serum CPK	129 U/L	526 U/L	185 U/L	TR
27	56	Serum total bilirubin	1.08 mg/dL	**1.38 mg/dL**	**1.75 mg/dL** (Lost to follow up)	RT

Reviewer's Comments:

- According to the labeling, Atorvastatin, like other statins, occasionally cause myopathy, defined as muscle aches or muscle weakness in conjunction with increases

in CPK values > 10 times ULN. Lipitor® therapy should be discontinued if markedly elevated CPK levels occur or mayopathy is diagnosed or suspected.

- In fed study, subject #14 has significant increased CPK level (2137 U/L) which was approximately 10 times of the upper limit of the normal (ULN) range (24-195 U/L), after the period I (dosed with test product). The firm indicated that the subjects with abnormal values of certain parameters (serum CPK, SGOT, SGPT) who require withdrawal of the treatment were withdrawn from the study and only those were documented as adverse events and were followed-up. Therefore, there is no concern that subject #14 was 'selected' to be dropped out while other subjects with elevated CPK continued the study. Based on the table the firm provided for the abnormal lab parameter, there was no subject with elevated CPK levels over 10 times of the ULN, except subject #14.

- Subject 56 was found to have increased serum total bilirubin (1.38 mg/dl) (the normal range is 0.10-1.20 mg/dl). This level was near the level associated with a liver condition called jaundice[3] (i.e., 1.5 mg/dL). There was no subject with similar lab assessment. Therefore, the dropping of this subject is acceptable.

- The firm's responses to deficiency 3 are acceptable.

Deficiency 4:

For the original fed bioequivalence study (Study No. 023-08), please submit the complete study report, which should include the clinical report (with complete adverse events and clinical laboratory results), bioanalytical report and statistical analysis report as well as the study datasets in SAS Transport format.

Firm's Response:

Complete study report which includes clinical report (complete adverse events and clinical laboratory results), Bioanalytical report and statistical analysis report is enclosed as Attachment # 13. Study datasets in SAS transport format and summary tables are also being provided with this amendment.

Reviewer's Comments:

- The firm's first pivotal fed BE study (study # 023-08) failed due to the reason that the 90% CIs of Cmax for the parent drug (atorvastatin) were not within the acceptable range (75.72-93.67%). The firm provided the following justifications for the failed study: '*under fed conditions the AUCT and AUCI for the parent drug and the Cmax, AUCT and AUCI for the metabolites were within the bioequivalence acceptance range. But, the Cmax for the parent atorvastatin was slightly on the lower side of the 90% CI limits. The T/R ratio for Cmax was 84.22%, which is*

[3] See http://en.wikipedia.org/wiki/Jaundice

within the acceptable range for T/R ratio, but the 90% confidence interval is out side the acceptance limits and is mainly due to at least three subjects (subject #23, 39 and 51) showed lower T/R ratios in Cmax values as the Reference Cmax value were almost twice the average Cmax values, whereas Test product has shown the values close to the global average. Since absorption is erratic and unpredictable for parent compound, the lower or higher T/R ratios are not surprising. However, for AUC the T/R ratios are close to 100% and the confidence interval limits are well within the limits of 80-125%. Hence the non compliance of the 90% confidence interval is not because of inadequate sample size, it is because of the transient Cmax which is single point estimation'.

- The firm conducted a repeat fed study (study #162-08) with the same sample size and design. According to the firm, additional precaution to include the biochemical investigation was done at the time of period II check-in. For study #162-08, there were two subjects (#14 and #56) dropped out of the study before period II due to abnormal lab assessment, as discussed in the deficiency #3. The 90% CI for Cmax of the repeated fed study (study # 162-08, reviewed previously) with the same study design was well within the 90% CI, as shown in the following table:

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 162-08					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	249.53	262.50	0.95	88.92	101.62
AUC∞ (hr *ng/ml)	255.29	268.22	0.95	89.10	101.67
Cmax (ng/ml)	47.30	49.35	0.96	86.49	106.23

- The firm provided the full study report of the failed fed study in this amendment which is briefed reviewed in section 6.

- The firm indicated that the first pivotal fed BE study (study # 023-08) was failed not because of inadequate sample size, it is because of the transient Cmax of the parent drug which is single point estimation. The firm identified that for subject #23, 39 and 51, the T/R ratios in Cmax (parent drug) were very low.

- The reviewer examined the failed study data and found that the Cmax (parent drug) for these three subjects on both test product and reference product were within the ranges of all subjects', i.e., they were neither the lowest nor the highest Cmax; however, the T/R ratios of these three subjects' Cmax were on the lowest end of the range. The reviewer run the Maximum Studentized Residual Test to check if the T/R ratios of these three subjects are 'outliers' and found none of them are 'outliers'. Therefore, the data of these three subjects should not be excluded from the statistical analysis.

- The reviewer also analyzed the data for the two active metabolites in the failed fed study. For both active metabolites (Orthohydroxy Atorvastatin and parahydroxy Atovastatin), the 90% CIs of all PK parameters are within the acceptable range, including all subjects' data (please see section 6.4 for details).

- The reviewer checked the case report forms of these three subjects, there were no significant abnormal biochemical parameters during the study.

- The reviewer agreed with the firm that the non compliance of the 90% confidence interval is not because of inadequate sample size, it is because of the transient Cmax which is single point estimation. For all three studies that the firm conducted (1 fasting and 2 fed), it is showed that the Cmax of parent drug is highly variable. The RMSE (root mean square error) values are 0.4432, 0.3248 and 0.3455 for fasting study (# 022-08), fed study (#162-08) and fed study (023-08), respectively.

- In conclusion, the reviewer does not have any concern about the formulation of the firm's test product even though the 90% CIs for the Cmax of the parent drug in the firm's first fed BE study (study # 023-08) were not within the 80-125%, based on the following reasons: 1) Cmax of the parent drug is a highly variable parameter as demonstrated in all three BE studies that the firm conducted; 2) although Cmax of the parent drug failed to meet 80-125% BE limit in study #023-08, the 90% CIs of AUCt and AUCi of the parent drug were well within the acceptable range; 3) In addition, in study #023-08, for both active metabolites, the 90% of all PK parameters were within the acceptable range; and 4) for the repeated fed BE study (# 162-08) with the same study design, for parent drug, the 90% CIs of all PK parameters were within the acceptable range.

- The firm's responses to the deficiency #4 are acceptable.

3 DEFICIENCY COMMENT:

None.

4 RECOMMENDATIONS

1. The Division of Bioequivalence (DBE) tentatively accepts the fasting bioequivalence (BE) study # 022-08, conducted by the Matrix Laboratories Limited on its Atorvastatin Calcium Tablets, 80 mg (lot #1004891), comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, 80 mg (lot #17995V).

2. The Division of Bioequivalence (DBE) tentatively accepts the fed bioequivalence (BE) study # 162-08, conducted by the Matrix Laboratories Limited on its Atorvastatin Calcium Tablets, 80 mg (lot #1004891), comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, 80 mg (lot #17995V).

3. The *in vitro* dissolution testing on the 10 mg, 20 mg, 40 mg and 80 mg strengths conducted by the firm, using the FDA-recommended dissolution method is acceptable. The dissolution testing should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37 °C ±5 °C, using USP apparatus II (paddle) at 75 rpm. The firm's test product should meet the following specification: NLT (b)(4)% (Q) in 15 minutes.

5 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
DSI	The DSI inspection of the clinical site is pending

6 REVIEW OF THE FAILED FED STUDY

6.1 Study Design

The study design is the same as the fed study submitted in the original submission (DARRTS, ANDA 091226, REV-BIOEQ-01, check in date: 09/02/2010).

6.2 Clinical Results

Table 1. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No-023-08		
	Treatment Groups	
	Test Product N=59	Reference Product N=59
Age (years)		
Mean ± SD	26.7 ± 6.13	26.7 ± 6.13
Range	19-44	19-44
Age Groups		
< 18	0	0
18-40	58 (98.3 %)	58 (98.3 %)
41-64	1 (1.7 %)	1 (1.6 %)
65-75	0	0
>75	0	0
Sex		
Female	0	0
Male	59 (100.0 %)	59 (100.0 %)
Race		
Asian	59 (100.0 %)	59 (100.0 %)
Black	0	0
Caucasian	0	0
Hispanic	0	0
Other	0	0
BMI		
Mean ± SD	20.95 ± 2.221	20.95 ± 2.221
Range	18.5 – 24.8	18.5 – 24.8
Other Factors	Nil	Nil

Table 1. Dropout Information, Fed Bioequivalence Study

Study No.023-08				
Subject Number	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
12	Subject was withdrawn from the study at 10:00 hours on 25 Jun 2008 after administration of test treatment due to adverse event vomiting in period 01 in-house.	01	No	NA

Table 3. Study Adverse Events, Fed Bioequivalence Study

Body system/adverse event	**Reported incidence by treatment groups**		
	Fed condition Comparative Bioavailability study		
	Study No. 023-08 (N=60)		
	Test (N=60)	**Reference (N=59)**	**NA[#]**
Gastro intestinal			
Vomiting	1 (1.67%)	-	-
Nausea	-	1 (1.7%)	-
Nervous system disorders			
Vaso vagal pre syncope	1 (1.67%)	-	-
Investigations			
Increased triglycerides	-	-	1 (1.67%)
Decreased Total WBC	-	-	1 (1.67%)
Increased Lymphocytes	-	-	2 (3.34%)
Increased total protein	-	-	1 (1.67%)
Increased total WBC count	-	-	1 (1.67%)
Total	**2 (3.34%)**	**1 (1.7%)**	**6 (10.00%)**

Table 4. Protocol Deviations, Fed Bioequivalence Study

Study No.023-08		
Type	**Subject Numbers (Test)**	**Subject Numbers (Reference)**
Pharmacokinetic blood sample deviation at 72.0 hour due to Subject reported late to facility for ambulatory sample in period II.	03	21
Pharmacokinetic blood sample deviation at 12.0 hour due to Difficulty in blood Drawing in period II.	26	None
Deviation in post study safety evaluation: Serum CPK test was not estimated for all the subjects during post study safety assessment as CPK was not mentioned in the "Requisition for tests to be conducted for safety evaluation of subjects" form due to rare oversight.	NA	

Comments on Adverse Events/Protocol Deviations:

- In period I, subject #12 experienced two episodes of vomiting at 9:50 hours and 10.02 hours respectively. The subject was withdrawn from study during period I.
- All of the sample collection time deviations were not significant (± 5%). Both the firm and the reviewer used the actual sampling time for the statistical analysis.
- The protocol deviations are not expected to influence the outcome of the study.

6.3 Bioanalytical Results

Table 5. Assay Validation – Within the Fed Bioequivalence Study

a) Atorvastatin

Bioequivalence Study No. 023-08									
Analyte Name: Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.251	0.491	5.381	15.653	50.521	100.555	148.090	189.349	228.117
(Nominal value)	0.250	0.500	4.980	14.930	49.780	99.550	149.330	199.100	248.880
Inter day Precision (%CV)	2.11	4.46	2.40	2.09	1.34	1.43	1.56	2.22	3.10
Inter day Accuracy (%Actual)	100.40	98.24	108.06	104.84	101.49	101.01	99.17	95.10	91.66
Linearity	0.9966-0.9997								
Linearity Range (ng/mL)	0.250-248.880								
Sensitivity/LOQ (ng/mL)	0.250								

Bioequivalence Study No. 023-08				
Analyte Name: Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.774	26.799	82.891	172.997
(Nominal value)	0.750	25.050	80.160	180.360
Inter day Precision (%CV)	3.37	2.17	1.89	2.80
Inter day Accuracy (%Actual)	103.19	106.98	103.41	95.92

b) O-OH-Atorvastatin

Bioequivalence Study No. 023-08									
Analyte Name: O-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.252	0.484	2.453	9.370	31.733	58.808	85.756	112.305	143.614
(Nominal value)	0.250	0.490	2.460	9.850	29.550	59.100	83.730	113.280	147.750
Inter day Precision (%CV)	2.34	4.86	1.83	1.73	1.18	1.55	1.60	1.77	1.71
Inter day Accuracy (%Actual)	100.68	98.73	99.72	95.13	107.39	99.51	102.42	99.14	97.20
Linearity	0.9983-0.9995								
Linearity Range (ng/mL)	0.250-147.750								
Sensitivity/LOQ (ng/mL)	0.250								

Bioequivalence Study No. 023-08				
Analyte Name: O-OH-Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.778	19.336	49.095	102.967
(Nominal value)	0.760	20.140	50.350	105.740
Inter day Precision (%CV)	4.69	2.72	2.86	3.03
Inter day Accuracy (%Actual)	102.37	96.01	97.51	97.38

c) P-OH-Atorvastatin

Bioequivalence Study No. 023-08									
Analyte Name: P-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.051	0.094	0.495	0.991	1.991	3.984	5.721	7.842	10.075
(Nominal value)	0.050	0.100	0.490	0.980	1.970	3.940	5.910	7.880	9.850
Inter day Precision (%CV)	2.73	5.52	2.63	4.03	2.61	2.40	3.04	2.58	3.31
Inter day Accuracy (%Actual)	102.40	94.20	101.02	101.14	101.05	101.13	96.79	99.52	102.28
Linearity	0.9957-0.9999								
Linearity Range (ng/mL)	0.050-9.850								
Sensitivity/LOQ (ng/mL)	0.050								

Bioequivalence Study No. 023-08				
Analyte Name: P-OH-Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.149	1.557	3.466	7.520
(Nominal value)	0.150	1.490	3.480	7.160
Inter day Precision (%CV)	7.23	4.79	4.92	4.63
Inter day Accuracy (%Actual)	99.60	104.51	99.59	105.03

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.

Table 6. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	27-08-2009	Sample Reassay and Reporting of Final concentration

Table 7. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A (no PK repeats)
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Acceptable

6.4 Pharmacokinetic Results

Table 8. Arithmetic Mean Pharmacokinetic Parameters

Parent Drug (Atovastatin):

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	310.037	35.36	112.82	635.15	353.229	40.28	151.45	829.21	0.88
AUCI	ng hr/mL	315.728	34.81	118.86	638.71	359.600	39.93	155.03	839.57	0.88
CMAX	ng/mL	58.696	54.87	11.17	177.25	68.687	49.92	16.64	198.07	0.85
TMAX	hr	3.500	.	1.00	8.00	2.500	.	1.00	6.00	1.40
KE	hr-1	0.099	38.73	0.04	0.24	0.100	42.40	0.05	0.23	0.99
THALF	hr	7.833	31.48	2.87	16.75	7.958	33.31	3.03	15.00	0.98

Tmax values are presented as median, range

Supportive Metabolites:

1. Orthohydroxy Atovastatin:

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	237.366	34.95	104.93	545.68	259.110	35.07	138.27	557.71	0.92
AUCI	ng hr/mL	244.630	33.62	110.28	551.23	266.836	34.21	141.83	564.10	0.92
CMAX	ng/mL	28.503	44.60	6.91	76.60	31.986	45.55	10.91	79.04	0.89
TMAX	hr	5.000	.	1.00	8.00	4.000	.	1.00	8.00	1.25
KE	hr-1	0.082	26.55	0.04	0.17	0.082	33.05	0.04	0.18	1.00
THALF	hr	8.967	24.54	4.07	19.26	9.311	32.06	3.84	19.48	0.96

2. Parahydroxy Atovastatin:

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	62.623	42.11	18.37	159.13	66.241	44.51	17.60	198.28	0.95
AUCI	ng hr/mL	70.558	40.29	21.26	162.21	74.722	47.27	26.56	207.28	0.94
CMAX	ng/mL	3.389	57.83	0.70	11.73	3.932	58.23	0.86	13.67	0.86
TMAX	hr	6.000	.	2.50	12.00	5.000	.	1.50	36.00	1.20
KE	hr-1	0.031	31.29	0.01	0.05	0.033	27.08	0.01	0.06	0.94
THALF	hr	24.905	40.97	13.35	72.39	23.833	64.93	11.46	130.11	1.04

Table 9. Geometric Means and 90% Confidence Intervals - Firm Calculated

Parent Drug: Atorvastatin

Atorvastatin Calcium tablets 80 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Comparative Oral Bioavailability Study (Study No. 023-08)				
Atorvastatin				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max}	51.4528	61.0963	84.22	75.72-93.67
AUC_{0-t}	292.7259	329.2236	88.91	84.41-93.66
AUC_{0-INF}	297.6096	334.5579	88.96	84.52-93.62

Supportive Metabolites: The firm did not provide the results of the 90% CIs for the metabolites. Instead, the firm provided the summary tables of the PK parameters as followings:

Orthohydroxy Atorvastatin:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Parameters +/-SD (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T½ (hr)	Kel (hr-1)	
023-08	To compare the single dose oral bioavailability of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fed condition	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fed condition.	**Test (T)** Atorvastatin Calcium Tablets, 1 x 80 mg, Batch (B) No.: 1004891, Mfg Date: MAY 2008 Exp Date: APR 2010, Route of administration: Oral	Participated Subjects: 60, Clinical Phase Completed Subjects: 59, (59 males, 0 females) Mean age: 26.7 (19-44) normal, healthy, adult, human subjects	28.5030 ± 12.7112 (44.6)	5.000 (1.00-8.00)	237.3659 ± 82.9493 (34.9)	243.2621 ± 82.9192 (34.1)	7.6477 ± 2.7570 (36.1)	0.1012 ± 0.0323 (31.9)	Section 11.4, Table-11 and Table-12, Pg# 44 and 45 of 334 main report
			Reference (R) Lipitor® (Atorvastatin Calcium) tablets, 1 x 80 mg, Batch No. 17995V Mfg Date: NAV Exp Date: Sep 2008, Route of administration: Oral		31.9860 ± 14.5711 (45.6)	4.000 (1.00-8.00)	258.8108 ± 91.2005 (35.2)	264.6948 ± 92.0628 (34.8)	7.3897 ± 2.9101 (39.4)	0.1051 ± 0.0329 (31.3)	

Parahydroxy Atovastatin:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Parameters +/-SD (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T½ (hr)	Kel (hr-1)	
023-08	To compare the single dose oral bioavailability of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fed condition	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fed condition.	**Test (T)** Atorvastatin Calcium Tablets, 1 x 80 mg, Batch (B) No.: 1004891, Mfg Date: MAY 2008 Exp Date: APR 2010, Route of administration: Oral	Participated Subjects: 60, Clinical Phase Completed Subjects: 59, (59 males, 0 females) Mean age: 26.7 (19-44) normal, healthy, adult, human subjects	3.3886 ± 1.9596 (57.8)	6.000 (2.50-12.00)	62.6235 ± 26.3708 (42.1)	67.7961 ± 25.9239 (38.2)	20.0230 ± 6.4471 (32.2)	0.0377 ± 0.0104 (27.7)	Section 11.4, Table-15 and Table-16, Pg# 48 and 49 of 334 main report
			Reference (R) Lipitor® (Atorvastatin Calcium) tablets, 1 x 80 mg, Batch No. 17995V Mfg Date: NAV Exp Date: Sep 2008, Route of administration: Oral		3.9323 ± 2.2899 (58.2)	5.000 (1.50 - 36.00)	66.2406 ± 29.4853 (44.5)	71.8684 ± 31.9534 (44.5)	18.6344 ± 6.5007 (34.9)	0.0407 ± 0.0118 (29.0)	

Table 10. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Parent drug:

Atorvastatin Calcium Tablets 80 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Comparative Oral Bioavailability Study (Study No. 023-08)				
Atorvastatin				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max}	51.45	61.10	0.84	75.72-93.67
AUC_{0-t}	292.73	329.73	0.89	84.33-93.46
AUC_{0-INF}	298.52	336.18	0.89	84.42-93.40

Supportive metabolites:

Orthohydroxy Atorvastatin:

Atorvastatin Calcium Tablets 80 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Comparative Oral Bioavailability Study (Study No. 023-08)				
Atorvastatin				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max}	26.02	29.16	0.89	82.72-96.29
AUC_{0-t}	224.68	245.18	0.92	87.71-95.74
AUC_{0-INF}	232.51	253.28	0.92	88.00-95.76

2. Parahydroxy Atovastatin:

Atorvastatin Calcium Tablets 80 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Comparative Oral Bioavailability Study (Study No. 023-08)				
Atorvastatin				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max}	2.97	3.39	0.88	81.54-94.34
AUC_{0-t}	57.70	60.76	0.95	89.96-100.23
AUC_{0-INF}	65.33	68.01	0.96	90.43-102.04

Table 11. Additional Study Information

Parent Drug: Atorvastatin

Root mean square error, AUC0-t	0.1669	
Root mean square error, AUC∞	0.1643	
Root mean square error, Cmax	0.3455	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	59	59
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	59	0.98	0.91	1.00
Reference	59	0.98	0.92	1.00

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer use SAS code 'CALKE' for the statistical analysis. The calculation of the elimination rate constant (Kel) was based on the concentrations of the samples in the terminal log-liner phase of each individual subject.

- For parent drug, the 90% CI of Cmax was 75.72-93.67% which is out of the acceptance range. Please see the reviewer's comments for the firm's responses to Deficiency #4 in section 3 for details.

- The review calculated the 90% CIs for all PK parameters of the metabolites (Orthohydroxy Atorvastatin and parahydroxy Atovastatin) and found the 90% CIs for all PK parameters of both metabolites are within the acceptable range of 80-125%.

- The reviewer agrees with the firm's statistical analysis of the study.

Note to Project Manager: This application is acceptable pending the DSI inspections of the clinical facility. Please hold this letter until the DSI inspection is completed and found acceptable for the clinical site (Related (b) (4))

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091226

APPLICANT: Matrix Laboratories Limited, India

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time.

We acknowledge that you will conduct dissolution testing for your test product, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, using the following FDA-recommended dissolution method and specification:

Medium: 0.05 M 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 labeled amount of Atorvastatin in the dosage form is dissolved in **15 minutes**

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

7 OUTCOME PAGE

ANDA: 091226

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13101	11/9/2010	Other	Study Amendment	1	1
				Bean Total:	1

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/s/

HONGLING ZHANG
02/17/2011

BING V LI
02/17/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/17/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091226		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg		
Applicant Name	Matrix Laboratories Limited, India		
Address	Matrix Laboratories Limited. 4th Floor, Sairam Towers, Alexander Road, Secunderabad 500 003 INDIA		
Authorized US Agent	Keith J. Giunta, Director		
Contact's Telephone Number	(304) 554-5899 (800) 848-0461, Ext. 5899		
Contact's Fax Number	(304)-285-6407		
Original Submission Date(s)	12/30/2008		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	Hongling Zhang, Ph.D.		
Study Number (s)	022-08	162-08	023-08
Study Type (s)	Fasting	Fed	Fed (failed study)
Strength (s)	80 mg	80 mg	80 mg
Clinical Site	GVK Biosciences Pvt Limited		
Clinical Site Address	7th Floor Swarna jayanthi Commercial Complex, Ameerpet, Hyderabad-500037, India Tel: +91-40-66275566, Fax: +91-40-66275599		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
DSI INSPECTION RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**

#1, #7	Dissolution	10 mg, 20 mg, 40 mg and 80 mg	ADEQUATE
#1	Fasting Study	80 mg	ADEQUATE
#1	Fed Study	80 mg	ADEQUATE

1 EXECUTIVE SUMMARY

This is the review of the DSI findings from the inspection of the clinical site, GVK Biosciences Pvt Limited, conducted for another ANDA ([(b) (4)] This review evaluates the impact of the inspection findings on the BE studies of the current ANDA.

The fasting and fed BE studies of the current application were found acceptable pending the outcome of the DSI inspection of the **clinical site** (GVK Biosciences Pvt Limited)[1]. The last routine DSI inspection of the **analytical site** was completed on [(b) (4)] and the outcome was NAI (no action indicated) (Ref. ANDA [(b) (4)]).

The fasting and fed BE studies were conducted between July 1, 2008 to September 28, 2008. The DSI inspected **the clinical site** on [(b) (4)] 2007 for routine inspection (Ref. [(b) (4)] The outcome of the DSI inspection was VAI (voluntary action indicated).

There were two findings by DSI for the clinical site, as follows[2]: *'1) Dispensing record, Form* [(b) (4)]*, does not give a description of the product dispensed other than an indication of test "A" or reference "B". There is also no other description on the subject dosing record describing the investigational product nor on the dosing peel off label; and 2) Failure to maintain reserve samples in sufficient quantity from the initial shipment used in the studies.'* The above two findings are deemed as minor findings and are not expected to affect the outcome of the fasting and fed BE studies for the current application.

The firm's fasting and fed BE studies are now found acceptable and the application is **adequate.**

[1] DARRTS, ANDA 091226, REV-BIOEQ-01 (General Review), check in date: 2/17/2011
[2] DARRTS, [(b) (4)] CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review), check in date:

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3 OUTCOME PAGE

ANDA: 091226

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13244	11/9/2010	Other	DSI Inspection Report	0	0
				Bean Total:	0

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/s/

HONGLING ZHANG
02/17/2011

BING V LI
02/17/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/17/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091226
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg
Applicant Name	Matrix Laboratories Limited, India
Address	Matrix Laboratories Limited. 4th Floor, Sairam Towers, Alexander Road, Secunderabad 500 003.INDIA.
Authorized US Agent	Ronald T. Groman, Director
Contact's Telephone Number	(304) 554-5899 (800) 848-0461, Ext. 5899
Contact's Fax Number	(304)-285-6407
Original Submission Date(s)	12/30/2008
Submission Date(s) of Amendment(s) Under Review	9/30/2009
Reviewer	Hongling Zhang, Ph.D.

Study Number (s)	022-08	162-08	023-08
Study Type (s)	Fasting	Fed	Fed
Strength (s)	80 mg	80 mg	80 mg
Clinical Site	GVK Biosciences Pvt Limited		
Clinical Site Address	7th Floor Swarna jayanthi Commercial Complex, Ameerpet, Hyderabad-500037, India Tel: +91-40-66275566, Fax: +91-40-66275599		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI INSPECTION RESULT	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
#1, #7	**Dissolution**	**10 mg, 20 mg, 40 mg and 80 mg**	**ADEQUATE**
#1	**Fasting Study**	**80 mg**	**INADEQUATE**
#1	**Fed Study**	**80 mg**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfzier's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The results are summarized in the tables below.

Parent drug:

Atorvastatin, 1 X 80 mg
Fasting Bioequivalence Study No. 022-08, N=67 (all male)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	325.18	308.06	1.06	99.01	112.53
AUC∞ (ng·hr/mL)	329.12	312.10	1.05	98.97	112.37
Cmax (ng/mL)	78.65	73.27	1.07	94.47	121.99

Atorvastatin, 1 X 80 mg
Fed Bioequivalence Study No. 162-08, N=56 (all male)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	249.53	262.50	0.95	88.92	101.62
AUC∞ (ng·hr/mL)	255.29	268.22	0.95	89.10	101.67
Cmax (ng/mL)	47.30	49.35	0.96	86.49	106.23

Orthohydroxy Atorvastatin:

Orthohydroxy Atorvastatin
Fasting Bioequivalence Study No. 022-08, N=67(all male)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	295.44	280.94	1.05	99.25	111.43
AUC∞ (hr *ng/ml)	300.91	287.17	1.05	98.96	110.95
Cmax (ng/ml)	42.64	40.29	1.06	94.42	118.65

Orthohydroxy Atorvastatin
Fed Bioequivalence Study No. 162-08 N=56 (all male)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	183.56	201.98	0.91	85.86	96.20
AUC∞ (hr *ng/ml)	190.92	209.02	0.91	86.56	96.39
Cmax (ng/ml)	22.89	24.98	0.92	84.38	99.47

Parahydroxy Atorvastatin:

Parahydroxy Atorvastatin Fasting Bioequivalence Study No. 022-08, N=67 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	67.12	59.81	1.12	105.74	119.09
AUC∞ (hr *ng/ml)	72.50*	64.23	1.13	106.94	119.15
Cmax (ng/ml)	3.85	3.16	1.22	108.46	136.99

*n=66 for this parameter

Parahydroxy Atorvastatin Fed Bioequivalence Study No. 162-08, N=56 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	40.47	44.35	0.91	85.02	97.99
AUC∞ (hr *ng/ml)*	46.54	50.84	0.92	85.38	98.13
Cmax (ng/ml)	2.04	2.45	0.83	74.41	93.50

*n=55 for this parameter

The firm's fasting and (repeat) fed BE study are inadequate due to the deficiencies related to the clinical and bioanalytical studies. The firm also provided inadequate report of the failed fed BE study.

The firm's dissolution testing using the FDA-recommended dissolution method was found acceptable. In the amendment with the letter dated 9/30/2009, the firm acknowledged the FDA-recommended dissolution method and specification [NLT (b) (4)% (Q) in 15 minutes].

The waiver requests for *in vivo* BE study requirements for the firm's lower strengths of the test product, 10 mg, 20 mg and 40 mg, can **NOT** be granted at this time, pending the firm's acceptable fasting and fed BE studies.

No Division of Scientific Investigations (DSI) inspection is pending or necessary[1].

The application is **inadequate** with deficiencies.

[1] A routine inspection was last completed for the clinical site on (b) (4) 2007 for (b) (4) The outcome was Voluntary Action Indicated (VAI). The application has been tentative approved (DARRTS, (b) (4) COR-ANDAACTION-03 (Tentative Approval). A routine inspection was completed for the analytical site on (b) (4) for ANDA (b) (4). The outcome was No Action Indicated (NAI).

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Atorvastatin Calcium Tablets, EQ. 10 mg, 20 mg, 40 mg, and 80 mg Base
Reference Product	Lipitor® (atorvastatin calcium) Tablets, EQ. 10 mg, 20 mg, 40 mg, and 80 mg Base (EQ. 80 mg Base is designated as the RLD strength)
RLD Manufacturer	Pfizer, Inc.
NDA No.	020702
RLD Approval Date	07 April 2000 (EQ 80 mg Base) 17 December 1996 (EQ 10 mg, 20 mg, and 40 mg Base)
Indication[3]	LIPITOR® is an inhibitor of HMG-CoA reductase (statin) indicated for the followings: **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** LIPITOR® is indicated:

[2] Electronic Orange Book: http://www.accessdata fda.gov/scripts/cder/ob/default.cfm. Last accessed: 2 August 2010.
[3] Drugs at FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 2 August 2010.

	• 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

Bioavailability	LIPITOR® is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to LIPITOR® 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. Plasma LIPITOR® concentrations are lower (approximately 30% for Cmax 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.
Food Effect	Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether LIPITOR® is given with or without food.
Tmax	1 to 2 hours.
Metabolism	LIPITOR® 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 LIPITOR®. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR® metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of LIPITOR® in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes

	further glucuronidation.
Excretion	LIPITOR® and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Less than 2% of a dose of LIPITOR® is recovered in urine following oral administration.
Half-life	Mean plasma elimination half-life of LIPITOR® 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.
Drug Specific Issues (if any)	**N/A**

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:	N/A

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:	N/A

Analytes to measure (in plasma/serum/blood):	Atorvastatin, ortho- and parahydroxylated metabolites of atorvastatin[4]
Bioequivalence based on:	90% CI of Atorvastatin
Waiver request of in-vivo testing:	EQ.10 mg, 20 mg, and 40 mg Base based on (i) acceptable bioequivalence studies on the 80 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
Source of most recent recommendations[5]:	Draft Guidance on Atorvastatin (finalized 05/2008)

[4] The ortho- and parahydroxylated metabolites of atorvastatin are formed by ***presystemic metabolism*** and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

[5] Individual Product Bioequivalence Recommendations: http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. Last accessed: 22 July 2010.

Summary of OGD or DBE History (for details, see Appendix 4.4):	There are currently no approved generic drug products[2]. The DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets[6]: • ANDA 076477 (Ranbaxy Labs) • ANDA 078773 (Teva) • ANDA 077575 (Sandoz) • ANDA 091226 (Matrix Labs) • ANDA 090548 (Apotex) • ANDA 091624 (Kudco)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	4
Waiver requests	Yes	3
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	Yes	1
Amendments	Yes	1

[6] DARRTS Search: Submission Search Results: http://darrts.fda.gov:7777/darrts/submissionSearch.do.

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Study No:022-08; Volume 19; Page:5928 Study No:162-08;Volume 15 ;Page:11208

Analyte	Atorvastatin	O-OH-Atorvastatin	P-OH-Atorvastatin
Internal standard (IS)	Atorvastatin D5	Atorvastatin D5	Atorvastatin D5
Method description	Liquid-Liquid Extraction (method description is detailed in method SOP attached as appendix 1)	Liquid-Liquid Extraction (method description is detailed in method SOP attached as appendix 1)	Liquid-Liquid Extraction (method description is detailed in method SOP attached as appendix 1)
Limit of quantitation	0.250 ng/mL	0.250 ng/mL	0.050 ng/mL
Average recovery of drug (%)	70.00% (LQC), 65.43% (M2QC) & 70.31% (HQC)	77.61% (LQC), 70.26% (M2QC) & 71.48% (HQC)	75.40% (LQC), 68.62% (M2QC) & 71.90% (HQC)
Average recovery of IS (%)	71.41%	71.41%	71.41%
Standard curve concentrations (units/mL)	0.250, 0.500, 5.010, 15.040, 50.130, 100.250, 150.380, 200.500, 250.630 ng/mL	0.250, 0.500, 2.480, 9.930, 29.780, 59.550, 84.360, 114.140,148.880 ng/mL	0.050, 0.100, 0.500, 0.990, 1.990, 3.980, 5.960, 7.950, 9.940 ng/mL
QC concentrations (units/mL)	0.250 ng/mL (LLOQQC), 0.740 ng/mL (LQC), 24.560 ng/mL (M1QC), 78.600 ng/mL (M2QC), 176.850 ng/mL (HQC)	0.250 ng/mL (LLOQQC), 0.750 ng/mL (LQC), 19.900 ng/mL (M1QC), 49.750 ng/mL (M2QC), 104.480 ng/mL (HQC)	0.050 ng/mL (LLOQQC), 0.150 ng/mL (LQC), 1.490 ng/mL (M1QC), 3.480 ng/mL (M2QC), 7.160 ng/mL (HQC)
QC Intraday precision range (%)	1.44% to 6.07%	2.06% to 7.08%	1.67% to 7.26%
QC Intraday accuracy range (%)	83.12% to 109.56%	86.40% to 102.87%	96.42% to 107.40%
QC Interday precision range (%)	1.79 % to 7.72%	2.67% to 7.25%	4.25% to 12.72%
QC Interday accuracy range (%)	94.32% to 110.49%	93.20% to 102.71%	96.87% to 103.93%
Bench-top stability (hrs)	5 hrs	5 hrs	5 hrs
Stock stability (days)	Drug - 74 days & 72 days at 2-10ºC ISTD- 74 days & 68 days at 2-10ºC	Drug - 74 days & 72 days at 2-10ºC ISTD- 74 days & 68 days at 2-10ºC	Drug - 74 days & 72 days at 2-10ºC ISTD- 74 days & 68 days at 2-10ºC
Processed stability (hrs)	Auto Sampler about 46 hrs 20 min at 5ºC Dry Extract 23 hrs at 2-10ºC	Auto Sampler about 46 hrs 20 min at 5ºC Dry Extract 23 hrs at 2-10ºC	Auto Sampler about 46 hrs 20 min at 5ºC Dry Extract 23 hrs at 2-10ºC
Freeze-thaw stability (cycles)	4 Cycles	4 Cycles	4 Cycles
Long-term storage stability (days)	405 days@-20±5ºC and -70±15ºC	405 days@-20±5ºC and -70±15ºC	405 days@-20±5ºC and -70±15ºC
Dilution integrity	1/2 dilution – 1.88% (precision) 1/4 dilution – 11.28% (precision)	1/2 dilution – 2.84% (precision) 1/4 dilution – 11.78% (precision)	1/2 dilution – 4.78% (precision) 1/4 dilution – 11.22% (precision)
Selectivity	No interfering peaks were observed at the retention time of Drug and ISTD	No interfering peaks were observed at the retention time of Drug and ISTD	No interfering peaks were observed at the retention time of Drug and ISTD

SOPs submitted	Yes (SAP-005-00: Determination of Atorvastatin and its active metabolite Ortho Hydroxy Atorvastatin and Para Hydroxy Atovastatin in Human plasma using High performance liquid chromatography method with Tandem Mass Spectrometry.
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

- The firm did not specify the salt form of Ethylenediaminetetraacetic Acid (EDTA) in the blank plasma used for the pre-study method validation, except for the long-term stability (LTS) test, in which the blank plasma containing K_3EDTA as anticoagulant was used. The firm will be asked to specify the salt form of EDTA used for the pre-study method validation. The anticoagulant used in the clinical studies was K_3EDTA and in the bioanalytical study, the blank plasma used for the preparation of the plasma calibration standards and QC samples also contains K_3EDTA as anticoagulant.

- In the firm's original submission, the LTS test was conducted on the samples in frozen plasma stored for 73 days, which were not sufficient to cover the storage period of bio-study samples which was 81 days. In the dissolution review, the dissolution reviewer asked the firm to provide the LTS data to cover at least 81 days. In response to the DBE's deficient letter[7], the firm submitted an amendment with the letter dated of 9/30/2009. In the amendment, the firm submitted the new data of LTS test demonstrating that the analytes (atorvastatin, O-OH-atorvastatin and P-OH-atorvastatin) are stable in human plasma (contain K_3EDTA as anticoagulant) at -70±15°C and -20±15°C for 405 days. However, the long-term storage stability data was based on the comparison of the mean of back-calculated values for the stability samples with the nominal concentrations. For future submissions, the firm should be made aware that the concentrations of all the stability samples should be compared to the mean of back-calculated values for the fresh quality control (QC) samples at the appropriate concentrations from the first day of the long-term stability testing, according to the Guidance for Industry: Bioanalytical Method Validation, 2001.

The pre-study bioanalytical method validation is **inadequate.**

[7] DARRTS, ANDA 091226, COR-ANDADE-01(Bio Incomplete Deficiencies), check in date: 6/22/2009

3.6 *In Vivo* Studies

Table 1. Summary of all *in vivo* Bioequivalence Studies

1. Atovastatin

Study Ref.No	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Pharmacokinetic Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng.hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
022-08	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fasting condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fasting condition.	Test (T) Atorvastatin Calcium Tablets 80 mg Dose: 1 x 80mg B.No. 1004891 Route of administration: Oral	76 subjects were enrolled in the study and 67 subjects completed the study in its entirety (Male = 67) Mean Age = 24.6 Range = 18-39	89.2174 ± 48.0017 (53.8)	1.500 (0.33 - 5.00)	352.6492 ± 154.7122 (43.9)	356.8043 ± 155.4735 (43.6)	5.9626 ± 2.2985 (38.5)	0.1282 ± 0.0345 (26.9)	Volume No. : 01 Page:245
			Reference (R) Lipitor® (Atorvastatin Calcium) 80 mg tablets Dose: 1 x 80mg Batch No: 17995V Route of administration: Oral		80.5158 ± 36.4587 (45.3)	1.000 (0.33 - 5.00)	337.9534 ± 157.2330 (46.5)	342.3676 ± 159.2722 (46.5)	6.1849 ± 2.3201 (37.5)	0.1247 ± 0.0381 (30.5)	

Study Ref.No	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Pharmacokinetic Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
162-08	Title: Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fed condition.	A randomised, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fed condition.	Test (T) Atorvastatin Calcium Tablets 80 mg B.No. 1004891 Mfg Dose: 1 x 80mg Route of administration: Oral	60 subjects were enrolled in the study and 56 subjects completed the study in its entirety (Male = 56) Mean Age = 26.1 Range = 19-40	52.6040 ± 26.0841 (49.6)	3.500 (1.50 - 5.00)	264.6571 ± 97.6758 (36.9)	269.9172 ± 98.1082 (36.3)	7.8393 ± 4.0757 (52.0)	0.1055 ± 0.0390 (37.0)	Volume No. : 01 Page:6266
			Reference (R) Lipitor® (Atorvastatin Calcium) 80 mg tablets Batch No: 17995V Dose: 1 x 80mg Route of administration: Oral		58.9391 ± 41.0424 (69.6)	3.250 (1.25 - 6.00)	283.8306 ± 122.8935 (43.3)	289.6851 ± 123.0757 (42.5)	8.9796 ± 5.3843 (60.0)	0.1004 ± 0.0508 (50.6)	

2. Ortho hydroxylated atorvastatin

Study Ref.No.	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Pharmacokinetic Parameters						
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	Study Report Location
022-08	Title: Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fasting condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fasting condition.	Test (T) Atorvastatin Calcium Tablets 80 mg Dose: 1 x 80mg B.No. 1004891 Route of administration: Oral	76 subjects were enrolled in the study and 67 subjects completed the study in its entirety (Male = 67 Mean Age = 24.6 Range = 18-39	50.2772 ± 28.8505 (57.4)	2.000 (0.33-8.00)	318.8190 ± 132.4924 (41.6)	323.5106 ± 132.4330 (40.9)	6.4127 ± 1.5198 (23.7)	0.1136 ± 0.0249 (21.9)	Volume No. : 01 Page:246
			Reference (R) Lipitor® (Atorvastatin Calcium) 80 mg tablets Dose: 1 x 80mg Batch No: 17995V Route of administration: Oral		44.0051 ± 20.2056 (45.9)	2.000 (0.67 - 5.00)	300.4063 ± 119.1737 (39.7)	306.0843 ± 119.7632 (39.1)	6.6342 ± 2.4475 (36.9)	0.1125 ± 0.0257 (22.8)	

Study Ref.No.	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Pharmacokinetic Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng.hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
162-08	Title: Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fed condition.	A randomised, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fed condition.	Test (T) Atorvastatin Calcium Tablets 80 mg B.No. 1004891 Dose: 1 x 80mg Route of administration: Oral	60 subjects were enrolled in the study and 56 subjects completed the study in its entirety (Male = 56) Mean Age = 26.1 Range = 19-40	24.7544 ± 9.7119 (39.2)	5.000 (1.75 - 6.00)	192.0024 ± 61.4276 (32.0)	197.6665 ± 61.7488 (31.2)	7.7820 ± 3.6637 (47.1)	0.1031 ± 0.0343 (33.2)	Volume No. : 01 Page:6267
			Reference (R) Lipitor® (Atorvastatin Calcium) 80 mg tablets Batch No: 17995V Dose: 1 x 80mg Route of administration: Oral		28.0655 ± 14.2223 (50.7)	5.000 (1.50 - 6.00)	211.5707 ± 67.8141 (32.1)	217.8247 ± 68.5390 (31.5)	8.7259 ± 4.6047 (52.8)	0.0955 ± 0.0366 (38.3)	

3. Parahydroxylated atorvastatin

Study Ref.No.	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Pharmacokinetic Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
022-08	Title: Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fasting condition.	A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fasting condition.	Test (T) Atorvastatin Calcium Tablets 80 mg Dose: 1 x 80mg B.No. 1004891 Route of administration : Oral	76 subjects were enrolled in the study and 67 subjects completed the study in its entirety (Male = 67 Mean Age = 24.6 Range = 18-39	4.5849 ± 3.0362 (66.2)	5.000 (1.00-16.00)	73.1839 ± 32.2657 (44.1)	77.7556 ± 32.6936 (42.0)	16.2752 ± 4.5636 (28.0)	0.0455 ± 0.0111 (24.4)	Volume No. : 01 Page:247
			Reference (R) Lipitor® (Atorvastatin Calcium) 80 mg tablets Dose: 1 x 80mg Batch No: 17995V Route of administration : Oral		3.7022 ± 2.2521 (60.8)	5.000 (0.33-16.00)	66.2768 ± 30.1961 (45.6)	70.3267 ± 31.1404 (44.3)	16.9632 ± 6.6519 (39.2)	0.0450 ± 0.0120 (26.5)	

Study Ref.No.	Study Objective	Study design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject (No. M/F) Type Age: mean (Range)	Pharmacokinetic Parameters						Study Report Location
					C_{max} (ng/mL) Mean ± SD (CV %)	t_{max} (hr) Median (Range)	AUC_{0-t} (ng.hr/mL) Mean ± SD (CV %)	AUC_{0-INF} (ng.hr/mL) Mean ± SD (CV %)	$t_{½}$ (hr) Mean ± SD (CV %)	K_{el} (hr^{-1}) Mean ± SD (CV %)	
162-08	Title: Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Atorvastatin Calcium tablets 80 mg, Matrix Laboratories Limited, India and Lipitor® (Atorvastatin Calcium) 80mg tablets, Manufactured by Pfizer Ireland Pharmaceuticals, Dublin, Ireland and Distributed by Pfizer Labs, Division of Pfizer Inc, NY, 10017 in normal, healthy, adult, human subjects under fed condition.	A randomised, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study in normal, healthy, adult, human subjects under fed condition.	Test (T) Atorvastatin Calcium Tablets 80 mg B.No. 1004891 Mfg Date: MAY 2008 Exp Date: APR 2010 Route of administration: Oral	60 subjects were enrolled in the study and 56 subjects completed the study in its entirety (Male = 56) Mean Age = 26.1 Range = 19-40	2.3682 ± 1.4418 (60.9)	6.000 (5.00 - 12.00)	44.4220 ± 24.3093 (54.7)	50.2090 ± 26.8043 (53.4)	22.1379 ± 8.6447 (39.0)	0.0350 ± 0.0105 (29.9)	Volume No. : 01 Page:6268
			Reference (R) Lipitor® (Atorvastatin Calcium) 80 mg tablets Batch No: 17995V Mfg Date: NAV Exp Date: Sep 2008 Route of administration: Oral		2.9431 ± 1.9098 (64.9)	6.000 (4.00 - 16.00)	47.5982 ± 20.0081 (42.0)	52.7103 ± 21.4023 (40.6)	20.5447 ± 8.5629 (41.7)	0.0376 ± 0.0106 (28.3)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Parent drug:

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 022-08, N=67 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	325.18	308.06	1.06	99.01	112.53
AUC∞ (ng·hr/mL)	329.12	312.10	1.05	98.97	112.37
Cmax (ng/mL)	78.65	73.27	1.07	94.47	121.99

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. 162-08, N=56 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	249.53	262.50	0.95	88.92	101.62
AUC∞ (ng·hr/mL)	255.29	268.22	0.95	89.10	101.67
Cmax (ng/mL)	47.30	49.35	0.96	86.49	106.23

Supportive Active Metabolites:

Orthohydroxy Atorvastatin:

Orthohydroxy Atorvastatin Fasting Bioequivalence Study No. 022-08, N=67(all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	295.44	280.94	1.05	99.25	111.43
AUC∞ (hr *ng/ml)	300.91	287.17	1.05	98.96	110.95
Cmax (ng/ml)	42.64	40.29	1.06	94.42	118.65

Orthohydroxy Atorvastatin Fed Bioequivalence Study No. 162-08 N=56 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	183.56	201.98	0.91	85.86	96.20
AUC∞ (hr *ng/ml)	190.92	209.02	0.91	86.56	96.39
Cmax (ng/ml)	22.89	24.98	0.92	84.38	99.47

Parahydroxy Atorvastatin:

Parahydroxy Atorvastatin Fasting Bioequivalence Study No. 022-08, N=67 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	67.12	59.81	1.12	105.74	119.09
AUC∞ (hr *ng/ml)	72.50*	64.23	1.13	106.94	119.15
Cmax (ng/ml)	3.85	3.16	1.22	108.46	136.99

*n=66 for this parameter

Parahydroxy Atorvastatin Fed Bioequivalence Study No. 162-08, N=56 (all male) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	40.47	44.35	0.91	85.02	97.99
AUC∞ (hr *ng/ml)*	46.54	50.84	0.92	85.38	98.13
Cmax (ng/ml)	2.04	2.45	0.83	74.41	93.50

*n=55 for this parameter

Table 3. Reanalysis of Study Samples

1. Fasting Study:

a) Atorvastatin

Fasting Bioequivalence Study (Study No. 022-08) Additional information in Volume(14), Page(3956-3969)								
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
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Code B (Unacceptable internal standard response)	30	30	1.95%	1.95%	30	30	1.95%	1.95%
Code L (Concentration in subject blank and subject zero (more than 20% area response but less than LOQ concentration)	0	3	0.00%	0.19%	0	3	0.00%	0.19%
Code D (Sample concentration above upper limit of quantification)	1	0	0.06%	0.00%	1	0	0.06%	0.00%
Code Q (Rejected analytical run)	23	23	1.49%	1.49%	23	23	1.49%	1.49%
Total	54	56	3.50%	3.63%	54	56	3.50%	3.63%

Note: Number of plasma samples exposed with the test product; 1539
Number of plasma samples exposed with the Reference product; 1540

b) Ortho-Hydroxy Atorvastatin

Fasting Bioequivalence Study (Study No. 022-08) Additional information in Volume(14), Page(3956-3969)								
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
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Code B (Unacceptable internal standard response)	30	30	1.95%	1.95%	30	30	1.95%	1.95%
Code L (Concentration in subject blank and subject zero (more than 20% area response but less than LOQ concentration))	0	3	0.00%	0.19%	0	3	0.00%	0.19%
Code D (Sample concentration above upper limit of quantification)	1	0	0.06%	0.00%	1	0	0.06%	0.00%
Total	31	33	2.01%	2.14%	31	33	2.01%	2.14%

Note: Number of plasma samples exposed with the test product; 1539
Number of plasma samples exposed with the Reference product; 1540

c) Para- Hydroxy Atorvastatin

Fasting Bioequivalence Study (Study No. 022-08) Additional information in Volume(14), Page(3956-3969)								
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
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Code B (Unacceptable internal standard response)	30	30	1.95%	1.95%	30	30	1.95%	1.95%
Code D (Sample concentration above upper limit of quantification)	10	5	0.65%	0.32%	10	5	0.65%	0.32%
Total	40	35	2.60%	2.27%	40	35	2.60%	2.27%

Note: Number of plasma samples exposed with the test product; 1539
Number of plasma samples exposed with the Reference product; 1540

2. Fed study:

a) Atorvastatin

Fed Bioequivalence Study (Study No. 162-08) Additional information in Volume(12), Page(9571-9576)								
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
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Code B (Unacceptable internal standard)	11	14	0.86%	1.09%	11	14	0.86%	1.09%
Code L (Concentration in subject blank and subject zero (more than 20% area response but less than LOQ concentration))	27	26	2.10%	2.02%	27	26	2.10%	2.02%
Code C (Instrument or equipment malfunction)	1	1	0.08%	0.08%	1	1	0.08%	0.08%
Code G (Repeats due to other Justifiable causes)	2	0	0.16%	0.00%	2	0	0.16%	0.00%
Total	41	41	3.20%	3.19%	41	41	3.20%	3.19%

Note: Number of plasma samples exposed with the test product; 1286
Number of plasma samples exposed with the Reference product; 1284

b) Ortho-Hydroxy Atorvastatin

Fed Bioequivalence Study (Study No. 162-08) Additional information in Volume(12), Page(9571-9576)								
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
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Code B (Unacceptable internal standard)	11	14	0.86%	1.09%	11	14	0.86%	1.09%
Code L (Concentration in subject blank and subject zero (more than 20% area response but less than LOQ concentration))	1	2	0.08%	0.16%	1	2	0.08%	0.16%
Code C (Instrument or equipment malfunction)	1	1	0.08%	0.08%	1	1	0.08%	0.08%
Code G (Repeats due to other Justifiable causes)	2	0	0.16%	0.00%	2	0	0.16%	0.00%
Total	15	17	1.18%	1.33%	15	17	1.18%	1.33%

Note: Number of plasma samples exposed with the test product; 1286
Number of plasma samples exposed with the Reference product; 1284

c) Para- Hydroxy Atorvastatin

Fed Bioequivalence Study (Study No. 162-08) Additional information in Volume(12), Page(9571-9576)								
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
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Code B (Unacceptable internal standard)	11	14	0.86%	1.09%	11	14	0.86%	1.09%
Code C (Instrument or equipment malfunction)	1	1	0.08%	0.08%	1	1	0.08%	0.08%
Code G (Repeats due to other Justifiable causes)	2	0	0.16%	0.00%	2	0	0.16%	0.00%
Total	14	15	1.10%	1.17%	14	15	1.10%	1.17%

Note: Number of plasma samples exposed with the test product; 1286
Number of plasma samples exposed with the Reference product; 1284

Did use of recalculated plasma concentration data change study outcome?

No.

Comments from the Reviewer:

- The firm stated that the repeat analysis was conducted according to the firm's SOP for repeat (SOP (b) (4): Sample reassay and reporting for final concentration, effective date: 08/06/2007).

Fasting Study:

- For fasting study, a total of 124 samples were repeated and some samples were repeated for 1 analyte and some samples were repeated for 2 or 3 analytes, which constituted to 4.03% of the total sample analyzed (124 out of 3079). Out of 124 samples, 46 samples (for subject 9, period I and period II) were repeated due to QC failure of the batch. The firm did not provide the QC data of the batch. The firm will be asked to provide the QC data of the rejected batch to clearly show the batch was rejected due to the QCs not meeting the acceptance criteria.

- There were 60 samples repeated due to the 'unacceptable internal standards'. According to the firm's SOP for repeat analysis, the definition of the unacceptable internal standard response is as followings: *'any study sample analysis presenting an internal standard response beyond ±30% (for HPLC methods) and ±50% (for LC/MS and LC/MS/MS method) of mean internal standard response of accepted calibrate standards and quality control samples shall be rejected unless documented technical reasons or specific criteria'.* Also according to the SOP, the original concentrations were reported as NRV (non reportable values).

- There were three (3) blank samples repeated and the repeats were conducted according to the firm's SOP. The original concentrations of these blank samples were significant higher than the concentrations of the first sampling time samples of the same subjects which were either '0' or close to '0'. The concentrations after repeat were "0".

- The firm indicated that the whole batch of subject No: 42 and 43 were reintegrated due to the reason that the responses in all the 3 analytes were low. The noise threshold of the batch was changed from 20 to 3. The firm's SOP does not have the criteria for reintegration. The firm did not provide the original concentrations for the batch. The firm will be asked to provide the provide the SOP for the reintegration and in addition, the firm should provide the concentrations of subject #42 and #43 obtained using the same integration parameter as other batches for further evaluation. Please note that for the parent drug, the reviewer did another statistical analysis by excluding the data of these two subjects and found the 90% CIs for all PK parameters still within the acceptable range of 80-125%.

- The repeat analysis for the fasting BE study is incomplete.

Fed Study:

- There were 82 samples repeated in the fed study, which constitute to 3.19% (82 out of 2570) of the total samples analyzed.

- Out of 82 samples, 46 samples (for subject #25) were repeated due to batch repeat for atorvastatin only. The firm indicated that the reason for the batch repeat was due to concentration in subject blank and subject zero (more than 20% area response but less than LOQ concentration). According to the firm's SOP for repeat analysis: *'if the interference in the subject zero is ≥ the LOQ (i.e. a measurable concentration) and an interference of this magnitude appears in the next sample in the phase making quantification of all samples questionable, first reassay the subject zero in question in duplicate. If the interference is confirmed, the mean of all data that agree within ±20% will be reported. If the interference is not confirmed, the subject in question will be reassayed and the result will be reported'*. The firm did not provide the original concentrations of the subject. The firm will be asked to provide the original concentrations of atorvastatin for subject #25 for further evaluation.

- There were 25 samples repeated due to the 'unaccceptable internal standards'. According to the firm's SOP for repeat analysis, the definition of the unacceptable internal standard response is as followings: *'any study sample analysis presenting an internal standard response beyond ±30% (for HPLC methods) and ±50% (for LC/MS and LC/MS/MS method) of mean internal standard response of accepted calibrate standards and quality control samples shall be rejected unless documented technical reasons or specific criteria'*. Also according to the SOP, the original concentrations were reported as NRV (non reportable values).

- There were two samples (2.25 hrs and 3.00 hrs) reanalyzed for all three analytes due to the instrument malfunction. The initial values for the analytes were '0' and the repeated values were reported.

- There were two samples reanalyzed for all three analytes due to 'other justifiable causes'. These repeats were deemed as the PK repeats. The firm provided the original concentrations and for atorvastatin, the reviewer did statistical analysis by using the original concentrations and found the 90% CIs for all PK parameters are still within the acceptable ranges.

- The firm indicated that the whole batch of subject No: 01 and 02 were reintegrated due to the reason that the responses in all the 3 analytes were low. The noise threshold of the batch was changed from 100 to 10 for atorvastatin, from 50 to 10 for O-OH atorvastatin and from 20 to 10 for P-OH atorvastatin. The firm's SOP does not have the criteria for

reintegration. The firm did not provide the original concentrations for the batch. The firm will be asked to provide the SOP for the reintegration and in addition, the firm should provide the concentrations of subject #01 and 02 obtained using the same integration parameter as other batches for further evaluation. Please note that for the parent drug, the reviewer did another statistical analysis by excluding the data of these two subjects and found the 90% CIs for all PK parameters still within the acceptable range of 80-125%.

- The repeat analysis for the fed BE study is incomplete.

Incurred sample reproducibility (ISR) was performed on about 5% of the total samples analyzed during fasting study according to the firm's SOP No. (b) (4) (Reanalysis of Incurred Bioanalytical Samples). The results of ISR indicated that total 100%, 97.44% and 98.72% of ISR samples of atorvastatin and its metabolites O-OH atorvastatin and P-OH atorvastatin respectively, were found to be within ±20% of their original values. Therefore, the ISR confirmed the validity and performance of the method.

Based on the above comments, the firm's repeat analysis is **incomplete**. The firm should submit the followings:

1) For the fasting study (study No. 022-08), the firm should provide the QC data of the run for the samples of subject # 09 to show clearly that the batch was rejected due to the QC data not meeting the acceptance criteria.

2) For the fed study (study No. 162-08), the firm should provide the original concentrations of atorvastin of subject No. 25 for further evaluation.

3) The firm should provide the Standard Operation Procedures (SOP) for the re-integration of the chromatograms. In addition, the firm should provide the concentrations of the three analytes of subject No. 42 and No. 43 in fasting study and subject No. 01 and No. 02 for fed study, obtained by using the same integration parameter as other batches in the fasting and fed study, respectively.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	Cannot be determined pending the safety evaluation from the Pharmacology/Toxicology Division, regarding the amount of the L-Arginine used in the test product.
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02(Dissolution Review). 06/16/2009.
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 Dissolving
Is method acceptable?	Acceptable
If not then why?	N/A

*From FDA Internal Dissolution Database.

Reviewer Comments:

According to the dissolution review, the firm's dissolution testing using FDA-recommended dissolution method was found acceptable. However, the firm proposed specification of "NLT (b)(4)% (Q) in (b)(4) minutes" was not acceptable. The firm was advised to acknowledge its acceptance of the FDA-recommended specification of "NLT (b)(4)% (Q) in 15 minutes". The firm's dissolution data met the FDA-recommended specification at S1 level. In the firm's amendment with the letter date of 9/30/2009, the firm acknowledged the FDA-recommended dissolution specification. Therefore, the firm's dissolution testing is complete and acceptable.

3.9 Waiver Request(s)

Strengths for which waivers are requested	10 mg, 20 mg, and 40 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS DENIED**
If not then why?	Due to deficiencies found in the BE studies conducted on 80 mg strength.

3.10 Deficiency Comments:

1. For pre-study method validation, the firm did not specify the salt form of the EDTA in the blank plasma. The firm should specify the salt form of the EDTA in the blank plasma used for making the samples.

2. The firm's repeat analysis is incomplete:

   1) For the fasting study (study No. 022-08), the firm should provide the QC data of the run for the samples of subject # 09 to show clearly that the batch was rejected due to the QC data not meeting the acceptance criteria.

   2) For the fed study (study No. 162-08), the firm should provide the original concentrations of atorvastin of subject No. 25 for further evaluation.

   3) The firm should provide the Standard Operation Procedures (SOP) for the re-integration of the chromatograms. In addition, the firm should provide the concentrations of the three analytes of subject No. 42 and No. 43 in fasting study and subject No. 01 and No. 02 for fed study, obtained by using the same integration parameter as other batches in the fasting and fed study, respectively.

3. The clinical study of the fed study is incomplete. The firm should provide the following information:

   Explanation why some elevated creatine phosphokinase (CPK) levels in some subjects during the post-study lab assessment were listed as adverse events (for example, increased CPK levels of 310 U/L in Subject #3), while some other similar increased CPK levels during the washout period were not listed as adverse events (for example, the CPK level of 410 U/L in Subject #16 and the CPK level of 342 U/L in Subject #49, based on the lab assessement conducted after Period I, were not listed as AE). The firm should provide a complete list of abnormal laboratory results obtained during the washout and post-study assessment even if the results were not considered clinically significant.

4. The firm should submit the complete study report, which should include the clinical report (with complete adverse events and clinical laboratory results), bioanalytical report and statistical analysis report as well as the study datasets in SAS Transport format.

5. The following recommendation is for the firm's future submissions:

   The firm should be aware that the concentrations of the long-term stability samples should be compared to the mean of back-calculated values for the fresh QC at the appropriate concentrations from the first day of the long-term stability testing, as recommended in the Guidance for Industry: Bioanalytical Method Validation, issued 2001.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (022-08) incomplete due to the deficiencies mentioned above. Matrix Laboratories Limited conducted the fasting BE study on its Atorvastatin Calcium Tablets, 80 mg (lot # 1004891) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, 80 mg (lot # 17995V).

2. The Division of Bioequivalence finds the fed BE study (162-08) incomplete due to the deficiencies mentioned above. Matrix Laboratories Limited conducted the fed BE study on its Atorvastatin Calcium Tablets, 80 mg (lot # 1004891) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, 80 mg (lot # 17995V).

3. The *in vitro* dissolution testing on the 10 mg, 20 mg, 40 mg and 80 mg strengths conducted by the firm, using the FDA-recommended dissolution method is acceptable. The dissolution testing should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8, at 37°C ±5°C, using USP apparatus II (paddle) at 75 rpm. The firm's test product should meet the following specification: NLT (b)(4)% (Q) in 15 minutes.

4. The waiver requests for in vivo BE study requirements for the firm's lower strengths of the test product, 10 mg, 20 mg and 40 mg, can NOT be granted at this time due to the above mentioned deficiencies for the fasting and fed studies.

The firm should be informed the above deficiencies and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
Division of Chemistry	The safety of the usage of the L-Arginine ((b)(4) mg/day based on MDD) in the test product is pending evaluation by the Division of Pharmacology/Toxicology.

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	022-08
Study Title	A Randomized open label, balanced, two treatment, two sequence, two period, single dose, crossover comparative oral bioavailability study of Atorvastatin calcium tablets 80 mg with that of Lipitor® (Atorvastatin calcium) 80 mg in normal, healthy, adult, human subjects under fasting conditions.
Clinical Site (Name, Address, Phone #)	GVK Biosciences Pvt Limited., 7th Floor Swarna jayanthi Commercial Complex, Ameerpet, Hyderabad-500037, India, Tel: +91-40-66275566, Fax: +91-40-66275599
Principal Investigator	Naba Kr. Talukdar, MD
Dosing Dates	Period 01: 01 Jul 2008 Period 02 : 15 Jul 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	Analysis Start Date: 05th Aug 2008 Analysis End Date: 20th Sep 2008
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	81 days (01 Jul 2008 to 20th Sep 2008)

Table 5. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Atorvastatin Calcium Tablets 80 mg	Lipitor® (atorvastatin calcium) Tablets 80 mg
Manufacturer	Matrix Laboratories Limited (A Subsidiary of MYLAN Laboratories Inc.) F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik-422 113, Maharashtra, INDIA	Manufactured by: Pfizer Ireland Pharmaceuticals Dublin, Ireland

		Distributed by: Parke-Davis, Division of Pfizer Inc, NY, NY 10017
Batch/Lot No.	1004891	17995V
Manufacture Date	MAY 2008	N/A
Expiration Date	APR.2010	SEP 08
Strength	80 mg	80 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	(b) (4)	(b) (4)
Content Uniformity (mean, %CV)	(b) (4) @	N/A
Dose Administered	1 x 80mg (one tablet)	1 x 80mg (one tablet)
Route of Administration	Oral	Oral

@ The current USP requires expression of content uniformity as an "AV" value. The expression using mean and % CV is redundant.

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 76 Completed: 67 Used for Statistical Analysis: 67
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	RT: 2, 3, 5, 7, 9, 12, 14, 16, 17, 19, 21, 24, 25, 28, 30, 32, 34, 35, 38, 40, 41, 43, 46, 48, 49, 51, 53, 56, 58, 60, 62, 64, 66, 67, 70, 71, 73, 75 TR: 1, 4, 6, 8, 10, 11, 13, 15, 18, 20, 22, 23, 26, 27, 29, 31, 33, 36, 37, 39, 42, 44, 45, 47, 50, 52, 54, 55, 57, 59, 61, 63, 65, 68, 69, 72, 74, 76 (note: the dropped out subjects were marked as yellow)
Blood Sampling Times	Pre-dose, 0.16, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0 hours after dosing.
Blood Volume Collected/Sample	5 ml/sample

Blood Sample Processing/Storage	At each time point, the blood samples were collected in pre-labeled vacuettes/vacutainers containing K_3EDTA as anticoagulant. After collection, samples were centrifuged with set condition at 3000 rpm for 10 minutes and at 4°C. After centrifugation the plasma samples were separated and transferred into respective prelabeled polypropylene tubes in duplicate (set #01 & set #02). These polypropylene tubes were stored below -20°C for a maximum period of 12 hours and then they were stored at -70°C ±20°C until shipped for analysis. Sample collection and separation were done under condition with minimal exposure to ultraviolet light.
IRB Approval	Yes: 6/10/2008
Informed Consent	Yes: 6/11/2008
Length of Fasting	Overnight for at least 10 hours prior to schedule time for dosing until 4 hours after dosing.
Length of Confinement	Not less than 10.5 hours pre-dose till at least 24 hours post-dose in each period.
Safety Monitoring	Clinical examination were carried out and recorded at check-in and at checkout. Vital signs measurement were carried out and recorded at check in, before dosing of investigational products and at checkout. Vital signs were measured and recorded 1, 2, 3, and 4 hours after dosing, within ±30 minutes of scheduled time.

Comments on Study Design:

The firm did not provide the mean and % CV of the content uniformity for the bio batch of the test products. Instead, the firm provided the calcucated Acceptance Value (AV = (b)(4)%) which is within the limit of the AV ((b)(4)%) as defined by the Charpter <905> of USP. Since the calculation of the AV is based on the mean and %CV and the AV of the bio batch of the test product was less than the maximum allowable value ((b)(4)%) that USP defined, the content uniformity of the firm's test product is acceptable. The firm will not be asked to provide the mean and %CV of the bio batch of the test product.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No .022-08			
		Treatment Groups	
		Test Product N=67	Reference Product N=67
Age (years)	Mean ± SD	24.6 ± 4.43	24.6 ± 4.43
	Range	18 - 39	18 - 39
Age Groups	< 18	0(0%)	0(0%)
	18 – 40	67 (100 %)	67 (100 %)
	41 – 64	0(0%)	0(0%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	67 (100 %)	67 (100 %)
	Female	0(0%)	0(0%)
Race	Asian	67 (100 %)	67 (100 %)
	Black	0(0%)	0(0%)
	Caucasian	0(0%)	0(0%)
	Hispanic	0(0%)	0(0%)
	Other	0(0%)	0(0%)
BMI	Mean ± SD	21.25 ± 1.966	21.25 ± 1.966
	Range	18.6-24.9	18.6-24.9
Other Factors		Nil	Nil

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No: 022-08						
Subject Number	**Reason for dropout/replacement**	**Period**	**Time of dropout**	**Treatment missed**	**Replaced?**	**Replaced with**
04	Subject withdrawn due to Emesis during period 01 in-house.	01	Subject was withdrawn from the study at 10.18 hrs on 01 July 08	R	No	NA
10	Subject withdrawn due to Emesis during period 01 in-house.	01	Subject was withdrawn from the study at 12.20 hrs on 01 July 08	R	No	NA
01	Subject withdrawn due to AE (Road traffic accident) during	02		R		

	period 02 check-in, and hence considered as drop-out.		NA		No	NA
45	Subject failed to report to the facility for period 02 check-in, and hence considered as drop-out.	02	NA	R	No	NA
62	Subject failed to report to the facility for period 02 check-in, and hence considered as drop-out.	02	NA	T	No	NA
73	Subject failed to report to the facility for period 02 check-in, and hence considered as drop-out.	02	NA	T	No	NA
54	Subject tested positive for Benzodiazepines at period 02 check-in and hence considered as drop out.	02	NA	R	No	NA
58	Subject tested positive for Benzodiazepines at period 02 check-in and hence considered as drop out.	02	NA	T	No	NA
60	Subject tested positive for Benzodiazepines at period 02 check-in and hence considered as drop out.	02	NA	T	No	NA

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body system/adverse event	Reported incidence by treatment groups		
	Fasting condition bioequivalence study Study No. 022–08 (N=76)		
	Test	Reference	NA[#]
Gastrointestinal Disorders			
Vomiting	2 (2.6%)	-	-
Nervous system disorders			
Headache	2 (2.6%)	-	-
Investigations			
Increased eosinophils	-	-	7 (9.2 %)
Decreased lymphocytes	-	-	1 (1.3%)
Increased SGPT	-	-	3 (3.9 %)
Increased CPK	-	-	7 (9.2 %)
Increased Monocytes	-	-	1 (1.3%)
Increased triglycerides	-	-	1 (1.3%)
RTA (Road Traffic Accident)	1 (1.3%)	-	-
Total	5 (6.6 %)	-	20 (26.32%)

NA[#] - clinically significant abnormal laboratory parameters evaluated during post study safety assessment, which could not be assigned to any one treatment.

N = Number of subjects reported AE/Total number of subjects participated in the study x 100

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Fasting Bioequivalence Study (Study No. 022-08)		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Sampling Time Point Protocol Deviations Period 01	11, 65	07
Sampling Time Point Protocol Deviations Period 02	21, 25, 32, 35 & 38	63
Other Deviations	Nil	

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Two subjects (#4 and #10) experienced emesis in period I at approximately 10 hours and 12 hours, respectively, after the administration of the test product. Both subjects also had headache. Even though the emesis happened after two times of the medians of Tmax of the parent drugs (Tmax=1.5 hours) and two metabolites (Tmax=2 hours and 5 hours, respectively), these two subjects were still dropped out of the study due to the adverse events (emesis and headache). The dropouts of other subjects were due to the non-compliance, except subject #1 who had a road traffic accident during the washout period.

- No serious adverse events were reported. Each during study adverse event was resolved. For the abnormal laboratory parameters evaluated during post study safety assessment, only two subjects came for the following-up and the adverse events were resolved. All other subjects (n=18) were considered as lost to follow up.

- The protocol deviations that occurred during the study were blood sample collection deviations (n=9). Most sample collection time deviations (8 out of 9) were not significant (± 5%). Both the firm and the reviewer used the actual sampling time for the statistical analysis.

- Both the test and the reference products were well tolerated by the healthy volunteers. The dropout of the subjects and the protocol deviations did not compromise the integrity of the study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

a) Atorvastatin

Bioequivalence Study No. 022-08									
Analyte Name: Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.255	0.475	5.275	15.288	49.937	101.406	149.981	193.740	235.387
(Nominal value)	0.250	0.500	4.980	14.930	49.780	99.550	149.330	199.100	248.880
Inter day Precision (%CV)	1.80	3.87	1.46	1.62	1.53	1.54	1.42	1.35	1.91
Inter day Accuracy (%Actual)	102.16	95.00	105.93	102.40	100.31	101.86	100.44	97.31	94.58
Linearity	0.9977-0.9997								
Linearity Range (ng/mL)	0.250-248.880								
Sensitivity/LOQ (ng/mL)	0.250								

Bioequivalence Study No. 022-08				
Analyte Name: Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.748	25.979	81.933	174.184
(Nominal value)	0.750	25.050	80.160	180.360
Inter day Precision (%CV)	3.56	2.62	2.77	2.83
Inter day Accuracy (%Actual)	99.72	103.71	102.21	96.58

b) O-OH-Atorvastatin

Bioequivalence Study No. 022-08									
Analyte Name: O-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.253	0.478	2.445	9.302	31.774	58.920	85.970	112.772	144.546
(Nominal value)	0.250	0.490	2.460	9.850	29.550	59.100	83.730	113.280	147.750
Inter day Precision (%CV)	2.33	4.87	1.70	1.53	1.70	1.89	1.38	1.76	1.69
Inter day Accuracy (%Actual)	101.36	97.55	99.37	94.43	107.52	99.70	102.68	99.55	97.83
Linearity	0.9942-0.9995								
Linearity Range (ng/mL)	0.250-147.750								
Sensitivity/LOQ (ng/mL)	0.250								

Bioequivalence Study No. 022-08				
Analyte Name: O-OH-Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.763	19.029	48.766	102.766
(Nominal value)	0.760	20.140	50.350	105.740
Inter day Precision (%CV)	5.70	3.24	3.86	3.69
Inter day Accuracy (%Actual)	100.42	94.48	96.85	97.19

c) P-OH-Atorvastatin

Bioequivalence Study No. 022-08									
Analyte Name: P-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.051	0.094	0.501	0.997	1.985	3.980	5.683	7.894	9.950
(Nominal value)	0.050	0.100	0.490	0.980	1.970	3.940	5.910	7.880	9.850
Inter day Precision (%CV)	3.13	6.17	3.61	4.07	3.03	3.01	4.14	3.42	2.94
Inter day Accuracy (%Actual)	102.40	94.00	102.22	101.70	100.76	101.03	96.16	100.18	101.01
Linearity	0.9956-0.9997								
Linearity Range (ng/mL)	0.050-9.850								
Sensitivity/LOQ (ng/mL)	0.050								

Bioequivalence Study No. 022-08				
Analyte Name: P-OH-Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.144	1.518	3.440	7.431
(Nominal value)	0.150	1.490	3.480	7.160
Inter day Precision (%CV)	7.87	4.59	5.19	5.02
Inter day Accuracy (%Actual)	95.67	101.87	98.84	103.78

Comments on Study Assay Validation: Incomplete due to deficiencies stated in section 3.10 Deficiency Comments.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

The chromatograms are **adequate**.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	08/06/2007	Sample reassay and reporting of final concentration

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Uncertain
Did recalculation of PK parameters change the study outcome?	Uncertain
Does the reviewer agree with the outcome of the repeat assays?	Uncertain
If no, reason for disagreement	Please see section 3.6 of this review.

Summary/Conclusions, Study Assays:

The study assay is **inadequate** due to deficiencies stated in section 3.10.

Please note that the information below is obtained based on the assumption that the firm's repeated assays are acceptable, and the reviewer used the firm's repeated assay values for the calculation. The PK parameter calculation results may change upon the DBE's receipt of additional information and re-evaluation of the firm's repeated assays.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Parent Drug:

Fasting Bioequivalence Study, Study No. 022-08 Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	352.65	43.87	122.67	914.94	337.95	46.53	131.84	868.70	1.04
AUC∞ (hr *ng/ml)	356.50	43.46	125.70	917.96	342.20	46.59	134.18	891.79	1.04
Cmax (ng/ml)	89.22	53.80	18.45	248.50	80.52	45.28	25.86	216.57	1.11
Tmax* (hr)	1.50	.	0.33	5.00	1.00	.	0.33	5.00	1.50
Kel (hr^{-1})	0.15	26.80	0.04	0.21	0.13	28.76	0.04	0.20	1.09
T1/2 (hr)	5.34	44.73	3.35	16.69	5.80	41.20	3.54	16.13	0.92

Tmax values are presented as median, range

Supportive Metabolites:

1. Orthohydroxy Atorvastatin

Fasting Bioequivalence Study, Study No. 022-08 Orthohydroxy Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	318.82	41.56	109.94	922.41	300.41	39.67	135.95	870.38	1.06
AUC∞ (hr *ng/ml)	323.80	40.83	119.03	925.06	306.44	38.94	141.77	872.77	1.06
Cmax (ng/ml)	50.28	57.38	8.71	147.43	44.01	45.92	14.68	117.32	1.14
Tmax* (hr)	2.00	.	0.33	8.00	2.00	.	0.67	5.00	1.00
Kel (hr^{-1})	0.11	19.96	0.06	0.19	0.11	23.27	0.05	0.20	1.03
T1/2 (hr)	6.69	19.48	3.61	10.70	6.70	25.07	3.42	13.36	0.96

Fasting Bioequivalence Study, Study No. 022-08 Parahydroxy Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	73.18	44.09	25.86	191.38	66.28	45.56	19.80	158.22	1.10
AUC∞ (hr *ng/ml)	78.61	41.13	33.26	195.30	70.73	44.24	22.09	160.36	1.11
Cmax (ng/ml)	4.59	66.22	1.00	16.73	3.70	60.83	0.71	11.31	1.24
Tmax* (hr)	5.00	.	1.00	16.00	5.00	.	0.33	16.00	1.00
Kel (hr^{-1})	0.04	27.95	0.02	0.06	0.04	24.98	0.02	0.06	0.98
T1/2 (hr)	19.30	36.13	11.66	39.98	18.50	30.15	11.17	43.22	1.04

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Parent Drug:

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 022-08				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	325.18	308.06	1.06	99.01-112.53
AUC∞ (hr *ng/ml)	329.35	312.27	1.05	98.97-112.39
Cmax (ng/ml)	78.65	73.27	1.07	94.47-121.99

Supportive Metabolites:

1. Orthohydroxy Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means and Ratio of Means					
Fasting Bioequivalence Study (Study No. 022-08)					
Parameter	Geometric Mean		Test	Reference	Ratio
	T	R			
C_{max} (ng/mL)	42.67	40.30	42.64	40.29	105.84
AUC_{0-t} (ng*h/mL)	295.44	281.42	295.44	280.94	105.16
AUC_{0-INF} (ng*hr/mL)	300.52	287.14	300.52	286.65	104.84

2. Parahydroxy Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means and Ratio of Means					
Fasting Bioequivalence Study (Study No. 022-08)					
Parameter	Geometric Mean		**Test**	**Reference**	**Ratio**
	T	R			
C_{max} (ng/mL)	3.8524	3.1621	3.8505	3.1589	121.89
AUC_{0-t} (ng*h/mL)	67.0632	59.9177	67.1155	59.8105	112.21
AUC_{0-INF} (ng*hr/mL)	71.8432	63.9183	71.4105	63.8112	111.91

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Parent Drug;

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 022-08					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	325.18	308.06	1.06	99.01	112.53
AUC∞ (hr *ng/ml)	329.12	312.10	1.05	98.97	112.37
Cmax (ng/ml)	78.65	73.27	1.07	94.47	121.99

Supportive Metabolites;

1. Orthohydroxy Atorvastatin

Orthohydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 022-08					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	295.44	280.94	1.05	99.25	111.43
AUC∞ (hr *ng/ml)	300.91	287.17	1.05	98.96	110.95
Cmax (ng/ml)	42.64	40.29	1.06	94.42	118.65

2. **Parahydroxy Atorvastatin**

Parahydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 022-08					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	67.12	59.81	1.12	105.74	119.09
AUC∞ (hr *ng/ml)	72.50	64.23	1.13	106.94	119.15
Cmax (ng/ml)	3.85	3.16	1.22	108.46	136.99

Table 17. Additional Study Information, Fasting Study No. 022-08

Parent Drug: Atorvastatin

Root mean square error, AUC0-t	0.2219	
Root mean square error, AUC∞	0.2202	
Root mean square error, Cmax	0.4432	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	67	67
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	67	0.99	0.91	1.00
Reference	67	0.99	0.94	1.00

Supportive Metabolites:

A. Orthohydroxy Atorvastatin

Root mean square error, AUC0-t	0.2009	
Root mean square error, AUC∞	0.1984	
Root mean square error, Cmax	0.3962	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	67	67
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	67	0.98	0.92	1.00
Reference	67	0.98	0.89	1.00

B. Parahydroxy Atorvastatin

Root mean square error, AUC0-t	0.2062	
Root mean square error, AUC∞	0.1875	
Root mean square error, Cmax	0.4051	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	66	67
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	66	0.93	0.77	0.99
Reference	67	0.93	0.69	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer use SAS code 'CALKE' for the statistical analysis. The calculation of the elimination rate constant (Kel) was based on the concentrations of the samples in the terminal log-liner phase of each individual subject.

- The firm did not calculate the 90% CIs of the metabolites, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin. Instead, the firm calculated the geometric means and the T/R ratios of the PK parameters. For both metabolites, the point estimates for all PK parameters were within the range of 0.80-1.25.

- The review calculated the 90% CIs for all PK parameters of the metabolites and found that the 90% CI for Cmax of para-hydroxyatorvastatin was not within the range of 80-125% (108.46-136.99). This is due to (1) high intrasubject variability of the para-hydroxyatorvastatin for Cmax (40.51%), (2) low plasma levels of the para-hydroxyatorvastatin as compared to the atorvastatin and ortho-hydroxyatorvastatin. According to the current BE Guidance for Atorvastatin Calcium Tablets, the bioequivalence of the drug product should be based on the 90% CIs of the parent drug (atorvastatin). For current study, the 90% CIs of the parent drug all within the acceptance range. Therefore, the statistical results for the fasting study are still acceptable. Similar observations were seen in ANDA 078773 for the same drug product, in which the 90% CI of para-hydroxyatorvastatin for Cmax was not within 80-125% and the study was found still acceptable (DARRTS, ANDA 078773, REV-BIOEQ-01, check in date: 3/10/2008).

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The study is **inadequate** due to deficiencies noted in Section 3.10 (Deficiency Comments).

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Parent drug: Atorvastatin:

	Test (n=67)		Reference (n=67)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.16	2.32	400.37	1.84	199.78	1.26
0.33	11.64	150.11	27.16	122.88	0.43
0.50	24.17	105.37	48.46	84.32	0.50
0.67	36.10	113.98	51.31	72.11	0.70
0.83	41.85	101.56	50.18	66.85	0.83
1.00	46.72	100.03	47.38	61.21	0.99
1.25	54.56	97.71	46.84	55.16	1.16
1.50	56.91	88.02	45.17	48.83	1.26
2.00	56.07	79.06	42.39	49.09	1.32
2.50	50.83	68.07	40.94	62.99	1.24
3.00	41.62	61.43	37.50	64.52	1.11
4.00	33.94	54.51	33.18	77.84	1.02
5.00	29.13	47.85	28.33	65.66	1.03
6.00	21.26	47.39	20.21	56.16	1.05
8.00	13.74	51.24	13.57	58.84	1.01
10.00	9.97	53.73	9.51	61.20	1.05
12.00	7.03	64.86	6.77	64.80	1.04
16.00	3.93	60.83	3.99	71.92	0.98
30.00	1.18	74.92	1.22	88.15	0.96
36.00	0.51	114.25	0.51	126.12	1.02
48.00	0.12	237.84	0.13	237.19	0.92
72.00	0.01	818.54	0.02	812.40	0.55

Supportive Metabolites:

1. Ortho-hydroxy Atorvastatin

	Test (n=67)		Reference (n=67)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.16	0.35	694.03	0.11	362.02	3.29
0.33	2.26	313.16	4.00	139.59	0.56
0.50	6.45	138.55	13.20	100.26	0.49

	Test (n=67)		Reference (n=67)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.67	13.54	128.99	20.47	87.49	0.66
0.83	19.34	120.79	25.03	78.61	0.77
1.00	24.48	109.65	25.93	72.00	0.94
1.25	30.57	99.50	27.82	61.40	1.10
1.50	34.26	88.21	28.90	50.97	1.19
2.00	36.52	80.47	29.83	46.67	1.22
2.50	36.62	70.70	29.88	50.75	1.23
3.00	33.37	65.64	28.84	52.81	1.16
4.00	30.25	59.49	28.09	59.21	1.08
5.00	25.62	44.47	24.62	56.56	1.04
6.00	21.26	44.63	20.05	51.13	1.06
8.00	16.09	42.28	15.75	53.94	1.02
10.00	12.58	40.57	11.83	45.17	1.06
12.00	9.19	40.62	8.76	48.93	1.05
16.00	4.94	39.61	4.86	44.98	1.02
30.00	1.53	42.52	1.52	50.80	1.01
36.00	0.72	54.19	0.72	57.30	1.00
48.00	0.11	171.10	0.11	215.18	1.01
72.00	0.00	.	0.00	.	.

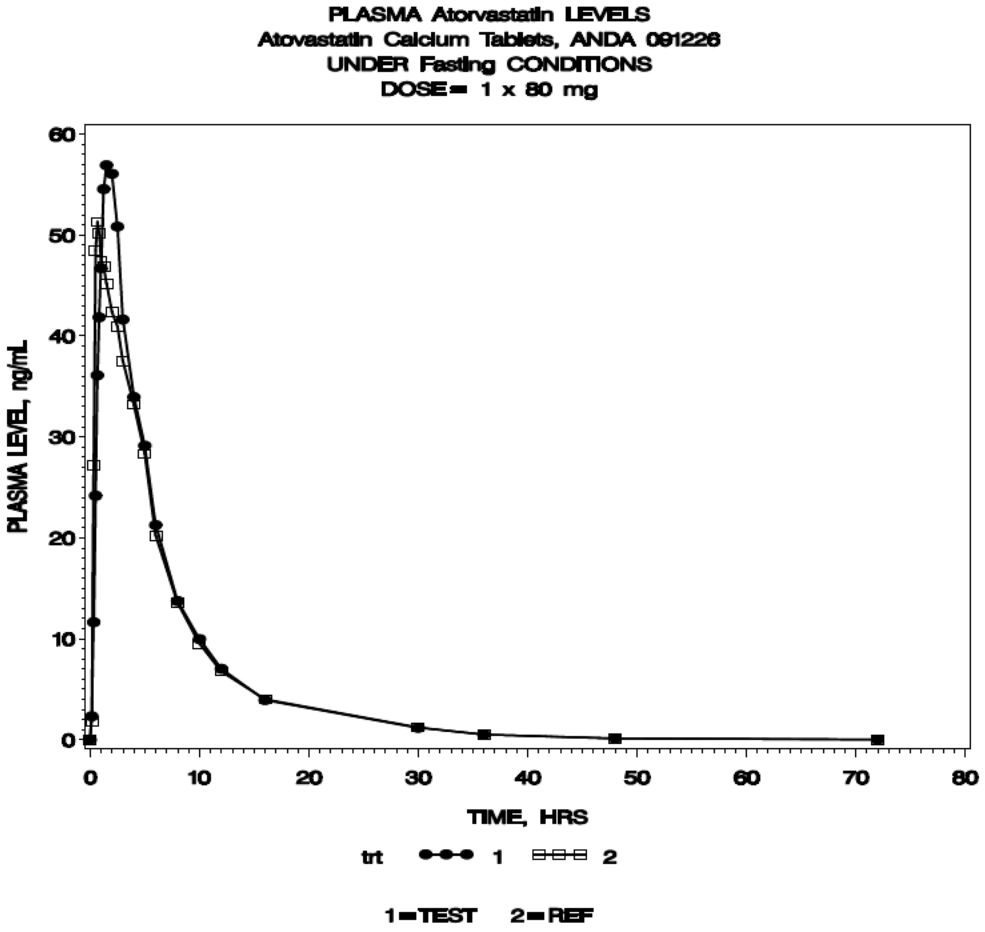
2. Para-hydroxy Atorvastatin:

	Test (n=67)		Reference (n=67)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.16	0.02	692.95	0.00	595.35	4.60
0.33	0.11	326.57	0.26	188.48	0.42
0.50	0.32	151.30	0.67	118.99	0.47
0.67	0.67	158.12	0.93	103.01	0.72
0.83	0.92	142.72	1.07	98.73	0.86
1.00	1.20	131.03	1.14	88.61	1.05
1.25	1.67	126.22	1.30	82.66	1.29
1.50	2.04	113.57	1.44	82.91	1.41
2.00	2.59	111.74	1.75	75.05	1.48
2.50	2.98	101.41	2.01	77.63	1.48
3.00	3.06	90.42	2.28	71.82	1.34
4.00	3.53	81.07	2.68	74.96	1.32

	Test (n=67)		Reference (n=67)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
5.00	3.40	57.05	2.82	63.21	1.21
6.00	3.01	53.65	2.65	56.53	1.13
8.00	2.91	52.34	2.63	61.39	1.11
10.00	2.83	48.37	2.50	51.88	1.13
12.00	2.57	50.85	2.25	53.04	1.14
16.00	1.88	53.23	1.79	48.30	1.05
30.00	0.91	46.64	0.87	47.43	1.05
36.00	0.65	51.28	0.62	58.89	1.04
48.00	0.32	50.17	0.34	65.68	0.94
72.00	0.14	63.45	0.13	71.54	1.06

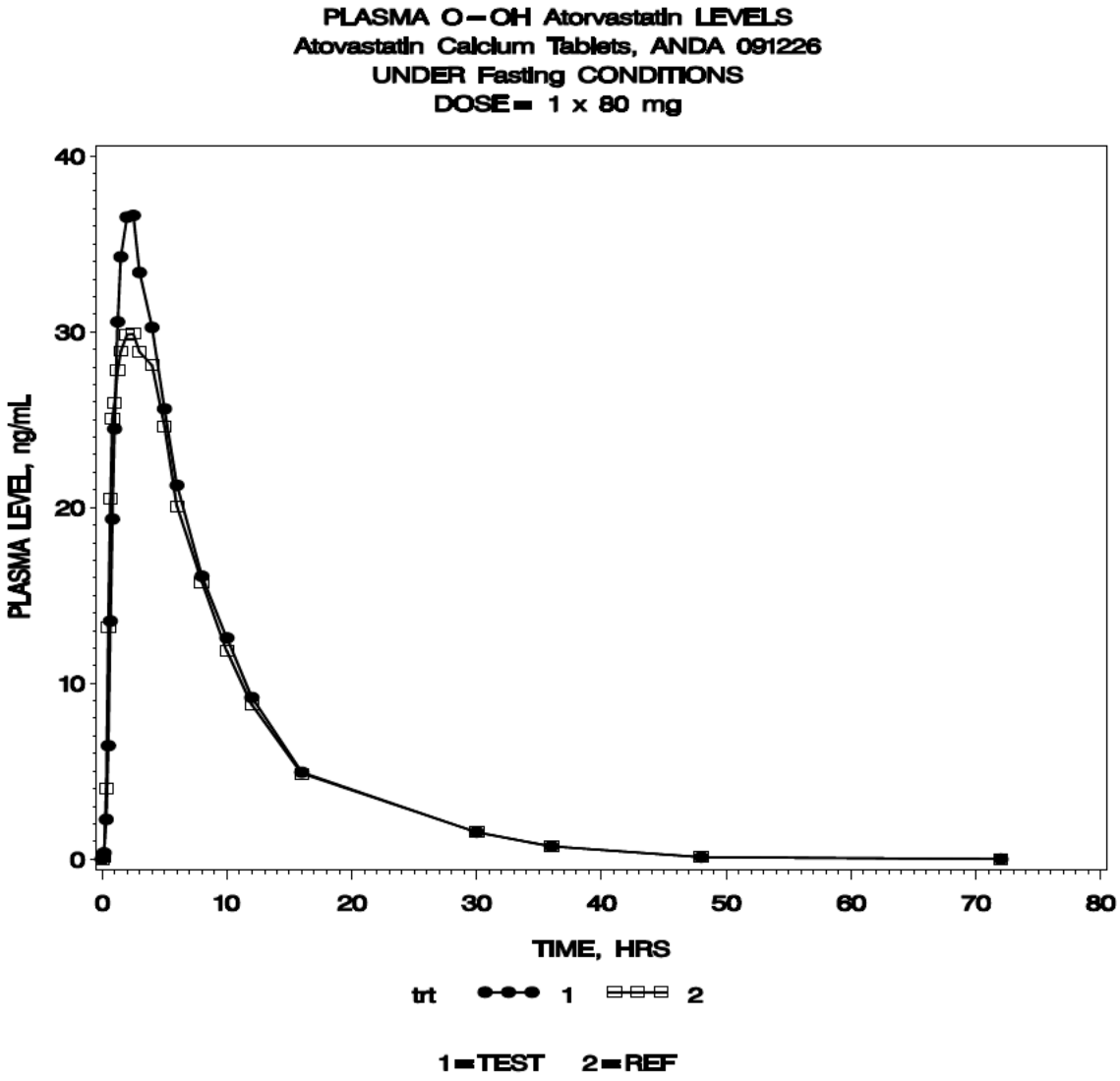
Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Parent drug: Atorvastatin

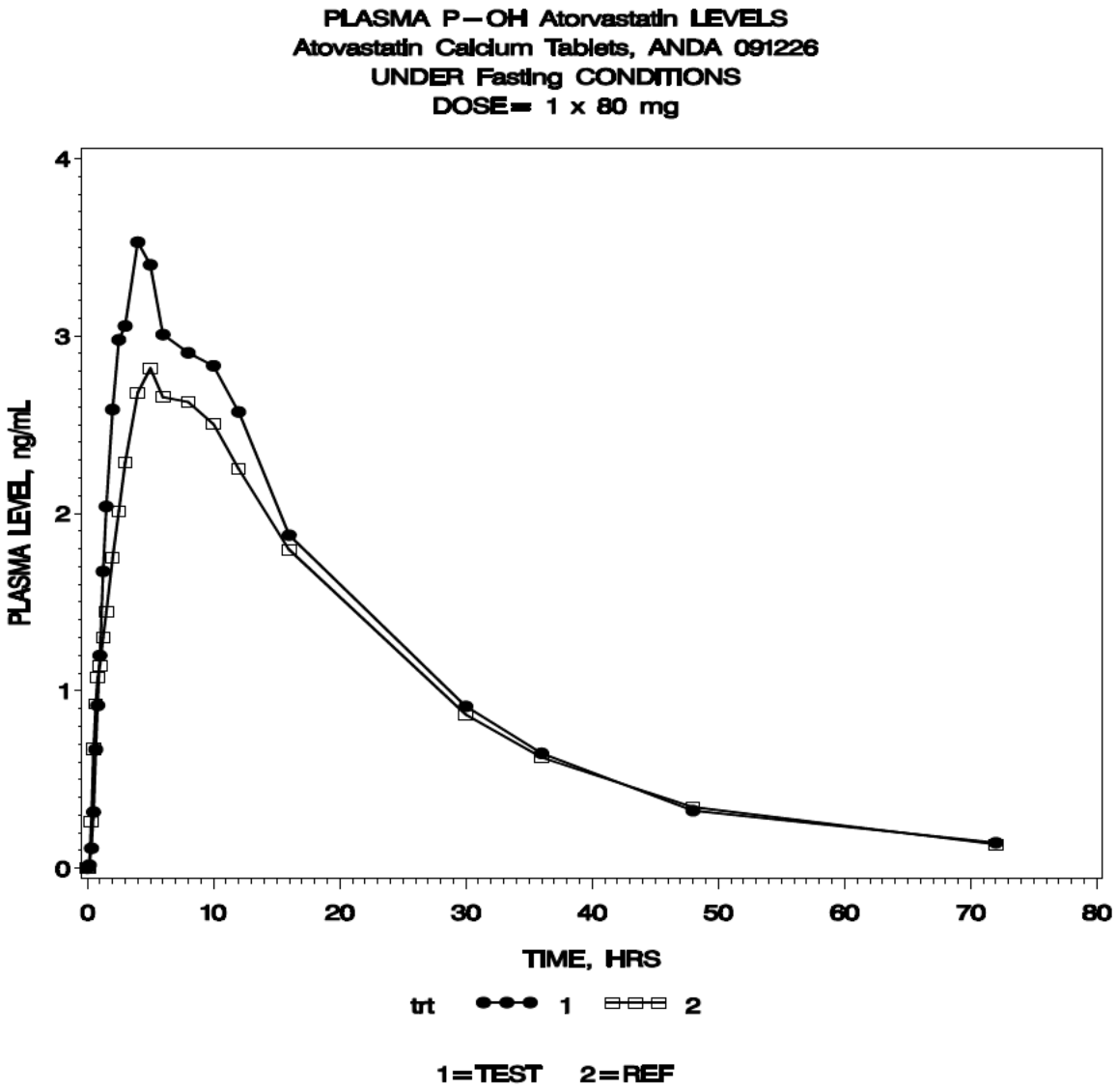


Supportive Metabolites:

A. Orthohydroxy Atorvastatin



B. Parahydroxy Atorvastatin



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	162-08
Study Title	A Randomized open label, balanced, two treatment, two sequence, two period, single dose, crossover comparative oral bioavailability study of Atorvastatin calcium tablets 80 mg with that of Lipitor® (Atorvastatin calcium) 80 mg in normal, healthy, adult, human subjects under fed conditions.
Clinical Site (Name, Address, Phone #)	GVK Biosciences Pvt Limited., 7th Floor Swarna jayanthi Commercial Complex, Ameerpet, Hyderabad-500037, India, Tel: +91-40-66275566, Fax: +91-40-66275599
Principal Investigator	Naba Kr. Talukdar, MD
Dosing Dates	Period 01: 13 Sep 2008 Period 02 : 28 Sep 2008
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	Analysis Start Date: 14th Oct 2008 Analysis End Date: 10th Nov 2008
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	58 days (13 Sep 2008 to 10th Nov 2008)

Table 20. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Atorvastatin Calcium Tablets 80 mg	Lipitor® (atorvastatin calcium) tablets 80 mg
Manufacturer	Matrix Laboratories Limited (A Subsidiary of MYLAN Laboratories Inc.) F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik-422 113, Maharashtra, INDIA	Manufactured by: Pfizer Ireland Pharmaceuticals Dublin, Ireland Distributed by: Parke-Davis, Division of Pfizer Inc, NY, NY

		10017
Batch/Lot No.	1004891	17995V
Manufacture Date	MAY 2008	N/A
Expiration Date	APR.2010	SEP 08
Strength	80 mg	80 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	(b) (4)	(b) (4)
Content Uniformity (mean, %CV)	(b) (4) @	N/A
Dose Administered	1 x 80mg (one tablet)	1 x 80mg (one tablet)
Route of Administration	Oral	Oral

@ The current USP requires expression of content uniformity as a "AV" value. The expression using mean and % CV is redundant

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Enrolled:60 Completed: 56 Used in statistical analysis: 56
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	15 days
Randomization Scheme	TR: 2, 3, 5, 8, 9, 12, 14, 15, 17, 19, 22, 23, 26, 27, 29, 31, 33, 35, 37, 40, 41, 44, 46 47, 49, 51, 53, 55, 58, 59 RT:1, 4, 6, 7, 10, 11, 13, 16, 18, 20, 21, 24, 25, 28, 30, 32, 34, 36, 38, 39, 42, 43, 45, 48, 50, 52, 54, 56, 57, 60 (note: the drop-out subjects were marked as yellow)
Blood Sampling Times	Blood samples (1 x 5 mL) were collected in blood collection tubes containing K3EDTA before dosing (hour 0) and at the following times thereafter: 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose.
Blood Volume Collected/Sample	10 ml for predose and 7 ml for pos dose/sample
Blood Sample Processing/Storage	At each time point, the blood samples were collected in pre-labeled vacuettes/vacutainers containing K_3EDTA as anticoagulant. After collection, samples were centrifuged with set condition at 3000 rpm for 10 minutes and at 4°C. After centrifugation the plasma samples were separated and transferred into respective prelabeled polypropylene tubes in duplicate (set #01 & set #02). These polypropylene tubes were stored below -20°C for a maximum period of 12 hours and then they were stored at -70°C ±20°C until shipped for analysis. Sample collection and separation were done under condition with minimal exposure to ultraviolet light.
IRB Approval	Yes: 09/09/2008
Informed Consent	Yes: 09/09/2008
Length of Fasting Before Meal	At least 10 hours prior to a high fat vegetarian breakfast.
Length of Confinement	Not less than 10.5 hours pre-dose till at least 24 hours post-dose in each period.
Safety Monitoring	Clinical examination were carried out and recorded at check-in and at checkout. Vital signs measurement were carried out and recorded at check in, before dosing of investigational products and at checkout. Vital signs were measured and recorded 1, 2, 3, and 4 hours after dosing, within ±30 minutes of scheduled time.

Standard FDA Meal Used?	No	
Composition of Meal Used in Fed Bioequivalence Study (Study No. 162-08)		
Composition	**Percent of total Kcal**	**Kcal**
Protein	15.45	146.20
Fat	54.94	519.75
Carbohydrates	29.60	280.04

Total Energy (Kcal)		945.99

Comments on Study Design:

The firm did not provide the mean and % CV of the content uniformity for the bio batch of the test products. Instead, the firm provided the calcucated Acceptance Value (AV = (b)(4)%) which is within the limit of the AV ((b)(4)%) as defined by the Charpter <905> of USP. Since the calculation of the AV is based on the mean and %CV and the AV of the bio batch of the test product was less than the maximum allowable value ((b)(4)%) that USP defined, the content uniformity of the firm's test product is acceptable. The firm will not be asked to provide the mean and %CV of the bio batch of the test product.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No.162-08			
		Treatment Groups	
		Test Product N =56	Reference Product N =56
Age (years)	Mean ± SD	26.1 ± 4.49	26.1 ± 4.49
	Range	19-40	19-40
Age Groups	< 18	0(0%)	0(0%)
	18 – 40	56 (100 %)	56 (100 %)
	41 – 64	0(0%)	0(0%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	56 (100 %)	56 (100 %)
	Female	0(0%)	0(0%)
Race	Asian	56 (100 %)	56 (100 %)
	Black	0(0%)	0(0%)
	Caucasian	0(0%)	0(0%)
	Hispanic	0(0%)	0(0%)
	Other	0(0%)	0(0%)
BMI	Mean ± SD	21.25 ± 2.013	21.25 ± 2.013
	Range	18.6-24.8	18.6-24.8
Other Factors		Nil	Nil

Table 23. Dropout Information, Fed Bioequivalence Study

Study No:162-08						
Subject Number	**Reason for dropout/replacement**	**Period**	**Time of dropout (hrs.)**	**Treatment missed**	**Replaced?**	**Replaced with**
14	Subject withdrawn due to AE (Abnormal high lab parameters), and hence considered as drop-out.	01	07:30	R	No	NA
56	Subject withdrawn due to AE (Abnormal high lab parameters), and hence considered as drop-out.	01	07:35	T	No	NA
22	Subject failed to report to the facility for period 02 check-in, and hence considered as drop-	02	NA	R	No	NA

	out.					
31	Subject failed to report to the facility for period 02 check-in, and hence considered as drop-out.	02	NA	R	No	NA

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body system/adverse event	Reported incidence by treatment groups		
	Fed condition bioequivalence study		
	Study No. 162–08 (N=60)		
	Test	Reference	NA[#]
Nervous system disorders			
Headache	2 (3.3%)	-	-
Investigations			
Increased serum CPK	2 (3.3%)	-	3 (5.0 %)
Increased SGPT	1 (1.7%)	-	3 (5.0 %))
Increased SGOT	-	-	1 (1.7%)
Increased serum amylase	-	-	1 (1.7%)
Increased serum triglycerides	-	-	1 (1.7%)
Increased total bilirubin	-	1 (1.7%)	-
Total	5 (8.33%)	1 (1.7%)	9 (15.0%)

NA[#] - clinically significant abnormal laboratory parameters evaluated during post study safety assessment, which could not be assigned to any one treatment.

N = Number of subjects reported AE/Total number of subjects participated in the study x 100

Table 25. Protocol Deviations, Fed Bioequivalence Study

Fed Bioequivalence Study (Study No. 162-08)		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Sampling Time Point Protocol Deviations Period 01	41, 44, 59	10, 39, 56

Sampling Time Point Protocol Deviations Period 02	10, 25, 60	41, 55, 59
Other Deviations	Nil	

Comments on Adverse Events/Protocol Deviations:

- No serious adverse events were reported. Each during study adverse event was resolved. For the abnormal laboratory parameters evaluated during post study safety assessment, only two subjects came for the following-up and the adverse events were resolved. All other subjects (n=9) were considered as lost to follow up.

- There were two subjects (#14 and #56) dropped out of the study before period II due to abnormal lab assessment conducted during the washout period[subject #14 had increased serum CPK (creatine phosphokinase) and SGPT (alanine aminotransferase), subject # 56 had increased total Bilirubin].

  - According to the labeling, Atorvastatin, like other statins, occasionally cause myopathy, defined as muscle aches or muscle weakness in conjuction with increases in CPK values > 10 times ULN. Lipitor® therapy should be discontinued if markedly elevated CPK levels occur or mayopathy is diagnosed or suspected.
  - According to the firm's study protocol, lab tests assessment should be conducted at pre-study and within 72 hours after each period. The firm did not include objective criteria of selecting the dropping out subjects based on abnormal lab assessement. However, the two subjects, #14 and 56, were dropped due to the clinically significant CPK and billirubin results as judged by the investigator, and the subject dropping appeared justified.
  - Subject #14 has significant increased CPK level (2137 U/L) which was approximately 10 times of the upper limit of the normal (ULN) range (24-195 U/L), after the period I (dosed with test product).
  - Based on the case report form (CRF) of individual subjects, there were also some other subjects with increased CPK levels exceeding the ULN after period I, but these other levels of CPK were not as high as the level of subject 14 (for example, the CPK level of subject #16 was 410 U/L, the CPK level of subject # 49 was 342 U/L). The firm did not consistently list all of these elevated CPK levels. The firm will be asked to provide a complete list of all adverse events and abnormal laboratory results.
  - Suject 56 was found to have increased serum total bilirubin (1.38 mg/dl) (the normal range is 0.10-1.20 mg/dl). This level was near the level associated with a liver condition called jaundice[8] (i.e., 1.5 mg/dL). The dropping of this subject is acceptable.

[8] See http://en.wikipedia.org/wiki/Jaundice

- Subject #14 and # 56 were not dosed for the period II and the samples of the period I were not analyzed before the subjects were dropped out of the study (The starting date of the bioanalytical study was Oct. 18, 2008 and the two subjects were dropped prior to September 28, 2008 (Day I of Period II)) .

- The protocol deviations that occurred during the study were blood sample collection deviations (n=13). All of the sample collection time deviations were not significant (± 5%). Both the firm and the reviewer used the actual sampling time for the statistical analysis.

- The clinical study is incomplete due to above mentioned deficiencies.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

a) Atorvastatin

Bioequivalence Study No. 162-08									
Analyte Name: Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.252	0.493	5.082	15.151	52.227	98.647	151.225	195.946	240.909
(Nominal value)	0.250	0.500	5.000	15.000	50.000	100.000	150.000	200.000	250.000
Inter day Precision (%CV)	1.07	2.13	3.19	1.65	1.48	2.19	2.46	1.31	2.37
Inter day Accuracy (%Actual)	100.64	98.50	101.65	101.01	104.45	98.65	100.82	97.97	96.36
Linearity	0.9983-0.9997								
Linearity Range (ng/mL)	0.250-250.000								
Sensitivity/LOQ (ng/mL)	0.250								

Bioequivalence Study No. 162-08				
Analyte Name: Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.722	27.070	83.220	170.425
(Nominal value)	0.750	25.060	80.200	180.450
Inter day Precision (%CV)	2.89	1.89	1.86	1.73
Inter day Accuracy (%Actual)	96.32	108.02	103.77	94.44

b) O-OH-Atorvastatin

Bioequivalence Study No. 162-08									
Analyte Name: O-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.250	0.499	2.547	9.764	31.428	60.753	83.639	110.370	142.421
(Nominal value)	0.250	0.500	2.480	9.920	29.760	59.520	84.320	114.080	148.800
Inter day Precision (%CV)	1.72	3.53	3.75	2.49	2.24	4.14	1.80	1.41	2.52
Inter day Accuracy (%Actual)	99.84	99.82	102.68	98.43	105.60	102.07	99.19	96.75	95.71
Linearity	0.9962-0.9997								
Linearity Range (ng/mL)	0.250-148.800								
Sensitivity/LOQ (ng/mL)	0.250								

Bioequivalence Study No. 162-08				
Analyte Name: O-OH-Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.717	19.114	49.442	97.940
(Nominal value)	0.750	19.910	49.780	104.530
Inter day Precision (%CV)	3.67	2.46	2.22	2.45
Inter day Accuracy (%Actual)	95.60	96.00	99.32	93.70

c) P-OH-Atorvastatin

Bioequivalence Study No. 162-08									
Analyte Name: P-OH-Atorvastatin									
Parameter	**Standard Curve Samples**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Mean Concentration (ng/mL)	0.050	0.098	0.508	0.958	2.143	4.028	5.948	7.898	9.648
(Nominal value)	0.050	0.100	0.500	0.990	2.000	3.990	5.990	7.980	9.980
Inter day Precision (%CV)	2.39	5.49	6.48	3.82	3.15	2.46	2.72	3.58	3.10
Inter day Accuracy (%Actual)	100.40	98.40	101.50	96.81	107.16	100.94	99.30	98.97	96.68
Linearity	0.9970-0.9995								
Linearity Range (ng/mL)	0.050-9.980								
Sensitivity/LOQ (ng/mL)	0.050								

Bioequivalence Study No. 162-08				
Analyte Name: P-OH-Atorvastatin				
Parameter	**Quality Control Samples**			
	QC Low (ng/ml)	**QC Medium (ng/ml)**	**QC Medium (ng/ml)**	**QC High (ng/ml)**
Mean Concentration (ng/mL)	0.145	1.446	3.464	6.930
(Nominal value)	0.150	1.500	3.510	7.210
Inter day Precision (%CV)	7.72	4.48	4.77	4.73
Inter day Accuracy (%Actual)	96.67	96.37	98.69	96.12

Comments on Study Assay Validation: Incomplete due to the deficiencies mentioned in section 3.10 Deficiency Comments.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

The chromatograms are **acceptable**.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	08/06/2007	Sample Reassay and Reporting of Final concentration

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Uncertain
Did recalculation of PK parameters change the study outcome?	Uncertain
Does the reviewer agree with the outcome of the repeat assays?	Uncertain
If no, reason for disagreement	Please see section 3.6 of this review.

Summary/Conclusions, Study Assays:

The study assay is **inadequate** due to deficiencies listed in Section 3.10 (Deficiency Comments).

Please note that the information below is obtained based on the assumption that the firm's repeated assays are acceptable, and the reviewer used the firm's repeated assay values for the calculation. The PK parameter calculation results may change upon the DBE's receipt of additional information and re-evaluation of the firm's repeated assays.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in

Table 33 and Figure 2

Parent Drug:

Fed Bioequivalence Study, Study No. 162-08 Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	264.82	36.90	101.03	654.64	284.00	43.23	106.86	768.26	0.93
AUC∞ (hr *ng/ml)	270.42	36.27	108.13	658.58	289.49	42.45	110.37	771.89	0.93
Cmax (ng/ml)	52.60	49.59	17.62	165.21	58.94	69.64	14.84	200.81	0.89
Tmax* (hr)	3.50	.	1.50	5.00	3.25	.	1.25	6.00	1.08
Kel (hr^{-1})	0.096	37.16	0.05	0.18	0.09	44.20	0.04	0.26	1.05
T1/2 (hr)	8.17	32.91	3.84	15.00	8.71	33.02	2.67	15.99	0.94

Tmax values are presented as median, range

Supportive Metabolites:

1. Orthohydroxy Atovastatin:

Fed Bioequivalence Study, Study No. 162-08 Orthohydroxy Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	192.13	31.97	94.74	395.47	211.73	31.94	91.17	445.06	0.91
AUC∞ (hr *ng/ml)	198.92	30.62	110.18	401.43	218.31	30.94	100.45	452.72	0.91
Cmax (ng/ml)	24.75	39.23	7.78	45.87	28.07	50.68	8.27	73.40	0.88
Tmax* (hr)	5.00	.	1.75	6.00	5.000	.	1.50	6.00	1.00
Kel (hr^{-1})	0.082	33.33	0.04	0.19	0.080	34.01	0.04	0.19	1.02
T1/2 (hr)	9.21	28.04	3.64	19.23	9.390	25.79	3.59	17.00	0.98

2. Parahydroxy Atovastatin:

Fasting Bioequivalence Study, Study No. 162-08 Parahydroxy Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	

AUC0-t (hr *ng/ml)	44.42	54.72	15.93	179.80	47.60	42.04	15.44	121.35	0.93
AUC∞ (hr *ng/ml)	51.16	52.90	18.07	191.42	54.30	41.21	17.89	146.55	0.94
Cmax (ng/ml)	2.37	60.88	0.66	8.06	2.94	64.89	0.57	8.95	0.80
Tmax* (hr)	6.00	.	5.00	12.00	6.00	.	4.00	16.00	1.00
Kel (hr^{-1})	0.029	26.87	0.01	0.04	0.30	27.77	0.01	0.04	1.00
T1/2 (hr)	25.97	32.99	15.49	51.76	26.17	35.83	15.52	55.94	0.99

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Parent Drug: Atorvastatin

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 162-08				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	249.3969	262.2604	95.10	88.88 – 101.74
AUC∞ (hr *ng/ml)	254.7854	268.3049	94.96	88.84 – 101.50
Cmax (ng/ml)	47.3025	49.3465	95.86	86.49 - 106.23

Supportive Metabolites:

A) Ortho hydroxylated Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means and Ratio of Means					
Fed Bioequivalence Study (Study No. 162-08)					
Parameter	Geometric Mean		**Test**	**Reference**	**Ratio**
	T	R			
C_{max} (ng/mL)	22.8342	24.9385	22.8862	24.9801	91.62
AUC_{0-t} (ng*h/mL)	182.8820	201.3834	183.4474	201.7287	90.94
AUC_{0-INF} (ng*hr/mL)	188.7548	207.7753	189.3092	208.1512	90.95

B) Para hydroxylated Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means and Ratio of Means					
Fed Bioequivalence Study (Study No. 162-08)					
Parameter	Geometric Mean		Test	Reference	Ratio
	T	R			
C_{max} (ng/mL)	2.0350	2.4456	2.0403	2.4461	83.41
AUC_{0-t} (ng*h/mL)	40.3879	44.2895	40.4747	44.3457	91.27
AUC_{0-INF} (ng*hr/mL)	45.6101	49.2533	45.6808	49.4030	92.47

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Parent drug:

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 162-08					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	249.53	262.50	0.95	88.92	101.62
AUC∞ (hr *ng/ml)	255.29	268.22	0.95	89.10	101.67
Cmax (ng/ml)	47.30	49.35	0.96	86.49	106.23

Supportive metabolites:

1. Orthohydroxy Atorvastatin:

Orthohydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 162-08					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	183.56	201.98	0.91	85.86	96.20
AUC∞ (hr *ng/ml)	190.92	209.02	0.91	86.56	96.39
Cmax (ng/ml)	22.89	24.98	0.92	84.38	99.47

2. Parahydroxy Atovastatin:

Parahydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 162-08					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	40.47	44.35	0.91	85.02	97.99
AUC∞ (hr *ng/ml)	46.54	50.84	0.92	85.38	98.13
Cmax (ng/ml)	2.04	2.45	0.83	74.41	93.50

Table 32. Additional Study Information

Parent Drug: Atorvastatin

Root mean square error, AUC0-t	0.2110	
Root mean square error, AUC∞	0.2086	
Root mean square error, Cmax	0.3248	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?		
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	56	0.98	0.92	0.99
Reference	56	0.98	0.94	1.00

Supportive Metabolites:

A. Orthohydroxy Atorvastatin

Root mean square error, AUC0-t	0.1798	
Root mean square error, AUC∞	0.1700	
Root mean square error, Cmax	0.2599	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	56	56
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0

Were the subjects dosed as more than one group?	0	0

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	56	0.96	0.78	0.99
Reference	56	0.97	0.88	0.99

B. Parahydroxy Atorvastatin

Root mean square error, AUC0-t	0.2244	
Root mean square error, AUC∞	0.2155	
Root mean square error, Cmax	0.3607	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	55	55
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	55	0.87	0.66	0.97
Reference	55	0.88	0.63	0.97

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer use SAS code 'CALKE' for the statistical analysis. The calculation of the elimination rate constant (Kel) was based on the concentrations of the samples in the terminal log-liner phase of each individual subject.

- The firm did not calculate the 90% CIs of the metabolites, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin. Instead, the firm calculated the geometric means and the T/R ratios of the PK parameters. For both metabolites, the point estimates for all PK parameters were within the range of 0.80-1.25.

- The review calculated the 90% CIs for all PK parameters of the metabolites and found the 90% CI for Cmax of para-hydroxyatorvastatin was not within the range of 80-125% (74.41-93.5%). This is due to (1) high intrasubject variability of the para-hydroxyatorvastatin for Cmax (36.07%), (2) low plasma levels of the para-hydroxyatorvastatin as compared to the atorvastatin and ortho-hydroxyatorvastatin. According to the current BE Guidance for Atovastatin Calcium Tablets, the bioequivalence of the drug product should be based on the

90% CIs of the parent drug (atorvastatin). For current study, the 90% CIs of the parent drug all within the acceptance range. Therefore, the statistical results for the fasting study are still acceptable. Similar observations were seen in ANDA 078773 for the same drug product, in which the 90% CI of para-hydroxyatorvastatin for Cmax was not within 80-125% and the study was found still acceptable (DARRTS, ANDA 078773, REV-BIOEQ-01, check in date: 3/10/2008).

- According to the RLD labeling, food decreases the rate and extent of the drug absorption. Similar observations were seen in the current application.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The study is **inadequate** due to deficiencies noted in Section 3.10 (Deficiency Comments.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Parent Drug: Atovastatin

	Test (n=56)		Reference (n=56)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.23	452.30	0.64	294.47	0.36
1.00	1.17	285.18	3.73	176.89	0.31
1.25	4.28	354.73	10.21	163.65	0.42
1.50	9.10	274.81	18.06	169.90	0.50
1.75	9.98	191.35	20.35	170.81	0.49
2.00	12.47	139.15	24.59	146.86	0.51
2.25	16.45	106.84	27.11	111.03	0.61
2.50	23.31	88.62	31.65	89.43	0.74
2.75	28.67	73.05	35.16	82.42	0.82
3.00	32.44	61.40	36.75	75.91	0.88
3.50	35.51	52.59	37.45	74.80	0.95
4.00	37.84	48.31	41.82	68.50	0.90
5.00	37.35	53.91	38.27	58.93	0.98
6.00	24.11	47.27	24.15	48.20	1.00
8.00	13.41	45.88	13.04	43.95	1.03
10.00	9.04	43.70	8.91	41.18	1.02
12.00	6.60	50.35	6.38	43.06	1.03
16.00	3.67	43.62	3.46	43.18	1.06
24.00	1.21	57.67	1.09	49.43	1.11
36.00	0.63	68.80	0.61	60.60	1.05
48.00	0.21	122.44	0.22	106.35	0.94
72.00	0.00	741.62	0.00	.	.

Supportive Metabolites:

A. Orthohydroxy Atorvastatin

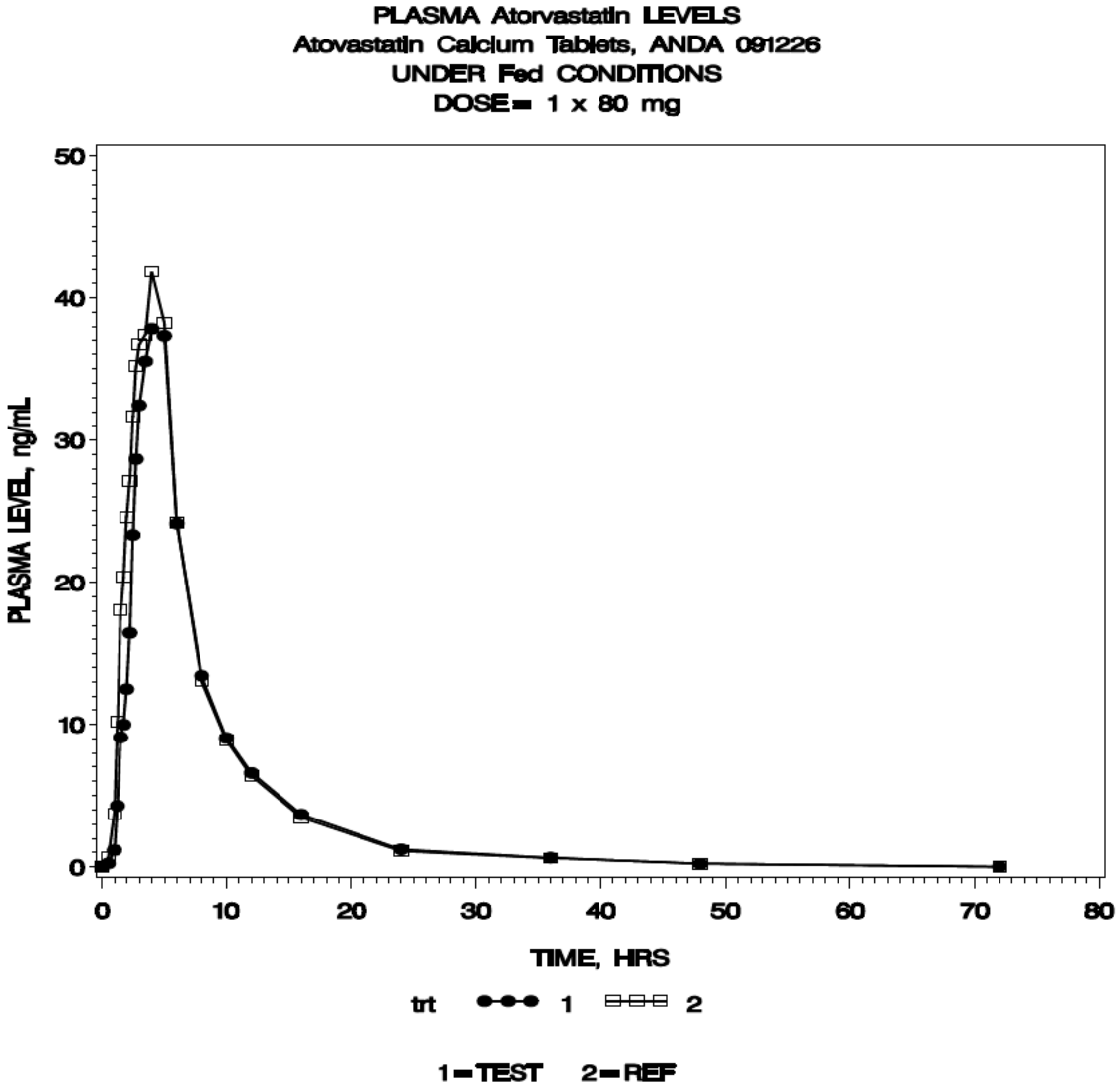
	Test (n=56)		Reference (n=56)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.03	748.33	0.07	693.45	0.52
1.00	0.19	420.74	0.72	221.03	0.26
1.25	0.59	296.39	2.23	182.78	0.27
1.50	1.98	272.37	4.49	160.93	0.44
1.75	2.89	223.28	6.18	153.09	0.47
2.00	3.87	166.77	8.11	140.85	0.48
2.25	5.64	132.56	9.67	112.97	0.58
2.50	8.42	106.66	12.23	87.78	0.69
2.75	10.95	85.72	14.38	74.99	0.76
3.00	13.01	69.08	15.90	63.46	0.82
3.50	17.37	52.30	19.67	52.40	0.88
4.00	19.98	41.41	24.10	55.11	0.83
5.00	22.33	41.73	25.22	50.48	0.89
6.00	18.04	42.06	19.66	45.30	0.92
8.00	12.59	40.54	13.09	38.57	0.96
10.00	8.97	38.33	9.49	38.64	0.95
12.00	6.82	41.60	7.06	34.11	0.97
16.00	3.61	41.47	3.59	33.99	1.00
24.00	1.23	40.23	1.23	33.33	1.00
36.00	0.70	51.57	0.72	47.70	0.98
48.00	0.17	133.51	0.21	111.54	0.82
72.00	0.02	420.48	0.00	.	.

B. Parahydroxy Atovastatin

	Test (n=56)		Reference (n=56)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.00	.	0.00	748.33	0.00
1.00	0.01	492.25	0.02	242.52	0.31
1.25	0.04	445.03	0.09	209.22	0.42
1.50	0.10	367.53	0.17	199.14	0.58
1.75	0.12	304.46	0.23	204.38	0.53
2.00	0.15	251.03	0.33	208.84	0.46
2.25	0.21	182.57	0.40	167.20	0.53
2.50	0.33	138.56	0.52	137.09	0.62
2.75	0.47	118.72	0.68	124.94	0.69
3.00	0.61	103.16	0.79	115.83	0.77
3.50	0.89	81.29	1.10	97.33	0.81
4.00	1.16	61.68	1.62	87.72	0.72
5.00	2.08	62.36	2.60	74.10	0.80
6.00	2.10	63.02	2.39	61.79	0.88
8.00	1.80	64.99	1.96	58.47	0.92
10.00	1.61	59.24	1.74	53.46	0.93
12.00	1.55	65.76	1.64	48.09	0.95
16.00	1.19	76.34	1.15	40.95	1.03
24.00	0.56	57.27	0.55	36.71	1.02
36.00	0.49	51.31	0.53	49.61	0.93
48.00	0.29	60.87	0.33	60.47	0.88
72.00	0.16	61.22	0.16	53.56	1.02

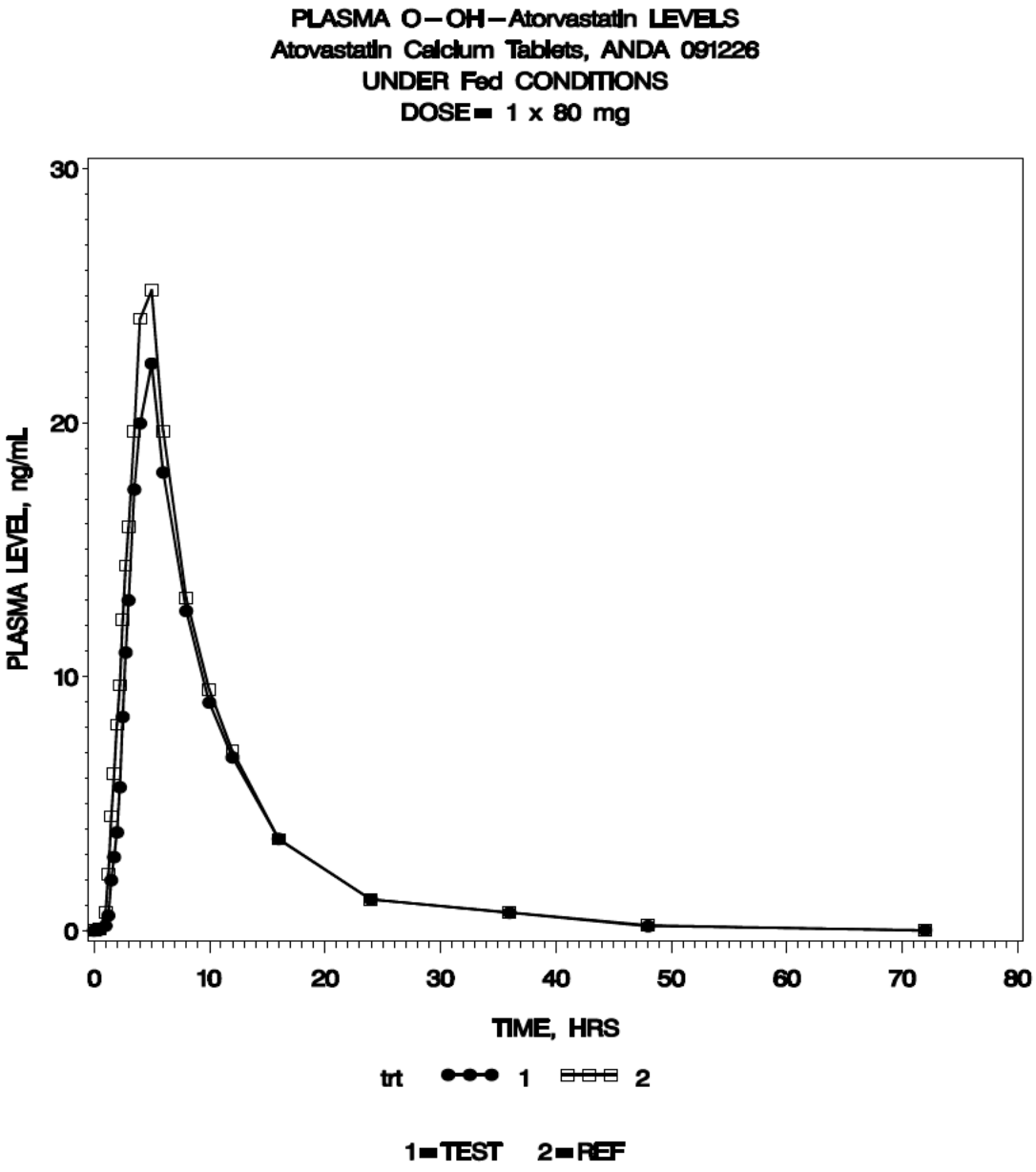
Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Parent Drug: Atorvastatin

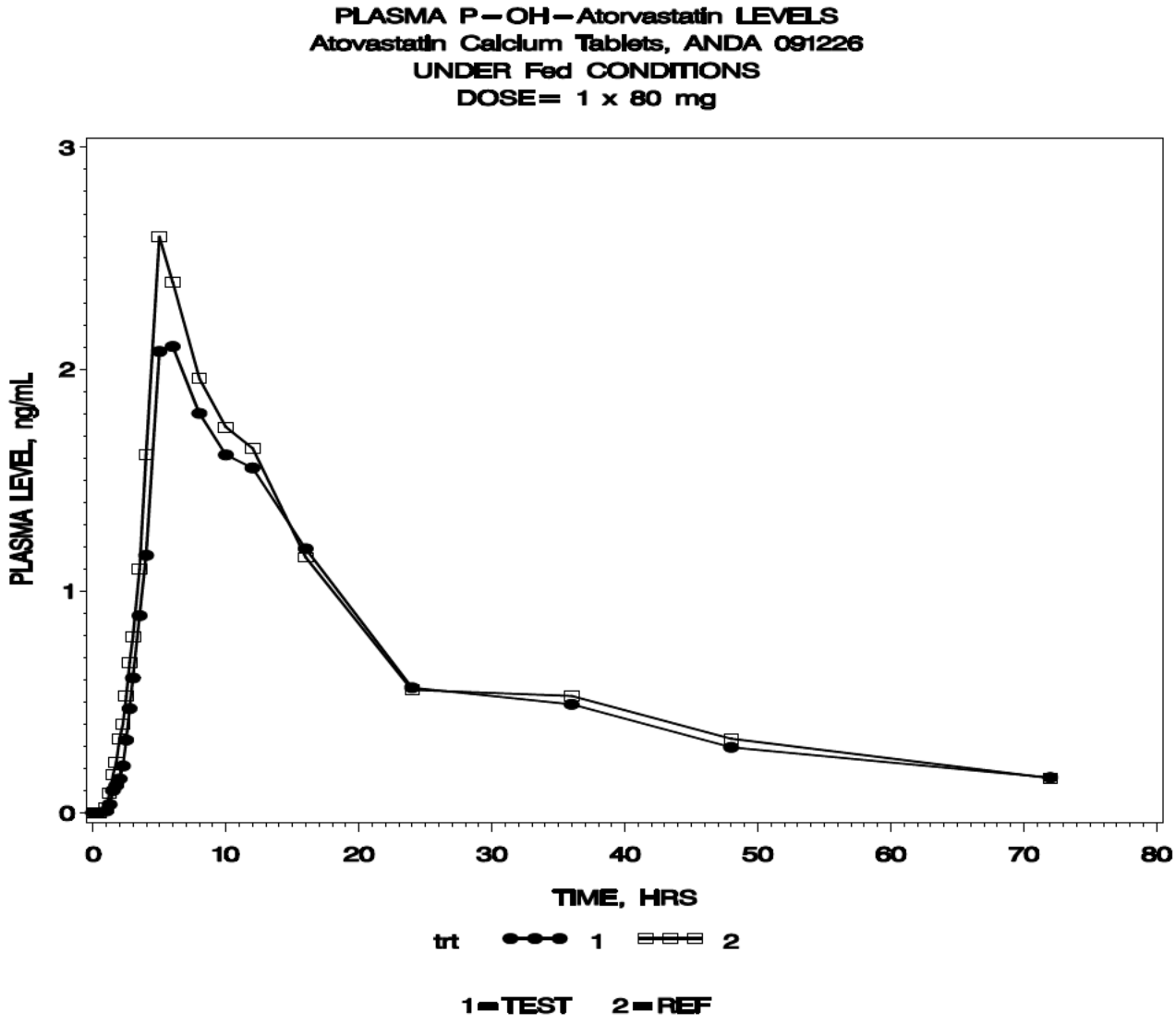


Supportive Metabolites:

A. Orthohydroxy Atorvastatin



B. Parahydroxy Atorvastatin



4.1.3 Single-Does Fed Bioequivalence Study (Failed Study)

The firm's first pivotal fed BE study (study # 023-08) failed due to the 90% CIs of Cmax for the parent drug (atorvastatin) were not within the acceptable range (75.72-93.67%). The firm provided the following justifications for the failed study: *'under fed conditions the AUCT and AUCI for the parent drug and the Cmax, AUCT and AUCI for the metabolites were within the bioequivalence acceptance range. But, the Cmax for the parent atorvastatin was slightly on the lower side of the 90% CI limits. The T/R ratio for Cmax was 84.22%, which is within the acceptable range for T/R ratio, but the 90% confidence interval is out side the acceptance limits and is mainly due to at least three subjects (subject #23, 39 and 51) showed lower T/R ratios in Cmax values as the Reference Cmax value were almost twice the average Cmax values, whereas Test product has shown the values close to the global average. Since absorption is erratic and unpredictable for parent compound, the lower or higher T/R ratios are not surprising. However, for AUC the T/R ratios are close to 100% and the confidence interval limits are well within the limits of 80-125%. Hence the non compliance of the 90% confidence interval is not because of inadequate sample size, it is because of the transient Cmax which is single point estimation'*.

The firm conducted a repeat fed study (study # 162-08, reviewed in the previous section) with the same sample size and design. According to the firm, additional precaution to include the biochemical investigation was done at the time of period II check-in. There were two subjects (#14 and #56) dropped out of the study before period II due to abnormal lab assessment [subject #14 had increased serum CPK (creatine phosphokinase and SGPT (alanine aminotransferase), subject # 56 had increased total Bilirubin] conducted during the washout period. Although the firm did not include objective criteria of excluding subjects with abnormal lab assessment, these two dropped subjects appeared to have clinically significant laboratory results compared with other subjects with abnormal laboratory results. Also, according to the study report, the bioanalytical study was started after the completion of the clinical study (the starting date of the bioanalytical study was Oct. 18, 2008 and the subjects were dropped prior to September 28, 2008 at the start of Period II). Therefore, it is unlikely that the firm analyzed the samples before period II and dropout the subjects with 'abnormal' plasma concentrations. The dropout of the subject #14 was according to the RLD labeling which indicates that Atorvastatin, like other statins, occasionally cause myopathy, defined as muscle aches or muscle weakness in conjuction with increases in CPK values > 10 times ULN. Lipitor® therapy should be discontinued if markedly elevated CPK levels occur or mayopathy is diagnosed or suspected. The CPK level of Subject #14 was 2137 U/L which was higher than the 10 time of the normal upper limit (195 U/L). Subject #56 whose total bilirubin level was 1.38 mg/dl, This level was near the level associated with a liver condition called jaundice (i.e., 1.5 mg/dL). The dropping of this subject is also acceptable.

For the failed study (#023-08), the firm only provided the PK table and summary statistics. The statistic results are shown as followings:

Table – 7: The summary statistics of log transformed primary pharmacokinetic parameters C AUC_{0-t} and AUC_{0-INF} from plasma concentration time profile of Atorvastatin for test and refere formulation are tabulated below:

Product/Statistics		**C_{max} (ng/mL)**	**AUC_{0-t} (ng.hr/mL)**	**AUC_{0-INF} (ng.hr/mL)**
Geometric Mean (T)		51.4144	292.9754	297.8660
Geometric Mean (R)		61.1615	329.6240	334.9502
N	T	59	59	59
	R	59	59	59
Anti log of Least Square Mean				
T		51.4528	292.7259	297.6096
R		61.0963	329.2236	334.5579
T /R Ratio (%)		84.22	88.91	88.96
90% confidence interval (LCL-UCL)		75.72 - 93.67	84.41 - 93.66	84.52 - 93.62
Power (%)		96.4	100.0	100.0
Intra-subject CV (%)		35.6	17.0	16.7
p-value				
Sequence		0.8718	0.1572	0.1604
Period		0.0983	0.4930	0.5513
Formulation		0.0091	0.0004	0.0003

Note: Statistical analysis was done on the log transformed values; the antilog of the mean is reported.

Table – 8: The summary statistics of log transformed primary pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-INF} from plasma concentration time profile of Orthohydroxylated atowastatin for test and reference formulation are tabulated below:

Product/Statistics		**C_{max} (ng/mL)**	**AUC_{0-t} (ng.hr/mL)**	**AUC_{0-INF} (ng.hr/mL)**
Geometric Mean (T)		25.9784	224.5065	230.6759
Geometric Mean (R)		29.1760	244.7652	250.7726
N	T	59	59	59
	R	59	59	59
Anti log of Least Square Mean				
T		26.0201	224.6808	230.8480
R		29.1556	244.7052	250.7116
T /R Ratio (%)		89.25	91.82	92.08
p-value				
Sequence		0.6084	0.7078	0.7175
Period		0.0041	0.0254	0.0261
Formulation		0.0152	0.0019	0.0020

Table – 9: The summary statistics of log transformed primary pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-INF} from plasma concentration time profile of Parahydroxylated atorvastatin for test and reference formulation are tabulated below:

Product/Statistics		**C_{max} (ng/mL)**	**AUC_{0-t} (ng.hr/mL)**	**AUC_{0-INF} (ng.hr/mL)**
Geometric Mean (T)		2.9704	57.7193	63.0775
Geometric Mean (R)		3.3945	60.8510	65.9339
N	T	59	59	56
	R	59	59	58
Anti log of Least Square Mean				
T		2.9709	57.6956	62.7495
R		3.3872	60.7597	65.7234
T /R Ratio (%)		87.71	94.96	95.48
p-value				
Sequence		0.3755	0.2727	0.2402
Period		0.0027	0.0516	0.0852
Formulation		0.0039	0.1152	0.1087

The PK parameters of the failed fed study were very similar to the fed study (#162-08).

The firm indicated that the failed study (#023-08) was designed the same as the repeated study (#162-08) with the same sample size. To evaluate the firm's failed study, the firm should be asked to provide the full study report, which should include the clinical report (with complete adverse events and clinical laboratory results), bioanalytical report and statistical analysis report as well as the study datasets in SAS Transport format.

4.2 Formulation Data

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet
	10 mg	20 mg	40 mg	80 mg	
[redacted]					(b) (4)
Atorvastatin Calcium					(b) (4)
Microcrystalline cellulose (b) (4)					
Colloidal silicon dioxide (b) (4)					
Sodium carbonate anhydrous					
L-Arginine					
Anhydrous lactose (b) (4)					
Croscarmellose sodium (b) (4)					
Hydroxypropyl cellulose (b) (4)					
Magnesium stearate (b) (4)					
(b) (4)					
[redacted]					(b) (4)
[redacted]					(b) (4)
[redacted]					
[redacted]					
[redacted]				

Polyvinyl alcohol	(b) (4)
Titanium dioxide	
Talc	
Lecithin	
Xanthan gum	

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:

- According to the drug labeling, the Maximal Daily Dose (MDD) of the drug product is 80 mg/day. According to the CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products, the inactive ingredients of the test product are all within the IIG limits based on the MDD of the drug products, except L-Arginine which has only been used in approved injectable drug products.

- The OGD requested a pharmacology/toxicology consult for the inactive ingredient L-Arginine, which is present at doses of (b) (4) based on MDD. The pharmacology/toxicology reviewer made the following recommendations to the firm: *'The long term effects of oral L-arginine are unknown. The generic atorvastatin calcium is for chronic use, it is important to know at what doses it produces toxicity, especially in patients with cardiovascular (CV) risk. Therefore, sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease). This data may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use here (* (b) (4) *)'.* [DARRTS, ANDA 091226, REV-NONCLINICAL-03 (General Review), check in date: 6/16/2009].

- The recommendations from Pharmacology/Toxicology Reviewer were sent to the firm in the chemistry deficiency letter on 8/28/2009 [DARRTS, ANDA 091226, COR-ANDAACTION-09 (Complete Response), check in date: 8/28/2009]. The firm included their responses in the Chemistry Amendment with the letter date of 4/8/2010, which was forwarded to the Pharmacology-Toxicology Division for evaluation ([DARRTS, ANDA 091226, FRM-CONSULT-01 (General Consult Request), check in date: 8/10/2010]. Up to date, the Pharmacology/Toxicology review of the firm's response has not been done.

- Therefore, the acceptance of the firm's formulation of the test product can not be determined, pending the evaluation from the Pharmacology/Toxicology Division, regarding the amount of the L-Arginine used in the test product.

4.3 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02(Dissolution Review). 06/16/2009.

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	75 RPM
	Medium:	6.8 pH phosphate buffer (Official medium as per FDA recommendation)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin (b) (4) hould be dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)** 5	10	15	30	45	**Study Report Location**
Study Report #: 022-08 & 162-08	18/05/ 2008	Test Product-Atorvastatin Calcium tablets, 80 mg Batch # 1004891 Mfg date- May 2008	80 mg Tablet	12	Mean	57	96	101	104	105	Module 1.12.15
					Range	(b) (4)					
					%CV	23.2	0.9	1.4	1.3	1.0	
	02/07/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 80 mg) Batch # 10857V Exp date: May 2010	80 mg Tablet	12	Mean	87	91	96	102	101	
					Range	(b) (4)					
					%CV	13.3	17.2	15.3	1.9	4.6	
	21/05/ 2008	Test Product-Atorvastatin Calcium tablets, 10 mg Batch # 1004888 Mfg date- May 2008	10 mg Tablet	12	Mean	70	93	97	102	103	
					Range	(b) (4)					
					%CV	8.7	2.4	2.6	2.5	1.8	
	24/12/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 10 mg) Batch # 13868V Exp date: Aug. 2011	10 mg Tablet	12	Mean	66	74	78	84	97	
					Range	(b) (4)					
					%CV	10.3	6.5	5.8	6.8	4.1	

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	75 RPM
	Medium:	6.8 pH phosphate buffer (Official medium as per FDA recommendation)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin (b) (4) should be dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)** 5	10	15	30	45	**Study Report Location**
Study Report #: 022-08 & 162-08	20/05/ 2008	Test Product-Atorvastatin Calcium tablets, 20 mg Batch # 1004889 Mfg date- May 2008	20 mg Tablet	12	Mean	55	88	95	100	103	Module 1.12.15
					Range	(b) (4)					
					%CV	9.5	1.5	2.1	1.9	2.5	
	23/11/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 20 mg) Batch # 0178017 Exp date: Dec 2009	20mg Tablet	12	Mean	98	104	104	104	104	
					Range	(b) (4)					
					%CV	5.8	0.8	0.6	0.6	0.6	
	19/05/ 2008	Test Product-Atorvastatin Calcium tablets, 40 mg Batch # 1004890 Mfg date- May 2008	40 mg Tablet	12	Mean	44	84	95	101	103	
					Range	(b) (4)					
					%CV	14.0	6.3	1.2	1.7	1.7	
	24/11/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 40 mg) Batch # 0117027 Exp date: Jan 2010	40 mg Tablet	12	Mean	96	102	103	103	101	
					Range	(b) (4)					
					%CV	8.1	0.5	0.7	0.5	3.7	

4.4 Detailed Regulatory History:

The current BE recommendations of the Atorvastatin Calcium Tablets are available on the FDA website for Guidance for Industry: Individual Product Bioequivalence Recommendations. The current recommendations are as follows (Finalized May, 2008):

Contains Nonbinding Recommendations

Guidance on Atorvastatin Calcium

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Atorvastatin Calcium

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 80 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments:

---

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 80 mg
   Subjects: Normal healthy males and females, general population.
   Additional comments:

Analytes to measure: Atorvastatin, ortho- and parahydroxylated metabolites of atorvastatin*

* The ortho- and parahydroxylated metabolites of atorvastatin are formed by presystemic metabolism and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): Atorvastatin

Waiver request of in-vivo testing: 10 mg, 20 mg, and 40 mg based on (i) acceptable bioequivalence studies on the 80 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Finalized May 2008

4.5 Consult Reviews

APPEARS THIS WAY ON THE ORIGINAL

4.6 SAS Outputs (for the parent drug, Atorvastatin only)

4.6.1 Fasting Study Data

(b) (4)



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BIOEQUIVALENCE DEFICIENCIES

ANDA:	091226
APPLICANT:	Matrix Laboratories Limited, India
DRUG PRODUCT:	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. For your pre-study method validation, please specify the salt form of the Ethylenediaminetetraacetic Acid (EDTA), the anticoagulant used in the blank human plasma of the method validation samples.

2. Your repeat analysis for both fasting and fed study is incomplete. Please provide the followings:

    1) For the fasting study (study No. 022-08), please provide the quality control (QC) data of the run for the samples of subject No. 09 to show clearly that the batch was rejected due to the QC data not meeting the acceptance criteria.

    2) For the fed study (study No. 162-08), please provide the original concentrations of atorvastin of subject No. 25 for further evaluation.

    3) Please provide the Standard Operation Procedures (SOP) for the re-integration of the chromatograms. In addition, please provide the concentrations of the three analytes of subject No. 42 and No. 43 in fasting study and subject No. 01 and No. 02 in fed study, obtained using the original integration parameters that were used for other batches in the fasting and fed study, respectively.

3. For the clinical report of the fed study, please explain why some elevated creatine phosphokinase (CPK) levels obtained in some subjects during the post-study lab assessment were listed as adverse events (For example, increased CPK levels of 310 U/L in Subject #3), while some other similar increased CPK levels obtained during the washout period were not listed as adverse events

(For example, the CPK level of 410 U/L in Subject #16 and the CPK level of 342 U/L in Subject #49). Please provide a complete list of abnormal laboratory results obtained during the washout and post-study assessment even if the results were not considered clinically significant.

4. For the original fed bioequivalence study (Study No. 023-08), please submit the complete study report, which should include the clinical report (with complete adverse events and clinical laboratory results), bioanalytical report and statistical analysis report as well as the study datasets in SAS Transport format.

5. The following recommendation is for your future submissions:

   Please note that the concentrations of the long-term stability samples should be compared to the mean of back-calculated values for the fresh QC at the appropriate concentrations from the first day of the long-term stability testing, as recommended in the Guidance for Industry: Bioanalytical Method Validation, issued 2001.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.7 Outcome Page

ANDA: 091226

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
11955	12/30/2008	Bioequivalence Study	Fasting Study	1	1
11955	12/30/2008	Bioequivalence Study	Fed Study	1	1
11955	12/30/2008	Bioequivalence Study	Failed Study	1	1
11955	12/30/2008	Other	Dissolution Waiver	1	1
11955	12/30/2008	Other	Dissolution Waiver	1	1
11955	12/30/2008	Other	Dissolution Waiver	1	1
				Bean Total:	6

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	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/

HONGLING ZHANG
09/02/2010

NILUFER M TAMPAL
09/02/2010
Signed for Dr. Bing Li

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/02/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	91-226	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength (s)	10mg, 20mg, 40mg, and 80 mg	
Applicant Name	Matrix Laboratories Limited, India	
Address	Matrix Laboratories Limited. 4th Floor, Sairam Towers, Alexander Road, Secunderabad 500 003. INDIA.	
Applicant's Point of Contact	Mylan Pharmaceuticals Inc. 781 Chestnut Ridge Road, P. O. Box 4310 Morgantown, WV 26504-4310, USA	
	Primary Contact: Ronald T. Groman, Director	Secondary Contact: S. Wayne Talton, Vice President Regulatory Affairs North America, Generics
Contact's Phone Number	Phone : (304) 554-5899 (800) 848-0461, Ext. 5899	Phone : (304) 554-6551 (800) 848-0461, Ext. 6551
Contact's Fax Number	(304)-285-6407	(304)-285-6407
Submission Date(s)	December 30, 2008	
First Generic	No	
Reviewer	Zakia R. Williams, Ph.D.	
Study Number (s)	022-08	162-08
Study Type (s)	Fasted	Fed
Strength(s)	80 mg	80 mg
Clinical Site	GVK Biosciences Pvt Limited.,	
Clinical Site Address	7th Floor Swarna jayanthi Commercial Complex, Ameerpet, Hyderabad-500037, India, Tel: +91-40-66275566, Fax: +91-40-66275599	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	INCOMPLETE	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). However the firm's proposed specification of NLT (b) (4)% in (b) (4) minutes is not the FDA-recommended specification. The firm should acknowledge the FDA-recommended method and specification of not less than (b) (4) % (Q) of the labeled amount of Atorvastatin dissolved in 15 minutes.

The firm's reported Long Term Storage Stability data are not sufficient to cover the storage period of bio-study samples for the Fasted Bioequivalence Study. The firm should submit additional Long Term Storage Stability data to cover a storage period of at least 81 days.

The Clinical Site routine inspection was completed on (b) (4) with outcome VAI per (b) (4)

The Analytical Site routine inspection was completed on (b) (4) with outcome VAI per (b) (4).

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: FDA-recommended method for Atorvastatin Calcium Tablets

Source: FDA Internal Dissolution Database

Dosage Form: Tablet

Medium: 0.05 M Phosphate buffer, pH 6.8

Apparatus: II (Paddle)

Speed/RPMs: 75

Modify Date: 1/15/2004

Sampling Times: 5, 10, 15 and 30

Volume: 900

Notes: From OCBP Review 2000 Update: 11/22/02 by NT

Specification: NLT (b)(4)%, 15 min

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	75 RPM
	Medium:	pH 6.8 phosphate buffer (Official medium as per FDA recommendation)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin (b) (4) should be dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)** 5	10	15	30	45	**Study Report Location**
Study Report #: 022-08 & 162-08	18/05/ 2008	Test Product-Atorvastatin Calcium tablets, 80 mg Batch # 1004891 Mfg date- May 2008	80 mg Tablet	12	Mean	57	96	101	104	105	Module 1.12.15
					Range	(b) (4)					
					%CV	23.2	0.9	1.4	1.3	1.0	
	02/07/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 80 mg) Batch # 10857V Exp date: May 2010	80 mg Tablet	12	Mean	87	91	96	102	101	
					Range	(b) (4)					
					%CV	13.3	17.2	15.3	1.9	4.6	
	21/05/ 2008	Test Product-Atorvastatin Calcium tablets, 10 mg Batch # 1004888 Mfg date- May 2008	10 mg Tablet	12	Mean	70	93	97	102	103	
					Range	(b) (4)					
					%CV	8.7	2.4	2.6	2.5	1.8	
	24/12/ 2008	Reference Product:	10 mg Tablet	12	Mean	66	74	78	84	97	
					Range	(b) (4)					

		LIPITOR® (Atorvastatin Calcium tablets, 10 mg) Batch # 13868V Exp date: Aug. 2011			%CV	10.3	6.5	5.8	6.8	4.1	

Dissolution Conditions	**Apparatus:**	USP-II (Paddle)
	Speed of Rotation:	75 RPM
	Medium:	6.8 pH phosphate buffer (Official medium as per FDA recommendation)
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin (b) (4) should be dissolved in (b) (4) minutes.	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)** 5	10	15	30	45	**Study Report Location**
Study Report #: 022-08 & 162-08	20/05/ 2008	Test Product-Atorvastatin Calcium tablets, 20 mg Batch # 1004889 Mfg date- May 2008	20 mg Tablet	12	Mean	55	88	95	100	103	Module 1.12.15
					Range	(b) (4)					
					%CV	9.5	1.5	2.1	1.9	2.5	
	23/11/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 20 mg) Batch # 0178017 Exp date: Dec 2009	20mg Tablet	12	Mean	98	104	104	104	104	
					Range	(b) (4)					
					%CV	5.8	0.8	0.6	0.6	0.6	
	19/05/ 2008	Test Product-Atorvastatin Calcium tablets, 40 mg Batch # 1004890	40 mg Tablet	12	Mean	44	84	95	101	103	
					Range	(b) (4)					
					%CV	14.0	6.3	1.2	1.7	1.7	

		Mfg date- May 2008									
	24/11/ 2008	Reference Product: LIPITOR® (Atorvastatin Calcium tablets, 40 mg) Batch # 0117027 Exp date: Jan 2010	40 mg Tablet	12	Mean	96	102	103	103	101	
					Range	(b) (4)					
					%CV	8.1	0.5	0.7	0.5	3.7	

II. COMMENTS:

1. Matrix's dissolution testing on its Atorvastatin Calcium Tablets using the FDA-recommended method is acceptable (at level S1); however, the firm's proposed specification of NLT (b)(4)% (Q) in (b)(4) minutes is not acceptable. The firm should be advised to acknowledge its acceptance of the FDA-recommended specification of NLT (b)(4)% (Q) in 15 minutes.

2. The firm reported long term storage stability data at 74 days. This is not sufficient to cover the 81 days of storage period of biostudy samples for the fasted BE study.

III. DEFICIENCY COMMENTS:

1. The dissolution testing is incomplete pending the firm's acknowledgement of the FDA-recommended dissolution method and specification.

2. The Long Term Storage Stability Data the firm provided are not sufficient to cover the storage period of the study samples for the fasting bioequivalence study (Study Number 022-08). The firm should provide Long Term Storage Stability data to cover at least 81 days.

IV. RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Matrix on its test products Atorvastatin Calcium Tablets 80 mg, Batch No. 1004891, Atorvastatin Calcium Tablets, 40 mg Batch # 1004890, Atorvastatin Calcium Tablets, 20 mg, Batch # 1004889, and Atorvastatin Calcium Tablets, 10 mg Batch # 1004888 using the FDA-recommended method is incomplete due to the deficiencies described above.

2. The dissolution testing should be conducted in 900 mL of 0.05 M phosphate buffer, pH 6.8, using USP apparatus 2 (paddles) at 75 rpm. The test product should meet the following specification: NLT (b)(4)% (Q) in 15 minutes. The firm should acknowledge the FDA-recommended dissolution method and specification.

3. The firm should provide Long Term Storage Stability data to cover a storage period of at least 81 days.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 91-226

APPLICANT: Matrix Laboratories Limited, India

DRUG PRODUCT: Atorvastatin Calcium Tablets 10mg, 20mg, 40mg, and 80 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver requests will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing using the FDA-recommended method is acceptable. However, your proposed specification of Not less than (b) (4) % (Q) in (b) (4) minutes is not acceptable. Based on the dissolution data submitted, the DBE recommends a different but more appropriate specification for the test product. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

   Medium: 0.05 M Phosphate buffer, pH 6.8
   Apparatus: II (Paddle)
   RPM: 75
   Volume: 900 mL

   Specification: Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin is dissolved in 15 minutes.

2. The Long Term Storage Stability Data you provided are not sufficient to cover the storage period of the bio-study samples for the fasting bioequivalence study (Study Number 022-08) you submitted. Please provide Long Term Storage Stability data to cover a storage period of at least 81 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 91-226

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

Reviewer: Williams, Zakia **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Dissolution: Atorvastatin Calcium Tablets 10mg, 20mg, 40mg, and 80 mg

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8456	12/30/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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

/s/

Zakia R Williams
6/16/2009 08:55:45 AM
BIOPHARMACEUTICS

Yih Chain Huang
6/16/2009 09:44:31 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
6/16/2009 02:18:20 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091226

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 #:091226
Firm Name:Mylan Laboratories Limited
ANDA Name:Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base)
RLD Name:Lipitor by Pfizer Inc.

Electronic AP Routing Summary Located:
Z:\Chemistry Division III\Team 34\Electronic AP Summary\91226.ap.doc

AP/TA Letter Located:
Z:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\91226.apltr.DOC

Project Manager Evaluation: **Date: 5/22/12 Initials:** RG

☒ Previously reviewed and tentatively approved --- Date 2/1/12
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 12/31/08	Date of Application 12/30/08	Date Acceptable for Filing 4/14/09
Patent Certification (type) P-IV	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** 21477 (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) _____ Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 5/22/12 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: 5/22/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 5/23/12

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 5/23/2012**

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:ANDA previously TA'd on 2/1/2012. At the time the TA was issued the reason cited for TA was another applicants (Ranbaxy) eligibility for 180 day exclusivity. Mylan had provided PIV certs to the '104, '156, and '971 patents-they were sued in the D of DE for infringement of the '156 patent with the 30 month stay of approval expiring on 11/4/2009. Applicant submitted a patent amendment on 6/30/2011 in which they informed the Agency that CA 09 CV 0441 which was pending in the D of DE was dismissed without prejudice on 6/30/2011. As noted in the TA routing summary this applicant has been providing serial PIV certifications to the '197 and '376 patents from 9/27/2011 through 11/23/2011. As of today's date 5/23/2012 these two patents remain unlisted in the OB.
Patent Amendment beginning 2/2/2012(day after TA): PIV to '197 and '376, certs through 5/23/2012 reviewed and all contain the same PIV certs to the '197 and '376 patents.
Applicant submitted their request for final approval on 3/13/2012.

ANDA eligible for Full approval once Ranbaxy's (ANDA 76477) exclusivity expires on 5/28/2012-since 5/28 is a Federal Holiday OGD will may approve on Tuesday 5/29.

2. ***Labeling Endorsement***

Reviewer, BT: Labeling Team Leader, RW:

Date5/22/12 Date5/22/12

InitialsBT/RG for InitialsRW/RG for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, May 23, 2012 1:57 PM
To: Turner, Betty; Gaines, Robert
Subject: RE: ANDA 91226

I concur.

Hi Bob,

According to the most recent 356H form, the current applicant is MYLAN LABORATORIES LIMITED. Betty also noticed that in the letter 5th paragraph, there is a big space between "Tablets and 10 mg" in the third sentence.

Ruby

From: Turner, Betty
Sent: Wednesday, May 23, 2012 11:54 AM
To: Gaines, Robert; Wu, Ruby (Chi-Ann)
Subject: RE: ANDA 91226

Hello Bob,

I have checked the OB, USP, Medwatch, REMS, Drugs@fda and DARRTS and there are no updates for the labeling since last labeling review was completed.

Thanks,

Betty

From: Gaines, Robert
Sent: Tuesday, May 22, 2012 3:21 PM

To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 91226

Hello Betty and Ruby.

The subject Atorvastatin application by Mylan is ready to go for approval. Please provide labeling endorsement.

Thanks

Bob

<< File: 91226 label rev.pdf >> << File: 91226.apltr.DOC >>

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date 5/23/12**
OGD Regulatory Counsel **Initials DTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes saved on v drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 5/24/12**

Chemistry Div. **III (Sayeed)** **Initials VAS**
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 2/1/12. Final approval was blocked at that time by Ranbaxy's ongoing 180-day generic drug 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, this ANDA becomes eligible for final approval.

Final-printed labeling (FPL) found acceptable for approval (Approval Summary #3) 5/10/12, as endorsed 5/22/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #5 - 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 5/21/12 (Verified 5/25/12). No "OAI" Alerts noted.

Matrix provided paragraph IV certifications to the '104, '156 and '971 patents, and was sued only on the '156 patent - Refer to text in the 2/1/12 tentative approval letter. The litigation on the '156 patent was subsequently dismissed. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product. In addition, Ranbaxy's 180-day generic drug exclusivity, which previously served as a block to final approval of Matrix's ANDA, will expire on May 28, 2012.

This ANDA is eligible for final approval upon 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. As May 28, 2012 is a non-work day, final approval may be granted on 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

31 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI) 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/

ROBERT T GAINES
05/29/2012

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad - 500 034, Andhra Pradesh, India
Tel: +91-40-30866666, 23550543, Fax: 30866699

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Mylan Laboratories Limited ("Mylan") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Mylan's certifications were and remain correct. This current amendment is submitted to address new patent filings (U.S. Patent Nos. 7,790,197 and 8,026,376) by the holder of the referenced drug (Lipitor®), which were filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent Nos. 7,790,197 and 8,026,376 are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95, Mylan certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Mylan commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

The patent information identified above is in addition to the patent and exclusivity information set forth in Mylan's previous submissions. This amendment is merely an update to address the newly filed patent information

Sincerely,

On behalf of Mylan Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad - 500 034, Andhra Pradesh, India
Tel: +91-40-30866666, 23550543, Fax: 30866699

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
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On behalf of Mylan Laboratories Limited

Sandeep K. Rathod/VHS

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Intellectual Property

Mylan Laboratories Limited
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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Date: May 15, 2012

GRATUITOUS CHEMISTRYAMENDMENT
(CHEMISTRY INFORMATION PROVIDED)

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Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
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RE: ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG.
ANDA 091226

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on February 1, 2012. The purpose of this gratuitous amendment is to update the subject ANDA with the following information:

In response to an Agency request, Mylan submitted a Gratuitous amendment dated June 28, 2011 wherein Mylan provided details of all facilities used in manufacturing or testing activities related to subject product. The June 28th amendment provided for partial testing of the drug substance, Atorvastatin calcium and excipient Magnesium Stearate at different contract testing labs. Since Mylan, Nashik is now equipped to conduct all testing related to drug substance, Atorvastatin calcium within its quality control set-up, Mylan is accordingly providing a revised outside testing plan. Also, Mylan laboratories limited, Unit-1/Unit-2 is being proposed for the partial testing of excipient (Magnesium Stearate) instead of earlier proposed (b) (4) A copy of the revised outside testing plan and cGMP certificate for Mylan laboratories limited, Unit-1/Unit-2 is enclosed in Section 3.2.P.3.1.A summary of all the manufacturing and testing establishments associated with this application (ANDA 091226) is provided as an attachment to FDA Form 356h including details about the facility, address, contact person, phone, fax, email and FEI number.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on September 9, 2011. Should you require any additional information, please contact Shane Shupe at (304) 554-4148, or by facsimile at (304) 285-6407.

Sincerely,
For Mylan Laboratories Limited, India

for

Nitin Bhattad
Regulatory Affairs
Mylan Laboratories Limited, INDIA

Shane Shupe
Mylan Pharmaceuticals Inc.
US-Agent, Mylan Laboratories Limited, INDIA

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Sincerely,

On behalf of Mylan Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad - 500 034, Andhra Pradesh, India
Tel: +91-40-30866666, 23550543, Fax: 30866699

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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ROUTING SHEET

☐ **APPROVAL** ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: III	**Team: 34**	**PM: Leigh Ann Bradford**

Electronic ANDA: Yes ☒ No ☒

ANDA #:91226
Firm Name:Matrix Laboratories Limited
ANDA Name:Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
RLD Name:Lipitor; Pfizer; 20702

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 31\Electronic AP Summary\ 91226_TA_ROUT_SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 31\Final Version For DARRTS Folder\APTA letters\ 91226 TA ltr .doc

Project Manager Evaluation: **Date: 11/22/11 Initials:** SN

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec′d date 12/31/08	Date of Application 12/30/08	Date Acceptable for Filing 12/31/08
Patent Certification (type) IV	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** 21477 (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: 12-15-11* ☐ 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) 1/26/2012 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 2/17/11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 12/29/10 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 11/22/11 & 1/26/2012 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: 11/23/2011**

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
Patent/Exclusivity Certification: Yes ☒ No ☐	Date Checked Granted
If Para. IV Certification- did applicant:	Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐	Written request issued ☐
Was applicant sued w/in 45 days:Yes ☒ No ☐	Study Submitted ☐
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 12/31/2008, BOS=Lipitor NDA 20-702, PIII to '893 and '995, PIV to '104, '156 and '971. Patent Amendment rec'd on 3/27/2009-PIII to '667. ANDA ack for filing with a PIV for the 10 mg, 20 mg, 40 mg and 80 mg strengths on 12/31/2008(LO dated 4/14/2009). Patent Amendment rec'd on 5/4/2009-statement that notice was sent. Patent Amendment rec'd on 7/30/2009-submission from Connolly, Bove(counsel for Pfizer)-CA 09-441 filed in the D of DE on 6/15/2009 and 09-79 in the D of WV for infringement of the '156 patent(listed patent) and the '511 patent(not a listed patent-this patent covers amorphous atorvastatin), the '740 patent(not a listed patent-this patent covers (b) (4) atorvastatin), both CAs were filed on 6/15/2009 and allege infringement of the same patents. Since the CA was filed within 45 days the 30 month stay of approval will expire on 11/1/2011-this is the date cited in the Cover Letter from Connolly Bove since they indicate that they rec'd notice on 5/1/2009. Patent Amendment rec'd on 8/13/2009-notice sent via Fed Ex to Warner-Lambert in Morris Plains NJ with notice rec'd on 5/4/2009, notice sent via Fed Ex to Pfizer in NY, NY with notice delivered on 5/4/2009, notice sent via Fed Ex to Warner Lambert in Ann Arbor MI with notice delivered on 5/4/2009, Matrix also provided copies of the CAs filed in the D of DE and D of WV. Since the actual delivery of notice took place on 5/4/2009 this date will be used to determine the 30 month stay which expired on 11/4/2009.

Patent Amendment rec'd on 12/22/2010-PIV to '197, again 12/23/2010, these serial certifications continued on a daily basis until 9/26/2011. A record of each of these amendments will not be transcribed on this Routing Summary as the daily submissions amount to approximately 200 submissions.

Patent Amendment rec'd on 9/27/2011-PIV to '197 and '376 again, 9/28/2011, these serial certifications continue on a daily basis up to the date this summary is being written. Again neither the '197 nor the '376 patents are listed so a record of the submission will not be memorialized.

Applicant provided PIII certs to the '995 and '667 patents both of which are now expired. Applicant provided PIV certs to the listed '104, '156 and '971 patents. Matrix was not sued with respect to the '104 and '971 patents. The 30 month stay of approval associated with the CA on the '156 patent expired on 11/4/2011. The only remaining barrier to the approval of this ANDA is Ranbaxy's eligibility for 180 day exclusivity.

ANDA is eligible for TA only due to Ranbaxy's 180 day exclusivity.

2. ***Labeling Endorsement***

Reviewer, Ann Vu:
Date11/23/11
InitialsLS For AV

Labeling Team Leader, John Grace:
Date11/23/11 and 1/26/2012
InitialsLS for JG

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:
concur.

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgement at this time.
It does not necessarily represent an advisory opinion or the formal position of FDA.
It does not bind or otherwise commit the Agency to the views expressed.

From: Vu, Thuyanh (Ann)
Sent: Wednesday, November 23, 2011 10:02 AM
To: Nguyen, Sarah; Grace, John F
Cc: Sears, Leigh Ann
Subject: RE: Labeling concurrence: ANDA 91226; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg base; Matrix Laboratories Limited

Please sign off for me. I checked OB, Drugs@FDA and DAARTS.

From: Nguyen, Sarah
Sent: Tuesday, November 22, 2011 3:50 PM
To: Vu, Thuyanh (Ann); Grace, John F
Cc: Sears, Leigh Ann
Subject: Labeling concurrence: ANDA 91226; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg base; Matrix Laboratories Limited

Please conduct labeling concurrence: ANDA 91226; Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg base; Matrix Laboratories Limited
<< File: 91226.ap_2.labeling[1].pdf >> << File: 91226_TA.DOC >>

Thanks,
Sarah

From: Grace, John F
Sent: Thursday, January 26, 2012 11:23 AM
To: Sears, Leigh Ann
Subject: RE: Labeling sign-off for ANDA 091226 (Atorvastatin Calcium Tablets by Mylan)
the AP summary that I signed on 12/29/2010 remains acceptable

From: Sears, Leigh Ann
Sent: Thursday, January 26, 2012 11:06 AM
To: Grace, John F
Subject: RE: Labeling sign-off for ANDA 091226 (Atorvastatin Calcium Tablets by Mylan)
John,

Please concur with the original email for this ANDA, so I can copy and enter onto the Approval Routing Summary.

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

From: Grace, John F
Sent: Thursday, January 26, 2012 10:57 AM
To: Sears, Leigh Ann
Subject: RE: Labeling sign-off for ANDA 091226 (Atorvastatin Calcium Tablets by Mylan)

you're probably right, I'll Ok
Ann not back till monday

From: Sears, Leigh Ann
Sent: Thursday, January 26, 2012 10:55 AM
To: Grace, John F; Vu, Thuyanh (Ann)
Subject: RE: Labeling sign-off for ANDA 091226 (Atorvastatin Calcium Tablets by Mylan)
Hello John,

This ANDA is for Atorvastatin Calcium. I don't think it has a BPCA consult, does it?

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

From: Grace, John F
Sent: Thursday, January 26, 2012 10:51 AM
To: Sears, Leigh Ann; Vu, Thuyanh (Ann)
Subject: RE: Labeling sign-off for ANDA 091226

Not sure about this. I'll have to check with ANN about any pending BPCA consult

From: Sears, Leigh Ann
Sent: Thursday, January 26, 2012 10:42 AM
To: Grace, John F; Vu, Thuyanh (Ann)
Subject: Labeling sign-off for ANDA 091226
Hello John and Ann,

Please perform labeling sign-off for this ANDA. It is ready for an immediate TA.

Thanks,

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read
OGD Regulatory Counsel

Date 23Nov2011
InitialsDTR

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to TA letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 1/26/12**
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. Refer to comment on Teva ANDA 78-773.

OGD Office Management Evaluation

6. Peter Rickman **Date 1/31/12**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 80 mg tablet strength found acceptable. In-vitro dissolution testing for all 4 tablet strengths also found acceptable. Waivers granted for the 10 mg, 20 mg, 40 mg and 80 mg tablet strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 9/2/10, 2/17/11.

Final-printed labeling (FPL) found acceptable for approval 3/11/10, as endorsed 11/23/11, and 1/26/12.
No REMS is required.

CMC found acceptable for approval (Chemistry Review #5) 1/26/12.

AND/OR

7. Robert L. West **Date 2/1/12**
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: Matrix provided paragraph IV certifications to the '104, '156, and '971 patents and was sued within the 45-day period over the '156 patent only. The 30-month statutory period associated with this litigation has expired. There are no additional unexpired patents or exclusivity listed in the current "Orange Book" for this drug product.

Acceptable EES dated 12/15/11 (Verified 2/1/12). No "OAI" Alerts noted. The re-evaluation date for this ANDA is 4/17/12. PM will be requested to contact OC as this ANDa is eligible for final approval on 5/28/12.

This ANDA is recommended for tentative approval. Final approval for this ANDA is currently blocked by Ranbaxy's eligibility for 180-day generic drug exclusivity under ANDA 76-477 for this drug product. Ranbaxy's 180-day generic drug exclusivity will expire on 5/28/12.

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 2/01/2012
Initials LS

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/

LEIGH A SEARS
02/01/2012

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad - 500 034, Andhra Pradesh, India
Tel: +91-40-30866666, 23550543, Fax: 30866699

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
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Sincerely,

On behalf of Mylan Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

Vu, Thuyanh (Ann)

From: Wayne.Talton@mylanlabs.com
Sent: Wednesday, February 01, 2012 12:47 PM
To: Vu, Thuyanh (Ann)
Subject: Re: 91226 (Matrix's atorvastatin) labeling revision before full approval

Hi Ann

This email is to acknowledge your request. We will make the requested change in our request for final approval that will include Final Printed Labeling. Thanks.

Wayne
Mylan
304.554.6551

From: "Vu, Thuyanh (Ann)" <Thuyanh.Vu@fda.hhs.gov>
To: "'Wayne.Talton@mylanlabs.com'" <Wayne.Talton@mylanlabs.com>
Date: 02/01/2012 12:43 PM
Subject: 91226 (Matrix's atorvastatin) labeling revision before full approval

Wayne,

Please make the following labeling revision prior to full approval of the drug product.

11 DESCRIPTION

Revise [redacted] (b) (4) to "Atorvastatin calcium is a white to off-white powder..[delete [redacted] (b) (4)]"

Please acknowledge this email.

Thanks
Ann

==========
CONFIDENTIALITY NOTICE: This e-mail message and all attachments transmitted with it
==========

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
02/01/2012

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Addendum

ANDA 091226 - Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, 80 mg
Matrix Pharmaceuticals, Ltd.

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

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

/s/

VILAYAT A SAYEED
01/26/2012

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Sandeep K. Rathod
Intellectual Property

Mylan Laboratories Limited
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
CDER/OND/ODE 2/DMEP

Memorandum

Date: January 17, 2012
From: Karen Davis-Bruno PhD; Pharmacology Supervisor; DMEP
Subject: Pharmacology/Toxicology Consult Request
To: ANDA 91226 atorvastatin calcium/Matrix

In a consult request from OGD 12/27/11, DMEP is asked to evaluate an amendment ANDA in the EDR Module 3 consisting of the following studies submitted in support of qualification of an [redacted] impurity: 1) Study #G11002- 28-Day Toxicity of Atorvastatin Calcium ± spiked [redacted] impurity in Wistar rats; 2) in vitro bacterial mutagenicity assay Study #G11032 and 3) in vitro chromosome aberration assay Study # G11033.

Study #G11002- 28-Day Toxicity of Atorvastatin Calcium ± [redacted] impurity in Wistar rats

Atorvastatin was administered by daily oral gavage at 40 and 80 mg/kg/day (10 ml/kg in 1% carboxymethyl cellulose) with and without the addition of [redacted]% [redacted] impurity. Therefore spiked [redacted] was tested at [redacted] and [redacted] mg/kg based on the total administered atorvastatin dose. Rats were observed for clinical signs, body weight and food consumption, ophthalmologic exam, hematology, clinical chemistry, functional observational battery (high dose and controls only), urinalysis, gross pathology, organ weights and histopathology. The sponsor concludes that the tox profile of atorvastatin ± spiked [redacted] are comparable and the no observed adverse effect level (NOAEL) is 80 mg/kg/day. This reviewer disagrees with the sponsor's interpretation based on the following observations.

In male rats given 80 mg/kg/ day atorvastatin + [redacted] mg/kg) there are statistically significant increases in AST, ALT, ALP, cholesterol, creatinine, total bilirubin and plasma chloride compared to controls. The magnitude of these increases are not observed consistently in the atorvastatin treated group without the [redacted] impurity. These findings were absent in the female rats, but GGT (200% increased) and CAA were the only clinical chemistry elevations observed in the highest [redacted] treatment female group. Corresponding hepatic histopathology was not observed in any group. Generally, the histopathology findings were sporadically greater in the atorvastatin + [redacted] mg/kg [redacted] treatment groups in both males and females in incidence and severity compared to any other groups. In females the incidences of nonglandular stomach findings (squamous cell hyperplasia, keratosis, edema, erosions and inflammatory cell infiltration) were greater with [redacted] treated groups ([redacted] and [redacted] mg/kg) compared to the atorvastatin only treated groups. The sponsor dismisses these findings as a class effect of

statins that isn't relevant to humans. While the human stomach doesn't contain squamous epithelium the human esophagus does and may be considered an analogous anatomical tissue. This suggests that 80 mg/kg/day is not the NOAEL for this study and that [redacted] mg/kg [redacted] atorvastatin is not comparable to [redacted] mg/kg [redacted]. This would suggest that [redacted] mg/kg [redacted] is without significant safety concerns compared to the higher [redacted] mg/kg concentration tested.

Bacterial mutagenicity assay Study #G11032

Atorvastatin calcium with and without the addition of the [redacted] impurity (spiked at [redacted]% atorvastatin dose) were tested for their potential to cause mutations in the standard tester strains of the Ames assay. Two trials were conduction with the battery of tester strains with and without metabolic activation in a standard plate incorporation assay. The results of both trials indicated that both atorvastatin calcium and atorvastatin calcium with the [redacted] impurity were not mutagenic and comparable up to concentrations of 5000 µg/plate in a valid bacterial mutagenicity (Ames) test.

Chromosome aberration assay Study # G11033

Atorvastatin calcium with and without the addition of the [redacted] impurity (spiked at [redacted]% of atorvastatin dose) were tested using a valid in vitro mammalian chromosome aberration test for their potential to cause mutations in the Chinese Hamster Ovary (CHO) cells with metabolic activation at short (175, 350, 700 µg /ml) and without metabolic activation for a long treatment period (150, 300, 600 µg /ml). The results indicate no clastogenic potential of either test article under the study conditions.

Interpretation: Matrix has provided these toxicology study reports to qualify the [redacted] impurity at [redacted]% and proposes to set a specification for the [redacted] in atorvastatin at ≤ [redacted]% which exceeds the reference listed atorvastatin specification for this impurity of [redacted]%. Based on the results of 28-day rat toxicity study G11002, the addition of [redacted] mg/kg [redacted] is not significantly different from atorvastatin alone. A [redacted] mg/kg [redacted] dose in rat corresponds to a human equivalent dose of [redacted] mg/kg or [redacted] mg based on a [redacted] human. This suggests that acceptance of a [redacted] specification of [redacted]% is reasonably safe based on qualification of [redacted] at [redacted] mg/kg/day in a 28-day rat tox study and two in vitro gentox assays for mutagenicity and clastogenicity. The results do not suggest that [redacted] levels of [redacted]% are qualified based on the adverse findings observed in the 28-day rat toxicity study G11002 as Matrix contends.

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

/s/

KAREN L DAVIS BRUNO
01/18/2012

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U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Mylan Laboratories Limited ("Mylan") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Mylan's certifications were and remain correct. This current amendment is submitted to address new patent filings (U.S. Patent Nos. 7,790,197 and 8,026,376) by the holder of the referenced drug (Lipitor®), which were filed subsequent to Mylan's previous submissions.

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Sincerely,

On behalf of Mylan Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2012-0592	
TO *(Division/Office)* DMEP - HFD-510 Thru: Leah Ripper, ODEII - HFD 102			FROM: Haitao Li	
DATE: 1/4/2012	IND NO.	ANDA NO. 091226	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 12/27/2011,
NAME OF DRUG Atorvastatin Calcium		PRIORITY CONSIDERATION 15 days	CLASSIFICATION OF DRUG Lipid Lowering Agent	DESIRED COMPLETION DATE 1/19/2012

NAME OF FIRM Mylan Laboratories Limited

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICIENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

□ DISSOLUTION
□ PROTOCOL-- BIOPHARMACEUTICS
□ IN--VIVO WAIVER REQUEST
□ DEFICIENCY LETTER RESPONSE
□ BIOAVAILABILITY STUDIES
□ PHASE IV STUDIES

IV.DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
□ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
□ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox review. "Impurities listed are higher than the RLD." Please evaluate the amendment in EDR module 3 (see attached documents for reference.Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.Sears@fda.hhs.gov) on the review when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Pharm-Tox consults-ANDA 91226CR05, Amendment submitted December 27, 2011.

HFD-630/H. Li/CR/1/3/12
HFD-630/L. Nagavelli/TL
HFD-617/L.A.Sears/PM

The following deficiencies were sent to the firm per Indra's consult review dated 4/22/2011 (document in DARRTS). The firm was trying to qualify (b) (4) with DEREK software in the previous amendment. In the Amendment dated 12/27/2011, the firm provided the toxicology study.

(b) (4)

Firm's response:

(b) (4)

(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/

SARAH K NGUYEN
01/04/2012

TRANG Q TRAN
01/04/2012

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad - 500 034, Andhra Pradesh, India
Tel: +91-40-30866666, 23550543, Fax: 30866699

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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December 27, 2011

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

Telephone CMC Amendment and Request for Telephone Conference

Subject: **ANDA # 091226,**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
(Response to Agency Correspondence dated December 16, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Agency's telephone CMC comments dated December 16, 2011. In the following lines we present the Agency's comments and our response thereto. DMF # 21477 for Atorvastatin Calcium referenced in this ANDA also received minor comments dated December 21, 2011, in relation to control for the drug substance which have not been issued to this ANDA. As a consequential action item, Matrix (Mylan) has revised the DS controls in accordance with the Agency's comments and in alignment with the DMF controls. The DMF holder (Matrix/Mylan) has responded to the DMF comments.

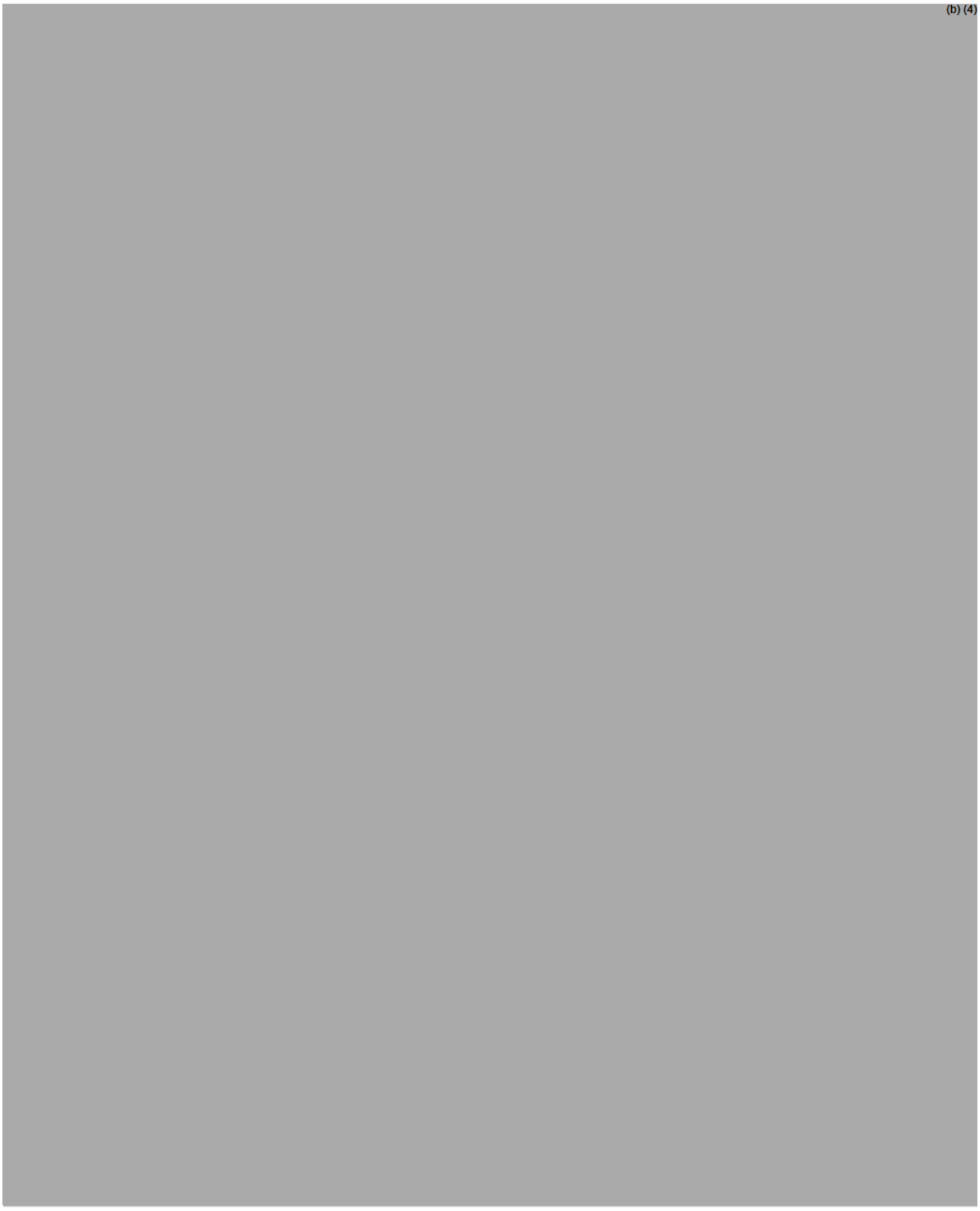
As discussed with Ms. Leigh Ann Sears, of your Office, Matrix/Mylan wishes to have a telephone conference with the Agency during the week of January 9, 2012 to discuss this Amendment.

Comment 1

(b) (4)

Response:

(b) (4)


(b) (4)

Comment 2

(b) (4)

Response:

(b) (4)

(b) (4)

Comment 3

(b) (4)

Response:

(b) (4)

Comment 4

(b) (4)

Response:

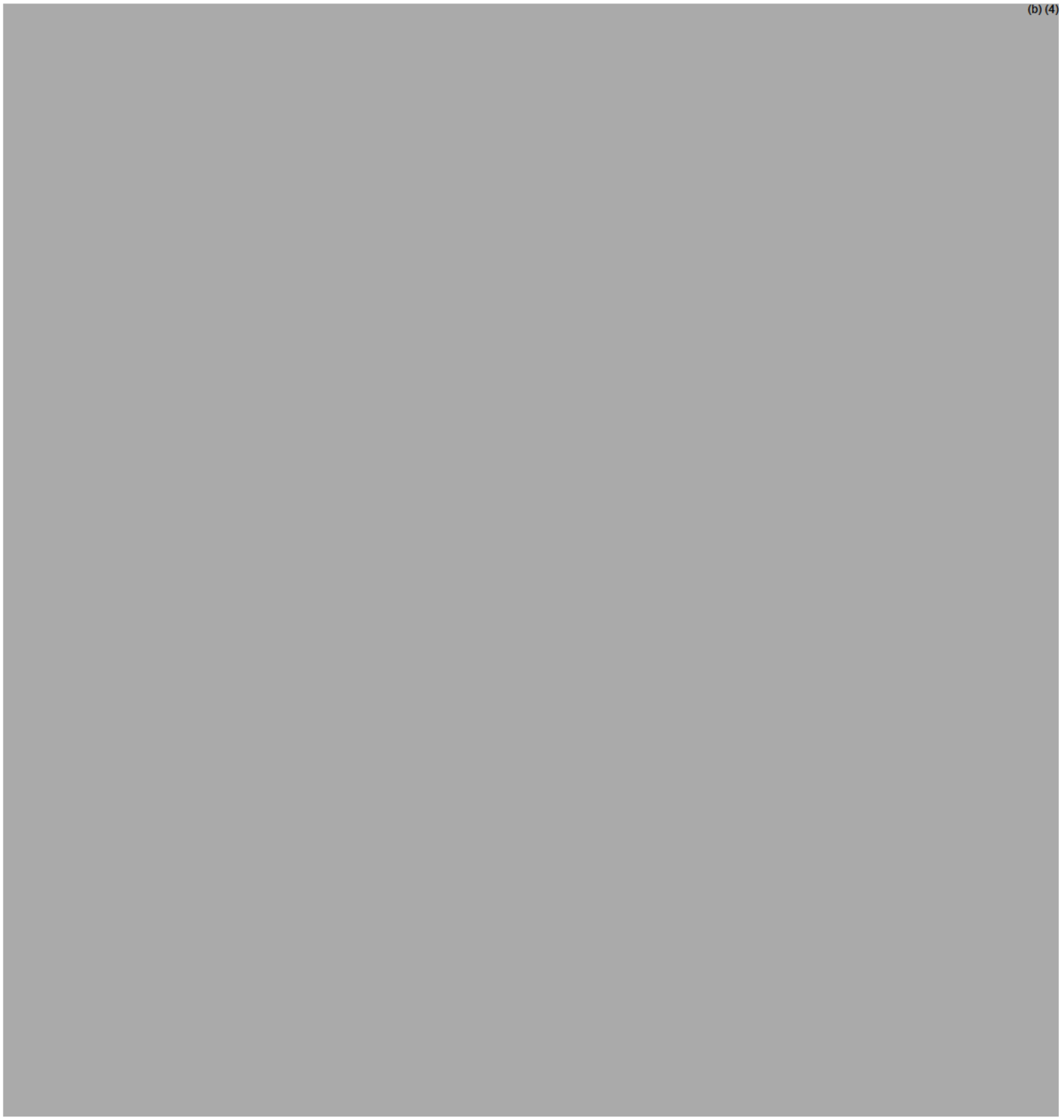
(b) (4)

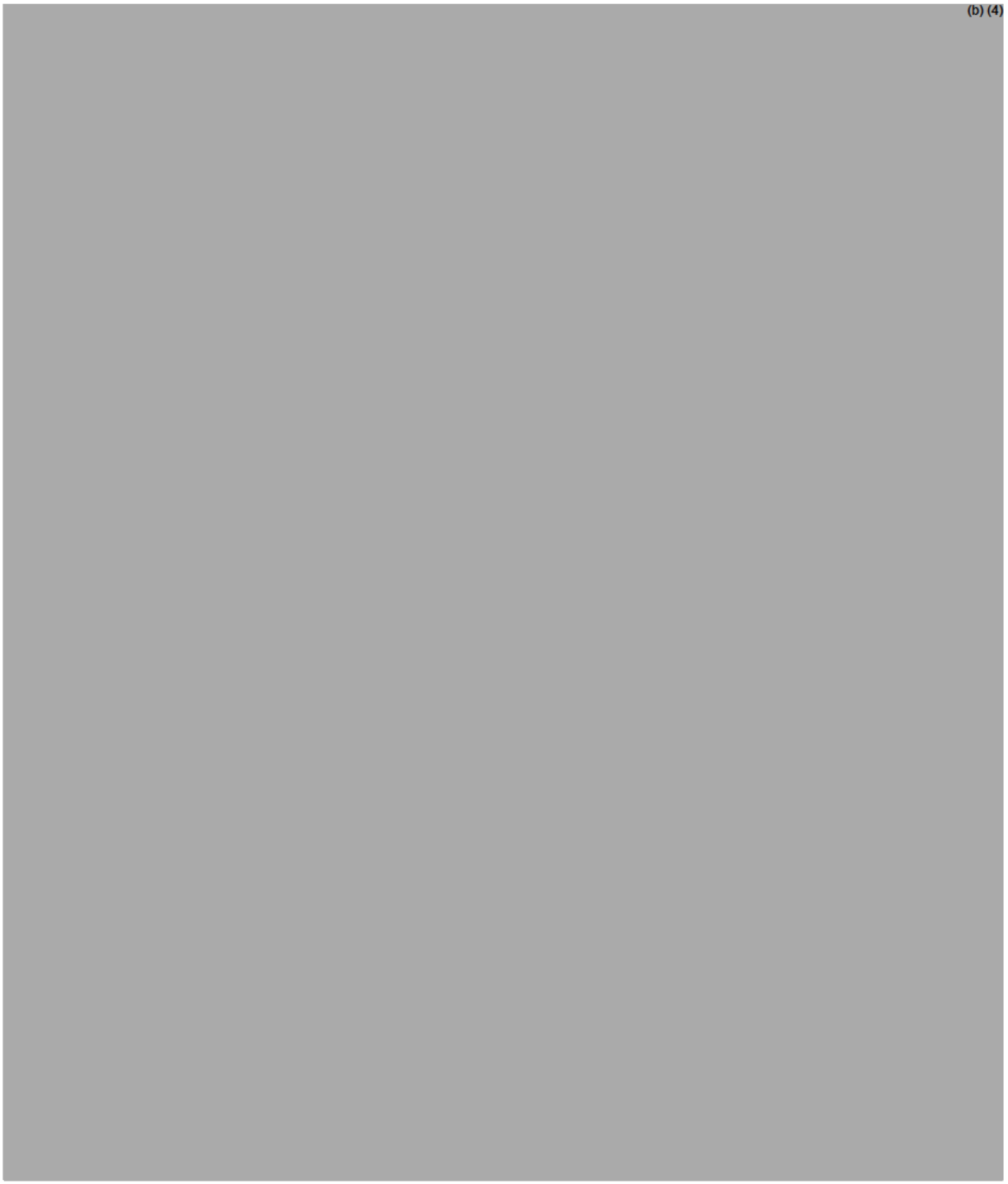
Comment 5

(b) (4)

Response:

(b) (4)


(b) (4)


(b) (4)

(b) (4)

Comment 6

(b) (4)

Response:

(b) (4)



Additionally, through this correspondence, we would like the Agency to take note of the rebranding of the company from 'Matrix Laboratories Limited' to Mylan Laboratories Limited' effective October, 2011. Mylan Laboratories Limited is a subsidiary of Mylan Inc. The change in name is an endeavor by our parent company Mylan Inc, based in Pittsburgh, Pennsylvania to bring various regional companies under one identity 'Mylan'. The establishment details in the Agency's records have already been updated for said name change.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on September 9, 2011. Should you require any additional information, please contact Wayne Talton at (304) 554-6551, or by facsimile at (304) 285-6407. We look forward to have a telephone conference with the Agency in the near future.

Sincerely,

For Mylan Laboratories Limited, India

S. Wayne Talton for NB

Nitin Bhattad
Regulatory Affairs
Mylan Laboratories Limited, India

MATRIX

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1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Sandeep K. Rathod/VHS

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On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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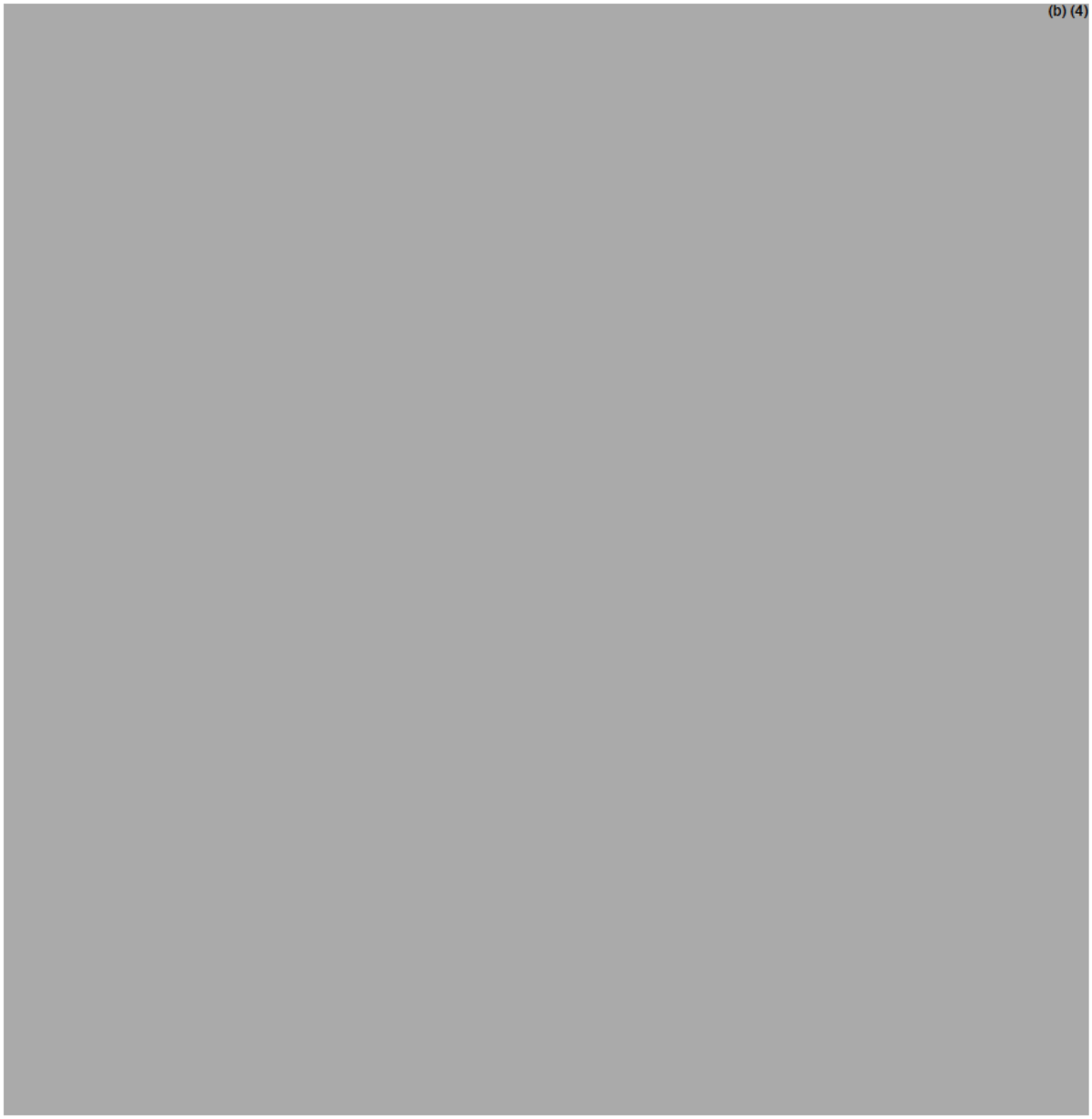
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(b) (4)

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
12/16/2011

LAXMA R NAGAVELLI
12/16/2011

TELEPHONE AMENDMENT FAX

ANDA 091226

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: Matrix Laboratories Ltd. TEL: 304-554-5899
ATTN: Keith Giunta FAX: 304-285-6407

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 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to the amendment dated Dec 01, 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 Haitao Li at 240-276-8747. 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: 091226

APPLICANT: Matrix Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The deficiencies presented below represent telephone deficiencies.

A. Deficiency:

With the revised stability specifications several of your presentations do not meet the 18 month expiry date. We recommend that you reduce the expiration date to 12 months and make a commitment that first 10 batches of all strength will be placed on stability program and tested as per the stability program.

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
12/16/2011

LAXMA R NAGAVELLI
12/16/2011

MATRIX

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Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address new patent filings (U.S. Patent Nos. 7,790,197 and 8,026,376) by the holder of the referenced drug (Lipitor®), which were filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent Nos. 7,790,197 and 8,026,376 are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95, Matrix certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to addres the newly filed patent information

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

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Intellectual Property

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722 Fax : 27700343
E-mail:matrix@matrixlabsindia.com

December 2, 2011

TELEPHONE AMENDMENT

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG
ANDA 091226
(Response to Agency Correspondence Received December 2, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to the Agency's correspondence received by facsimile on December 2, 2011 (refer to Section 1.4.4). In response to the Agency's December 2nd letter, Matrix wishes to amend this application as follows:

FDA COMMENT 1

(b) (4)

[redacted]

RESPONSE

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on September 9, 2011. Shoul you require any additional information, please contact Wayne Talton at (304) 544-6551, or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton for NB

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited India

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

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Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

MATRIX

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Tel : 91-40-27700363, 66327722 Fax : 27700343
E-mail:matrix@matrixlabsindia.com

December 1, 2011

TELEPHONE AMENDMENT

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG
ANDA 091226
(Response to Agency Correspondence Received December 1, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to the telephone conversation held December 1, 2011 between the Agency and representatives from Mylan (our US Agent) and subsequent correspondence received by facsimile on December 1, 2011 (refer to Section 1.4.4). In response to the Agency's December 1st letter, Matrix wishes to amend this application as follows:

FDA COMMENT 1

(b) (4)

RESPONSE

(b) (4)

FDA COMMENT 2

(b) (4)

RESPONSE

(b) (4)

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on September 9, 2011. Should you require any additional information, please contact Wayne Talton at (304) 544-6551, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

S. Wayne Talton for NB

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited India

MATRIX

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10 mg, 20 mg, 40 mg and 80 mg

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On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

DATE: 12/01/2011 @ 2 pm

ANDA 091226 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg)

Sponsors: Matrix Laboratories Ltd.

In-Conference: Wayne Talton and Andrea

Based on the discussion with pharm-tox reviewers, chemistry reviewer has conveyed the following to the firm:

(b) (4)



The firm said that they will discuss these options internally and get back to the Agency.

Agency representatives:
Haitao Li
Laxma Nagavelli
Karen Davis Bruno
Indra Antonipillai

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
12/01/2011

LAXMA R NAGAVELLI
12/01/2011

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
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Sandeep K. Rathod
Intellectual Property

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2011

FROM: Robert L. West, Deputy Director, Office of Generic Drugs, CDER

TO: ANDA 078773 (Teva)
ANDA 077575 (Sandoz)
ANDA 090548 (Apotex)
ANDA 091226 (Mylan/Matrix)

SUBJECT: Pre-Launch Activities Importation Requests (PLAIRs); Atorvastatin ANDAs

The Agency is in the process of developing a Guidance regarding pre-launch activities importation requests (PLAIRs). In the past, requests to permit importation of such unapproved finished dosage form drug products have been reviewed and informally granted or denied.[1] Recently the Agency has sought to standardize the process regarding how a PLAIR should be submitted and the circumstances under which the Agency may grant a PLAIR. This memorandum, the purpose of which is to explain the background under which the PLAIRs for ANDA 078773 (Teva), ANDA 077575 (Sandoz), ANDA 090548 (Apotex) were granted, reflects much of the work that has been done in developing the Guidance.

BACKGROUND

To allow domestic drug manufacturers to prepare and position products for market launch in anticipation of NDA/ANDA approval, for many years FDA has used its enforcement discretion and permitted certain interstate shipments of unapproved products in finished dosage form. (Such shipments have been allowed under certain controls and restrictions; for example, products may only be shipped to facilities identified in a pending NDA or ANDA or to facilities owned and controlled by the applicant.) Because foreign firms must bring their products through Customs, such an informal scheme has certain drawbacks. FDA's PLAIR program allows, on a case-by-case basis, the importation and warehousing of finished drugs when an NDA or ANDA is pending. The PLAIR program was developed to formalize the Agency's historical use of enforcement discretion and to allow foreign and domestic manufacturers to operate on a more or less equal footing in their ability to prepare and position products for rapid market launch upon approval.

[1] Section 505(a) of the Federal Food, Drug, and Cosmetic Act (the Act) prohibits the introduction or delivery for introduction into interstate commerce of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." Section 801(a)(3) of the Act states that a drug may be refused admission into the United States if, among other things, it appears that it violates section 505 of the Act.

It is the choice of an applicant who has a pending NDA or ANDA whether or not to submit a PLAIR. The unapproved finished dosage form drug products should either be in final packaged form or require minimal further processing, such as final packaging and/or labeling. A PLAIR includes information such as the drug product name and how supplied, the NDA or ANDA number, the name and address of the foreign manufacturer of the finished drug product, the name and address of the U.S. consignee, the name and address of the warehouse or distribution facility controlled by or under contract with the applicant where the finished dosage form product in final packaged form will be stored pending approval. A PLAIR also should include a signed statement that neither the applicant nor its consignees or distributors will sell, offer for sale, or distribute the drug product in U.S. commerce until FDA has approved the NDA or ANDA. When finished dosage form drug product in bulk is imported for further processing, a PLAIR includes information regarding the facility where further processing activities will occur, including the name and address of the facility, a description of the further processing activities, and information about where the finished dosage form product in final packaged form will be stored pending approval.

An ANDA applicant should not submit a PLAIR until after FDA has determined that the chemistry, manufacturing, and control (CMC) portion is acceptable. For an ANDA that is tentatively approved, a PLAIR should be submitted no more than 60 days prior to the anticipated full approval. Applicants submit a PLAIR by e-mail and one PLAIR should be submitted for each NDA or ANDA. After review of the PLAIR, the CDER Office of Drug Security, Integrity and Recalls (ODSIR), Division of Import Operations and Recalls notifies the applicant whether the PLAIR has been granted. The notification is sent by e-mail to the applicant, the appropriate CDER review division, and the Office of Regulatory Affairs/Division of Import Operations.[2]

Drug products offered for importation under a granted PLAIR are detained by FDA as unapproved drugs. However, rather than issuing a refusal of admission, the Agency exercises enforcement discretion and keeps the detention in place until the Agency either approves the NDA/ANDA or for 6 months, whichever occurs first. The drug product will be subject to refusal and either destruction or exportation if the Agency does not approve the sponsor's NDA/ANDA or if 6 months have passed since the entry date of the initial shipment under a PLAIR.

FDA's determination to grant a PLAIR is subject to the applicant's meeting the following conditions:

1. The PLAIR submission contains a written certification that neither the applicant nor the applicant's consignee will sell, offer for sale, or further distribute in domestic commerce the drug product without an approved application for the drug product.

2. The responsible foreign facility has a satisfactory inspectional history and is either the subject of an ongoing FDA GMP inspection or is in substantial conformity with applicable good manufacturing practices (21 CFR parts 210 and 211).

[2] If there are any changes made after the original PLAIR submission, an amended PLAIR should be submitted. If it is acceptable, CDER ODSIR will notify ORA of the amendment.

Reference ID: 3051613

3. Bulk unapproved finished dosage form drug products are to be delivered to a facility identified in the pending NDA or ANDA to permit further processing, after which the products should remain at the facility where the processing occurred or be transferred to a single site controlled by or under contract with the applicant. For unapproved finished dosage form drug products in final packaged form that do not require further processing, the applicant should state that the drug products will be delivered to a single site controlled by or under contract with the applicant. In both cases, the products should remain under quarantine pending final approval of the application, and remain subject to the terms and conditions of the U.S. Customs and Border Protection entry bond that covers the importation of the specific shipment. Warehouse/distribution facilities controlled by or under contract with the applicant must comply with applicable cGMPs, including proper storage conditions and appropriate temperature and humidity controls. See 21 CFR 211.42 and 211.46; see also 21 CFR 205.50(c)

Upon receiving notice from FDA that the NDA/ANDA is approved, the applicant should send a copy of the approval letter by e-mail to the district office. FDA will determine whether the product that was imported under a PLAIR meets all the requirements of the approved application. FDA's decision to grant a PLAIR is not binding on the Agency. The granting of a PLAIR is not a promise to approve the full application at any future time period and companies who import in reliance on a PLAIR do so at their own risk. FDA may elect to refuse admission of a drug if, for example, the applicant distributes the unapproved drug product in a manner not specified under the granted PLAIR, or 6 months have passed since the entry date of the initial shipment under a PLAIR and approval of the NDA or ANDA has not been granted. Within 90 days of an Agency decision to refuse admission into the United States, articles must be exported or destroyed, as required by section 801(a) of the Act. The Agency has encountered instances in which drug products that had been warehoused subject to a pending NDA/ANDA approval did not conform with late changes made to the approved drug product labeling, or instances in which the NDA/ANDA did not receive FDA approval.

ATORVASTATIN

The applicants of the four atorvastatin ANDAs to which this memorandum is addressed have each submitted a PLAIR. The PLAIRs of Teva, Sandoz, and Apotex were approved on November 21, 2011. As of the date of this memo, no decision has been made on the PLAIR of Mylan/Matrix.

All four of these ANDAs were submitted after ANDA 076477 was submitted by Ranbaxy. Ranbaxy's ANDA 076477 was the first substantially complete ANDA submitted with paragraph IV certifications to the patents listed in the Orange Book for Pfizer's Lipitor. Because of this, Ranbaxy is eligible for 180-day generic drug exclusivity.

The very complicated situation with atorvastatin is explained in detail elsewhere in the administrative records of the atorvastatin ANDAs (largely in Ranbaxy's ANDA 076477), and will not be repeated here. However, in summary, the status of Ranbaxy's ANDA has been the subject of widespread speculation, and the possibility of certain subsequent applicants being eligible for immediate full approval under various scenarios has also been widely speculated

Reference ID: 3051613

upon. FDA, moreover, does not have full knowledge of all aspects of the situation. In particular, there may (or may not) be contractual arrangements between the various parties, including Ranbaxy, the details of which may (or may not) affect the ability of one or more subsequent applicants to be fully approved before the expiration of Ranbaxy's 180-day exclusivity period.

The ANDAs of the four PLAIR applicants are all at an advanced stage of review.[3] In fact, during the month of November, OGD was anticipating that most, and perhaps all four, might be tentatively approved. To the best of our knowledge on November 21, when three of the PLAIRs were granted, Ranbaxy was eligible for 180-day exclusivity, and Ranbaxy's earliest launch date would be November 30, 2011 (as widely reported for more than three years, based on their 2008 settlement agreement with Pfizer). This would mean that no subsequent applicant could be approved until May 28, 2012, at the earliest, which being more than 6 months from November 21, 2011, is hardly "imminent" (at least one applicant claimed in its PLAIR that approval of its ANDA was imminent.) This, however, is not grounds for denying the PLAIR particularly in circumstances like those present here where applicants are aware of the exclusivity and considering whether to challenge it and/or to strike a deal that permits marketing before the exclusivity runs.

The PLAIRs were voluntarily submitted by the four applicants, and it is fair to assume that these applicants were fully aware of Ranbaxy's status as a first applicant and the significance of November 30. It is also fair to assume that these applicants are aware that the granting of a PLAIR is no guarantee of ANDA approval, imminent or otherwise, and that drug product will be subject to refusal and either destruction or exportation if 6 months have passed since the entry date of the initial shipment under a PLAIR. These are known risks. As noted above, the Agency does not necessarily know what has happened (or perhaps will happen) with respect to Ranbaxy's exclusivity. The possibility exists that Ranbaxy could, perhaps even in the very near future, relinquish or selectively waive its exclusivity, thereby permitting the approval of one or more of the PLAIRs ANDAs, assuming of course the ANDA is otherwise eligible for approval.

[3] According to our records, the CMC portions of ANDA 078773 (Teva), ANDA 077575 (Sandoz), ANDA 090548 (Apotex) all were considered "acceptable" when the PLAIRs were granted on Nov. 21. The record shows that, at that time, FDA was still in the process of finalizing its resolution of certain issues pertaining to these ANDAs and the current USP monograph for atorvastatin calcium. As of Nov 21, however, it appeared that the three ANDAs in question would meet the standards of identity in the current USP monograph. With regard to ANDA 091226 (Mylan/Matrix), there were impurity issues that, as of the date of this memorandum, were not yet fully resolved and therefore have precluded an "acceptable" finding.

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 29, 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 091226 - Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, 80 mg
Matrix Pharmaceuticals, Ltd.

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 Matrix in ANDA 091226 is atorvastatin calcium; it is [redacted] (b) (4) and in an [redacted] (b) (4) form.

There is a USP monograph for the atorvastatin calcium drug substance. Upon consideration of the USP monograph, FDA has determined that an ANDA applicant for generic atorvastatin calcium tablets can demonstrate active ingredient "sameness" for the purposes of section 505(j) by demonstrating that the active ingredient meets the standards for identity in the atorvastatin calcium drug substance monograph. The question considered in this memorandum is whether the active ingredient in Matrix's ANDA meets the standards for identity in the monograph notwithstanding differences in polymorphic form.

Both the trihydrate and the [redacted] (b) (4) 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 Matrix 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 Matrix to use the modified IR method. When Matrix 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 Matrix 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 Matrix'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 Matrix drug substance meets the standards of identity as prescribed in the current USP monograph for 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/

LEIGH A SEARS
11/30/2011

ROBERT L WEST
11/30/2011
Deputy Director, Office of Generic Drugs

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address new patent filings (U.S. Patent Nos. 7,790,197 and 8,026,376) by the holder of the referenced drug (Lipitor®), which were filed subsequent to Matrix's previous submissions.

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

MATRIX

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Date: November 23, 2011

TELEPHONE AMENDMENT

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Subject: **ANDA # 091226**,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review. Reference is also made to the telephone conversation held November 23, 2011 between the Agency and Mylan (our US Agent) in which the Agency requested that we tighten the stability limit for the (b) (4) impurity in the finished product specifications.

In accordance with the Agency's request and considering the observed highest level of (b) (4) % in the exhibit batch stability studies, Matrix is tightening the shelf life specification for (b) (4) impurity from (b) (4) % to (b) (4) % at this time. It is important to note that Matrix has previously qualified the (b) (4) impurity through toxicological studies to a level of (b) (4) %. These studies were provided in the May 26, 2011 Telephone Amendment. The proposed specification of NMT (b) (4) % is markedly lower than the previously qualified limit.

In consideration of the Agency's comments and in accordance with our previously submitted post approval stability protocol, we also commit to re-evaluate the appropriateness of the shelf life limit for the (b) (4) impurity in the drug product once we have obtained long term stability data on the 10 commercial batches that have been manufactured in accordance with the conditions outlined in the application. A copy of the revised shelf-life specifications are provided in this amendment (3.2.P.5)

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on September 9, 2011. Should you require any additional information, please contact Wayne Talton at (304) 554-6551, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

S. Wayne Talton for NB

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

MATRIX

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Tel : 91-40-27700363, 66327722 Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: November 22, 2011

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

TELEPHONE AMENDMENT

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to ANDA identified above which is currently under review and the chemistry Telephone Amendment submitted on November 21, 2011, in response to chemistry comments that were provided to Matrix by facsimile on November 21, 2011.

As requested by Ms. Sarah Nguyen, of your Office, the purpose of this Amendment to provide drug product related substances release testing data on the first 10 or all available (if less than 10) commercial batches of each strength of Atorvastatin Calcium Tablets for the Agency's information and review. For ease of reference, related substances release testing data for the original ANDA exhibit batch of each strength has also been provided (indicated within an "*" in each table).

Atorvastatin Calcium Tablets, 10 mg

BATCH #	Impurity (Limit %w/w) (b) (4)
1082787	
1073449	
1073451	
1004888*	

*ANDA Exh

Atorvastatin Calcium Tablets, 20 mg

BATCH #	Impurity (Limit %w/w) (b) (4)
1080522	
1080523	
1080524	
1081762	
1081764	
1081765	
1073242	
1073243	
1073489	
1080521	
1004889*	

*ANDA Exhibit batch

Atorvastatin Calcium Tablets, 40 mg

BATCH #	Impurity (Limit %w/w) (b) (4)
1073063	
1073064	
1073630	
1078265	
1078266	
1078267	
1078268	
1078269	
1077761	
1077762	
1004890*	

*ANDA Exhibit batch

Atorvastatin Calcium Tablets, 80 mg

BATCH #	Impurity (Limit %w/w) (b) (4)
1072366	
1072718	
1073656	
1077062	
1077063	
1077064	
1077324	
1077326	
1077327	
1077587	
1004891*	

*ANDA Exhibit batch

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on September 9, 2011. Should you require any additional information, please contact Shane Shupe at (304) 554-4148, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

S. Wayne Tal for NB

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

MATRIX

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
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RE: ATORVASTATIN CALCIUM TABLETS,
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ANDA # 091226

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PARAGRAPH IV CERTIFICATION

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

MATRIX

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November 21, 2011

TELEPHONE AMENDMENT

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Subject: **ANDA # 091226**,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

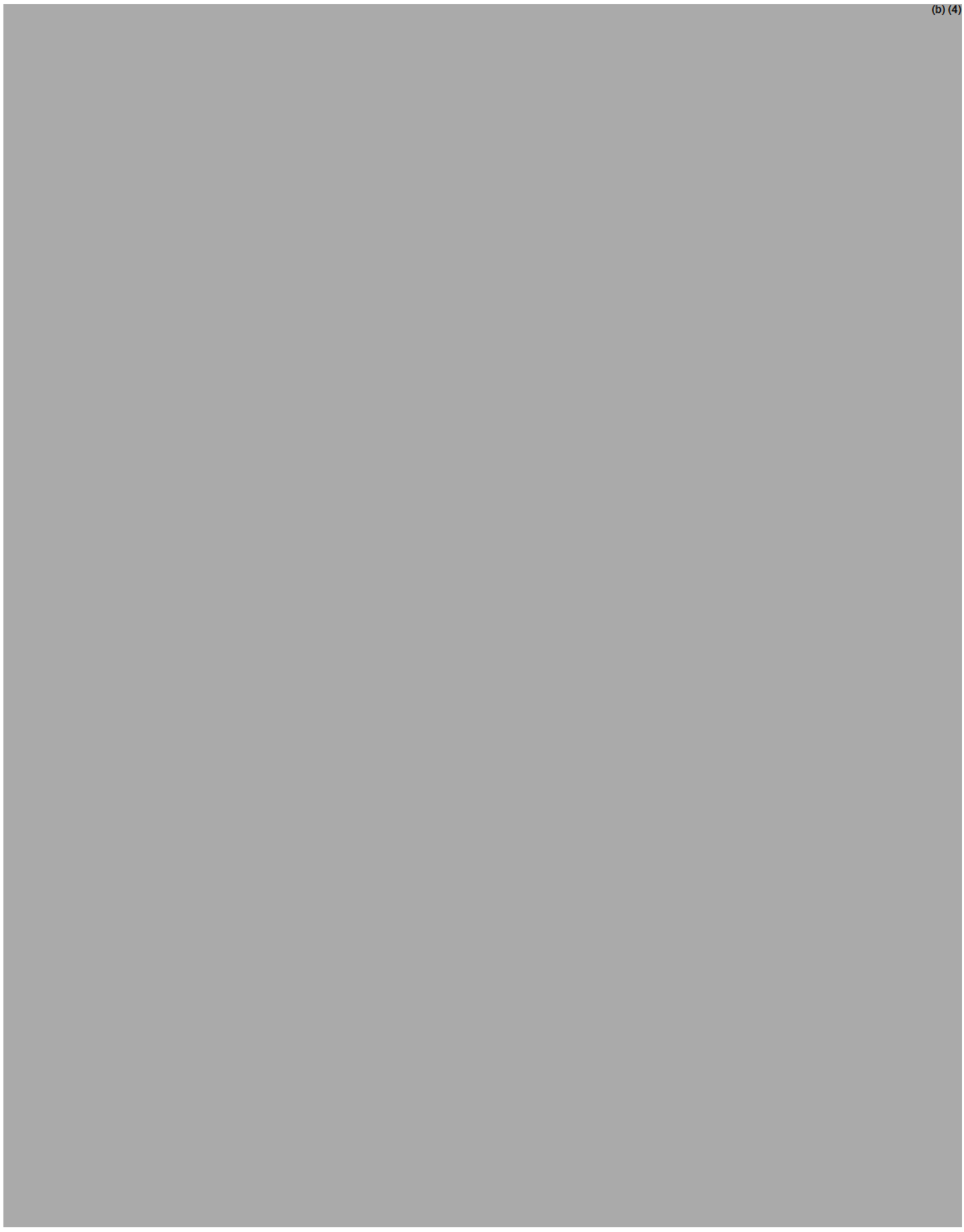
Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the chemistry comments pertaining to this application that were provided to Matrix by facsimile in correspondence dated November 21, 2011 (refer to Section 1.4.4, References) and to the November 21, 2011 teleconference between the Agency, Matrix, and Mylan. Minutes from the teleconference are provided in Section 1.4.4, References. In response to the Agency's November 21st comments, Matrix wishes to amend this application as follows:

FDA Comment 1

(b) (4)

Response:

(b) (4)


(b) (4)

(b) (4)

FDA Comment 2

(b) (4)

Response:

(b) (4)

(b) (4)

FDA Comment 3

(b) (4)

Response:

(b) (4)

FDA Comment 4

(b) (4)

Response:

(b) (4)

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Regulatory Affairs
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Sandeep K. Rathod/VHS

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Intellectual Property

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MATRIX

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Tel : 91-40-27700363, 66327722, Fax : 27700343
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

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10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NOS. 7,790,197 AND 8,026,376
PARAGRAPH IV CERTIFICATION

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On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

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Date: October 24, 2011

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Telephone CMC Amendment

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg
(Samples and IR spectra data per Agency's request)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review and to the Agency's telephone call (Haitao Li) dated October 20, 2011. Specifically Ms. Li requested for following additional data.

Comment # 1
Please conduct Identification by IR testing on the USP Reference Standard and Matrix's API according to USP <197K> and report the results individually and superimposed.

Response:
As requested, identification by IR testing has been conducted on the USP Reference Standard (Lot # F0I169) and Matrix's drug substance (QCD-3/ASC/WS001/10) according to USP <197> method. A copy of the FT-IR spectral data (individual and superimposed) is enclosed in **Section 3.2.S.4.4**.

Comment # 2
Please conduct Identification by IR testing on the same USP Reference Standard and Matrix API sample using the modified USP <197K> method. Again, report results individually and superimposed.

Response:
As requested, identification by IR testing has been conducted on the USP Reference Standard (Lot # F0I169) and Matrix's drug substance (QCD-3/ASC/WS001/10) according to modified USP <197> method. A copy of the FT-IR spectral data (individual and superimposed) is enclosed in **Section 3.2.S.4.4**.

Comment # 3
Please provide the detailed test procedure used to obtain the above data.

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Response:
As requested, a copy of the test procedure that was followed to obtain data on IR testing using both USP <197K> method and modified USP <197> method is enclosed in **Section 3.2.S.4.2**.

Comment # 4
Please discuss the results.

Response:
The IR spectra obtained for USP RS and Matrix drug substance is not found to be superimposable when tested using USP <197K> method however the same obtained using modified USP <197> method is found to be superimposable. Kindly note, Matrix manufactures [redacted] (b) (4) form of Atorvastatin Calcium whereas the USPRS represents a trihydrate crystalline morph.

Comment # 5
Please provide quantities sufficient to conduct the testing in triplicate of the same USP Reference Standard and Matrix API used to conduct the above tests to FDA's St. Louis laboratory. The Laboratory address and contact person are noted below:

James F. Allgire
Food and Drug Administration
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
314-539-3813

Response:
As requested, samples of USP Reference Standard and Matrix drug substance will be sent under separate cover to the attention of Mr. James F.Allgire.

#	Sample	Batch No.
1	USP Reference Standard	F0I169
2	Matrix Drug Substance	QCD-3/ASC/WS001/10

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Shane Shupe at (304) 554-4148, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

for

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Shane Shupe
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod/VHS

Sandeep K. Rathod
Intellectual Property

MATRIX

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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U.S. PATENT NO. 7,790,197
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The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 5,273,995 and RE40667 and their associated pediatric exclusivities; prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156; 6,126,971 and their associated pediatric exclusivities; and prior to the expiration of U.S. Patent No. 7,790,197.

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September 27, 2011

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PARAGRAPH IV CERTIFICATION

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Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 8,026,376) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 8,026,376 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95, Matrix certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod /MHS

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Tel : 91-40-27700363, 66327722, Fax : 27700343
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 5,273,995 and RE40667 and their associated pediatric exclusivities; prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156; 6,126,971 and their associated pediatric exclusivities; and prior to the expiration of U.S. Patent No. 7,790,197.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

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Intellectual Property

Signed off in DARRTS on 9/8/2011

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 91-226

Date of submission: 5/26/11.

Review Number: 4

Drug Names: Atorvastatin Calcium, 10, 20, 40, 80 mg tablets (Matrix Laboratories LTD.).

Consult #: 2011-0512

Consult from: Leigh Ann sears, and Trang Tran.

Request date: 8/29/2011. Desired completion date: 9/8/11

Generic drug name: Atorvastatin calcium tablets.

Drug class: Statins (generic atorvastatin). **Indication**: Lipid lowering.

Type of document: Electronic submission dated 5/26/11.

Subject of Consult: OGD is requesting the pharmacology /toxicology consult on the impurities (such as (b) (4)) in the generic atorvastatin calcium drug product under ANDA 91-226. Previously three pharmacology/toxicology consults have been signed off on this ANDA, including consult # 2011-0512 in DARRTS on 4/22/11. The current consult comments are stated below:

COMMENTS
OGD is requesting a Pharm/Tox Review.(EXPEDITED REVIEW) "Impurities listed are higher than the RLD." Please evaluate the amendment ANDA in EDR Module 3 (see attached documents for reference). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.sears@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.

Division: Division of Metabolic and Endocrinology products.

Review completion date: 9/7/11.

In a previous consult review signed off in DARRTS on 4/22/11, the pharmacology/ toxicology had recommended that sponsor respond to the deficiencies (listed below). The company has responded with their comments on 5/26/11. These are stated below

Deficiency # 1:

(b) (4)

(b) (4)

Firm's response is stated below

(b) (4)

Deficiency # 2:

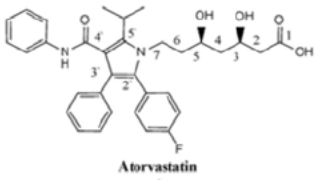
(b) (4)

Firm's response is stated below

(b) (4)

(b) (4)

Figure. (b) (4)



Atorvastatin

(b) (4)

(b) (4)

Genetic toxicology studies

(b) (4)

This study was conducted at (b) (4) on 8/18/2009, the details on test article and methods are described below:

(b) (4) Code Number	Test Article / Impurity ID	Batch No.	Purity (per protocol)	Test Article Description	Storage Conditions
AD24SA	Atorvastatin Calcium	1036244	(b) (4) %	White powder	2 to 8°C, stored protected from light without desiccant
AD25BJ	(b) (4)	ADL/1420(19)/0111	(b) (4) %	(b) (4)	

Methods:

The test articles, Atorvastatin Calcium (alone; Batch No. 1036244) and Atorvastatin Calcium spiked with (b) (4) (referred to as Atorvastatin Calcium with impurity; Batch No. of (b) (4): ADL/1420(19)/0111), were tested in the Bacterial Reverse Mutation Assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A in the presence and absence of Aroclor-induced rat liver S9. The assay was performed in two phases, using the plate incorporation method. The first phase, the initial toxicity-mutation assay, was used to establish the dose-range for the confirmatory mutagenicity assay and to provide a preliminary mutagenicity evaluation. The second phase, the confirmatory mutagenicity assay, was used to evaluate and confirm the mutagenic potential of the test article.

(b) (4) was selected as the solvent of choice based on information provided by the Sponsor, solubility of Atorvastatin Calcium and compatibility with the target cells. Atorvastatin Calcium formed a soluble and clear solution at approximately 500 mg/mL, the maximum concentration tested in the solubility test. The impurity, (b) (4) (b) (4) formed a (b) (4) (b) (4)

Results:

(b) (4)

1. Studies with the parent drug product (atorvastatin calcium)

Initial Toxicity-Mutation Assay

The results of the initial toxicity-mutation assay with Atorvastatin Calcium are presented in Tables 1 and 2. These data were generated in Experiment B1.

In Experiment B1 (Initial Toxicity-Mutation Assay), the maximum dose tested was 5000 µg per plate; this dose was achieved using a concentration of 100 mg/mL and a 50 µL plating aliquot. The dose levels tested were 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. Neither precipitate nor appreciable toxicity was observed. Based on the findings of the initial toxicity-mutation assay, the maximum dose plated in the confirmatory mutagenicity assay was 5000 µg per plate.

Confirmatory Mutagenicity Assay

The results of the confirmatory mutagenicity assay with Atorvastatin Calcium are presented in Tables 3 through 6. These data were generated in Experiments B2 and B3.

In Experiment B2 (Confirmatory Mutagenicity Assay), no positive mutagenic responses were observed with tester strains TA98, TA1535, TA1537 and WP2 *uvr*A in either the presence or absence of S9 activation. The dose levels tested were 50, 150, 500, 1500 and 5000 µg per plate. Neither precipitate nor appreciable toxicity was observed. Due to an unacceptable mean vehicle control value, tester strain TA100 in the presence of S9 activation was not evaluated for mutagenicity but was retested in Experiment B3. Tester strain TA100 in the absence of S9 activation was also not evaluated but was retested in Experiment B3 due to an unacceptable mean positive control value.

In Experiment B3 (Retest of the Confirmatory Mutagenicity Assay), no positive mutagenic responses were observed with tester strain TA100 in either the presence or absence of S9 activation. The dose levels tested were 50, 150, 500, 1500 and 5000 µg per plate. Neither precipitate nor appreciable toxicity was observed.

Table 1. Initial toxicity assay with atorvastatin calcium without S-9.

(b) (4)

(b) (4)

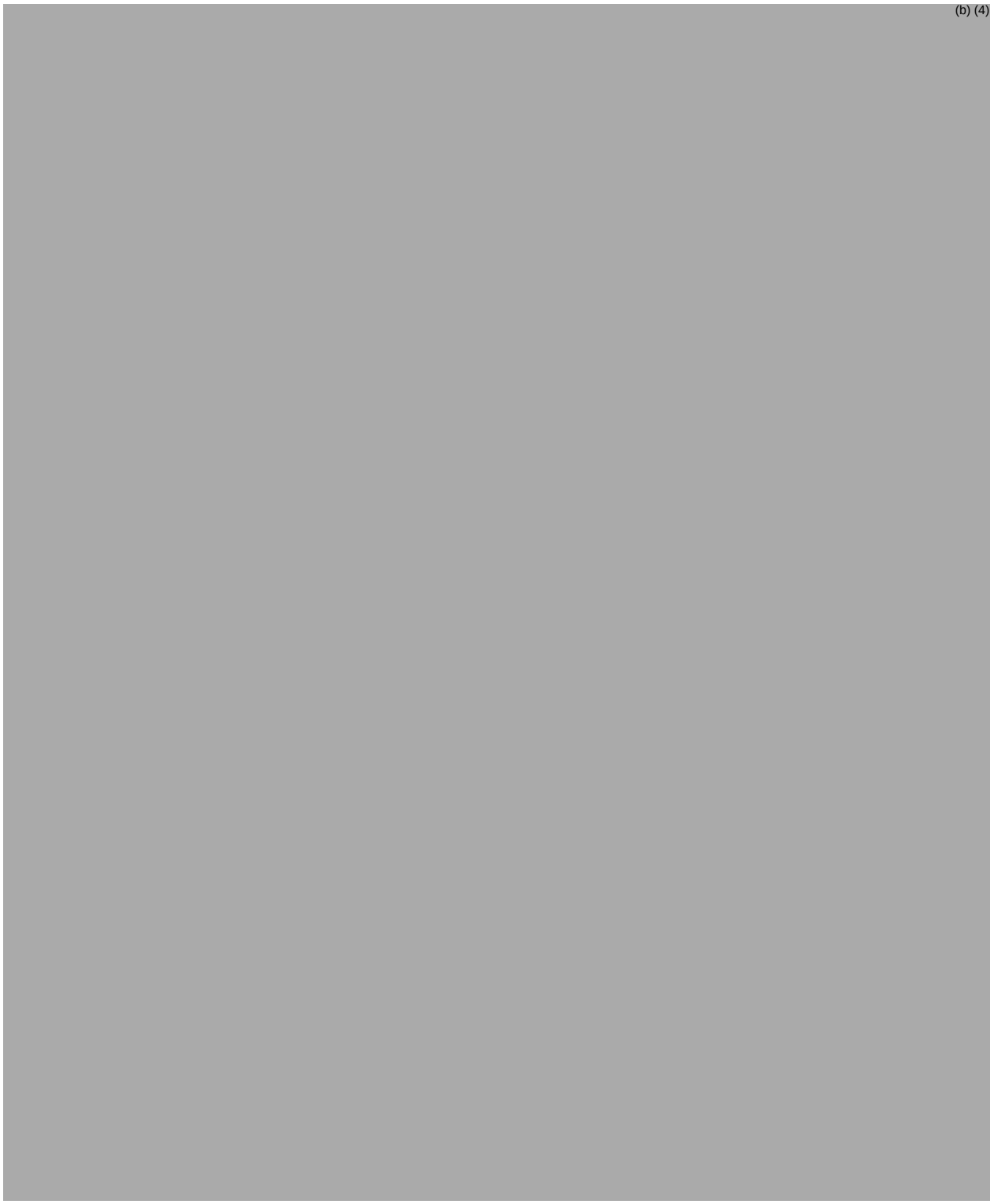
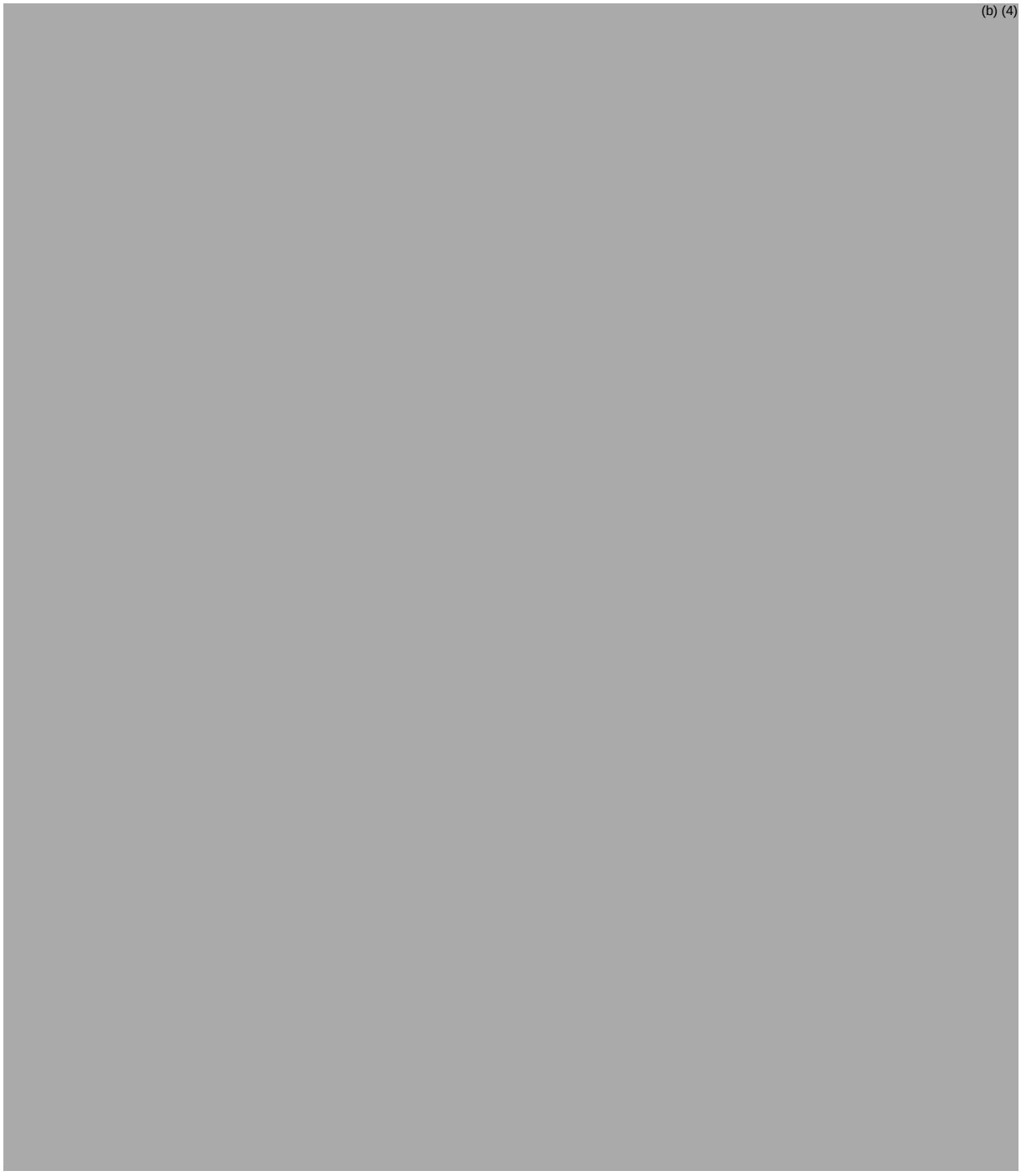


Table 2. Initial toxicity assay with atorvastatin calcium drug product in the presence of S-9

(b) (4)



Similar observations were made in the confirmatory assay with the atorvastatin calcium drug product.

2. Studies with the impurity in the drug product

Atorvastatin Calcium spiked with (b) (4)% (b) (4)

Tester Strain Titer Results

(b) (4)

Initial Toxicity-Mutation Assay

The results of the initial toxicity-mutation assay with Atorvastatin Calcium with impurity are presented in Tables 7 and 8. These data were generated in Experiment B1.

In Experiment B1 (Initial Toxicity-Mutation Assay), the maximum dose tested was 5000 µg per plate; this dose was achieved using a concentration of 100 mg/mL and a 50 µL plating aliquot. The dose levels tested were 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate, of which (b) (4)% was Atorvastatin Calcium and (b) (4)% was (b) (4) The dosing formulations were adjusted to compensate for the percentage of (b) (4) by weight using a correction factor of (b) (4) No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. No precipitate was observed. Toxicity was observed at 5000 µg per plate with all *Salmonella* tester strains. Based on the findings of the initial toxicity-mutation assay, the maximum dose plated in the confirmatory mutagenicity assay was 5000 µg per plate.

Confirmatory Mutagenicity Assay

The results of the confirmatory mutagenicity assay with Atorvastatin Calcium with impurity are presented in Tables 9 through 12. These data were generated in Experiments B2 and B3.

In Experiment B2 (Confirmatory Mutagenicity Assay), no positive mutagenic responses were observed with tester strains TA98, TA1535, TA1537 and WP2 *uvr*A in either the presence or absence of S9 activation. The dose levels tested were 50, 150, 500, 1500 and 5000 µg per plate, of which (b) (4)% was Atorvastatin Calcium and (b) (4)% was (b) (4) No precipitate was observed. Toxicity was observed at 5000 µg per plate with tester strains TA98, TA1535 and TA1537. Due to an unacceptable mean vehicle or positive control value, tester strain TA100 in the presence and absence of S9 activation was not evaluated for mutagenicity but was retested in Experiment B3.

In Experiment B3 (Retest of the Confirmatory Mutagenicity Assay), no positive mutagenic responses were observed with tester strain TA100 in either the presence or absence of S9 activation. The dose levels tested were 50, 150, 500, 1500 and 5000 µg per plate, of which (b) (4)% was Atorvastatin Calcium and (b) (4)% was (b) (4) Neither precipitate nor appreciable toxicity was observed.

Table 7. Initial assay with the atorvastatin calcium drug product with impurities (in the absence of S-9)

(b) (4)

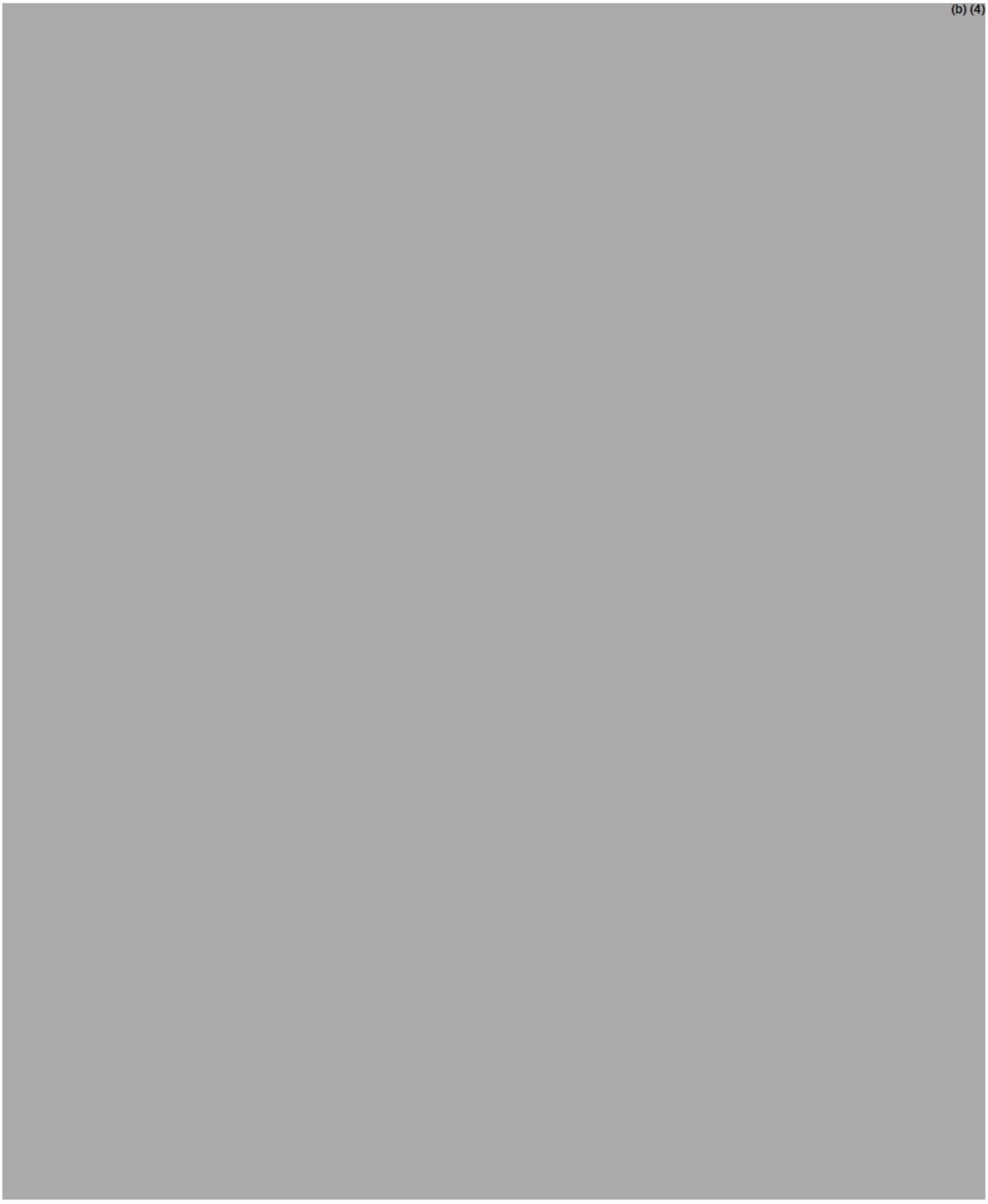
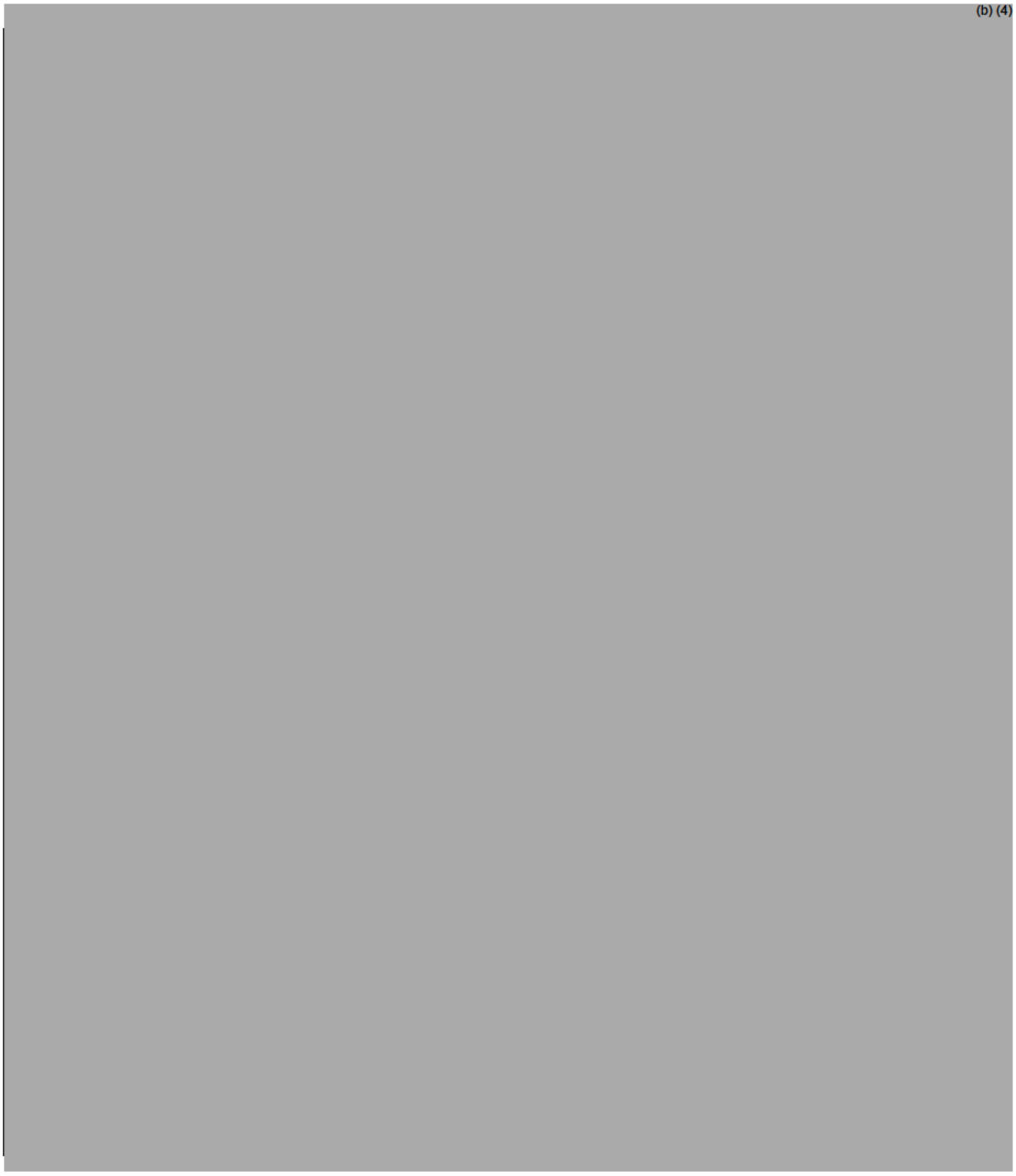

(b) (4)

Table 8. Initial assay with the atorvastatin calcium drug product with impurities (in the presence of S-9)

(b) (4)



Similar observations were made in the confirmatory assay.

In the confirmatory mutagenicity assay, no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. The dose levels tested were 50, 150, 500, 1500 and 5000 µg per plate, of which (b) (4)% was Atorvastatin Calcium and (b) (4)% was (b) (4) Based on formulation analysis results, the actual (b) (4) content was found to be approximately (b) (4) to (b) (4)% of the total dose content. N(b) (4) was observed. Toxicity was observed at 5000 µg per plate with most *Salmonella* test conditions.

Under the conditions of this study, test articles Atorvastatin Calcium and **Atorvastatin Calcium spiked with** [redacted] were concluded to be negative in the Bacterial Reverse Mutation Assay.

Sponsor's conclusions are provided below:

All criteria for a valid study were met as described in the protocol. The results of the Bacterial Reverse Mutation Assay indicate that, under the conditions of this study, neither **Atorvastatin Calcium** nor **Atorvastatin Calcium spiked with** [redacted] caused a positive mutagenic response with any of the tester strains in either the presence or absence of Aroclor-induced rat liver S9. A copy of the Common Technical Document Tables is included in Appendix VI.

2. *In Vitro* Mammalian Chromosome Aberration Test in Chinese Hamster ovary (CHO) cells with Atorvastatin Calcium (Batch No. 1036244) and Atorvastatin Calcium spiked with [redacted] [Batch No. ADL/1420(19)/0111]. Study # TOX 037-005.

Atorvastatin calcium spiked with impurities (with [redacted]) was tested in an 'in vitro mammalian chromosome aberration' test. The study was conducted at [redacted] on 2/17/2011, the details on test article and methods are described below:

Methods:

[redacted] Code Number	Test Article / Impurity ID	Batch No.	Purity/Potency	Test Article Description	Molecular Weight
AD24SA	Atorvastatin Calcium	1036244	[redacted]% (by HPLC)	White powder	1155.36
AD25BJ	[redacted]	ADL/1420(19)/0111	[redacted]%	[redacted]	590.65

The test article articles, Atorvastatin Calcium (alone; Batch No. 1036244) and Atorvastatin Calcium spiked with [redacted] (referred to as Atorvastatin Calcium with impurity; Batch No. of [redacted] ADL/1420(19)/0111), were tested in the chromosome aberration assay using Chinese hamster ovary (CHO) cells in both the absence and presence of an Aroclor-induced rat liver S9 metabolic activation system. A preliminary toxicity test was performed to establish the dose range for the chromosome aberration assay. The chromosome aberration assay was used to evaluate the clastogenic potential of the test article. Cytotoxicity in the preliminary and definitive chromosome aberration assays was determined based on the increase in cell counts relative to that of the baseline cell counts.

[redacted] was used as the solvent based on information provided by the Sponsor, solubility of Atorvastatin Calcium and [redacted] Atorvastatin Calcium was soluble in [redacted]

1. Chromosomal aberration assay with the atorvastatin calcium drug product.

***In Vitro* Mammalian Chromosome Aberration Test with Atorvastatin Calcium (AD24SA)**

In the preliminary toxicity assay using Atorvastatin Calcium, the maximum dose tested was 5000 µg/mL. Atorvastatin Calcium was soluble in [(b) (4)] at all concentrations tested. Visible [(b) (4)] was observed in the treatment medium at dose levels ≥ 1500 µg/mL, while dose levels ≤ 500 µg/mL were soluble in treatment medium at the beginning and conclusion of the treatment period. Selection of dose levels for the chromosome aberration assay was based on cell growth inhibition relative to the solvent control. Substantial toxicity (i.e., at least 50% cell growth inhibition, relative to the solvent control) was observed at dose levels 500 and 1500 µg/mL in both the non-activated and S9-activated 4-hour exposure groups, and at dose levels ≥ 150 µg/mL in the non-activated 20-hour continuous exposure group. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 25 to 450 µg/mL for the non-activated 4-hour exposure group, from 25 to 400 µg/mL for the S9-activated 4-hour exposure group, and from 6.25 to 250 µg/mL for the non-activated 20-hour continuous exposure group.

In the chromosome aberration assay, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. Atorvastatin Calcium was soluble in [(b) (4)] at all concentrations tested. At the beginning of the treatment period, visible [(b) (4)] that was observed in the treatment medium at dose levels ≥ 400 µg/mL, became soluble upon mixing. At the conclusion of the treatment period, all dose levels were soluble in the treatment medium. Selection of doses for microscopic analysis was based on toxicity (the lowest dose with at least 50% reduction in cell growth and two lower doses) in all harvests.

The percentage of cells with structural or numerical aberrations in the Atorvastatin Calcium-treated groups was not significantly increased relative to solvent control at any dose level ($p > 0.05$, Fisher's Exact test).

The results of the assay using Atorvastatin Calcium are summarized in the following table:

Treatment Time	Recovery Time	Harvest Time	S9	Toxicity* at highest dose scored (µg/mL)	Mitotic Index Reduction **	LED[1] for Structural Aberrations µg/mL	LED[1] for Numerical Aberrations µg/mL
4 hr	16 hr	20 hr	-	58% at 200	32%	None	None
20 hr	0 hr	20 hr	-	64% at 200	66%	None	None
4 hr	16 hr	20 hr	+	57% at 250	39%	None	None

*Cell growth inhibition
** Relative to solvent control at the highest dose evaluated for chromosome aberrations
[1] LED = lowest effective dose

Table. The results of the chromosomal aberration assay with the atorvastatin calcium drug product in the absence and presence of S-9 are shown below.

(b) (4)



2. Chromosomal aberration assay with the atorvastatin calcium drug product containing impurities

***In Vitro* Mammalian Chromosome Aberration Test with Atorvastatin Calcium spiked with [redacted]% impurity [redacted]**

In the preliminary toxicity assay using Atorvastatin Calcium with impurity, the maximum dose tested was 5000 µg/mL. The dosing formulations were adjusted to compensate for the percentage of [redacted] by weight using a correction factor of [redacted] Atorvastatin Calcium with impurity was soluble in [redacted] at all concentrations tested. Visible [redacted] was observed in the treatment medium at dose levels ≥ 1500 µg/mL, while dose levels ≤ 500 µg/mL were soluble in treatment medium at the beginning and conclusion of the treatment period. Selection of dose levels for the chromosome aberration assay was based on cell growth inhibition relative to the solvent control. Substantial toxicity (i.e., at least 50% cell growth inhibition, relative to the solvent control) was observed at dose levels ≥ 500 µg/mL in both the non-activated and S9-activated 4-hour exposure groups, and at dose levels ≥ 15 µg/mL in the non-activated 20-hour continuous exposure group. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 25 to 450 µg/mL for the non-activated 4-hour exposure group, from 12.5 to 350 µg/mL for the S9-activated 4-hour exposure group, and from 0.78 to 100 µg/mL for the non-activated 20-hour continuous exposure group. These dose levels were intended to contain [redacted]% Atorvastatin Calcium and [redacted]% [redacted] However, based on formulation analysis results, the actual [redacted] content was found to be approximately [redacted] to [redacted]% of the total dose content.

In the chromosome aberration assay, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. Atorvastatin Calcium with impurity was soluble in [redacted] and in the treatment medium at all concentrations tested at the beginning and conclusion of the treatment period. Selection of doses for microscopic analysis was based on toxicity (the lowest dose with at least 50% reduction in cell growth and two lower doses) in all harvests.

The percentage of cells with structural or numerical aberrations in the non-activated 4-hour exposure group was significantly increased relative to solvent control at 300 µg/mL ($p \leq 0.05$, Fisher's Exact test). However, the Cochran-Armitage test was negative for a dose response ($p > 0.05$). In addition, the percentage of cells with structural aberrations at 300 µg/mL ([(b) (4)]%) was within the historical solvent control range of [(b) (4)]% to [(b) (4)]%. Therefore, it was not considered to be biologically significant. The percentage of cells with numerical aberrations in the test article-treated group was not significantly increased relative to solvent control at any dose level ($p > 0.05$, Fisher's Exact test).

The percentage of cells with structural or numerical aberrations in the S9-activated 4-hour and the non-activated 20-hour exposure groups was not significantly increased relative to solvent control at any dose level ($p > 0.05$, Fisher's Exact test).

The results of the assay using Atorvastatin Calcium with impurity are summarized in the following table:

Treatment Time	Recovery Time	Harvest Time	S9	Toxicity* at highest dose scored (µg/mL)	Mitotic Index Reduction **	LED[1] for Structural Aberrations µg/mL	LED[1] for Numerical Aberrations µg/mL
4 hr	16 hr	20 hr	-	62% at 300	7%	None	None
20 hr	0 hr	20 hr	-	55% at 12.5	44%	None	None
4 hr	16 hr	20 hr	+	55% at 250	27%	None	None

*Cell growth inhibition
** Relative to solvent control at the highest dose evaluated for chromosome aberrations
[1] LED = lowest effective dose

Table. The results of the chromosomal aberration assay with the atorvastatin calcium drug product containing impurities in the absence and presence of S-9 are shown below.



The data on historical controls are shown below.

IN VITRO MAMMALIAN CYTOGENETIC TEST USING
CHINESE HAMSTER OVARY (CHO) CELLS

HISTORICAL CONTROL VALUES
STRUCTURAL ABERRATIONS
2007-2009

NON-ACTIVATED TEST SYSTEM

Historical Values	Solvent (%)	Positive Control[2] (%)
Mean	0.4	20.8
±SD[1]	0.7	4.2
Range	0.0-5.5	10.5-48.0

S9-ACTIVATED TEST SYSTEM

Historical Values	Solvent (%)	Positive Control[3] (%)
Mean	0.7	22.8
±SD[1]	0.9	8.2
Range	0.0-4.0	11.0-77.5

1 SD = standard deviation.
2 Positive control for non-activated studies, Mitomycin C (MMC, 0.05-0.3 µg/mL).
3 Positive control for S9-activated studies, cyclophosphamide (CP, 10-50 µg/mL).

Sponsor's conclusions are stated below

The positive and solvent controls fulfilled the requirements for a valid test. The Common Technical Data (CTD) Summary Table is included in Appendix V.

Using a 4 hour treatment with S9 and a 4 hour and 20 hour treatment without S9, the highest doses tested in the chromosome aberration assay were based on toxicity; they were 450 µg/mL for Atorvastatin Calcium and 450 µg/mL for Atorvastatin Calcium spiked with impurity, which corresponds to approximately (b) (4) µg/mL (b) (4)

Under the conditions of the assay described in this report, the test articles, Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4) were concluded to be negative for the induction of structural and numerical chromosome aberrations in CHO cells in both the non-activated and the S9-activated test systems.

Mutagenicity: In summary, mutagenicity studies show that atorvastatin calcium without and with impurity (spiked with [redacted] in the atorvastatin calcium drug product) was not mutagenic/cytogenic in the following 2 tests: Ames test at doses up to 5000 ug/plate, and in vitro in chromosomal aberration assay in cultured Chinese Hamster Ovary (CHO) cells at concentration up to 250-300 ug/ml.

Summary:
Two pharmacology/toxicology deficiencies were communicated to the sponsor (see review in DARRTS on 4/22/11). In response to the first deficiency, sponsor states that they can not qualify the [redacted] because it is an [redacted] in the formation of [redacted] and [redacted]. However they have performed the more recent version of Derek analysis on this structural impurity and the data show that no structural alerts were found for carcinogenicity, chromosomal damage, geno toxicity and/or mutagenicity.

The sponsor has also responded to our second concern on the cumulative effects of the multiple [redacted] (up to [redacted]%) in the drug product. They have conducted additional tests (such as Ames assay and chromosomal aberration assay) using [redacted]% levels of [redacted] as a representative epoxide in the atorvastatin drug product. Note that this impurity was used to qualify the cumulative effects of all epoxides; sponsor states that assuming that all [redacted] have similar mechanisms of exerting geno-toxicity as [redacted]. The total levels of [redacted] in the chromosomal aberration assay was 31.5 ug/ml. These assays showed that the above concentration of the epoxide impurities in the drug product produced negative results, suggesting that impurities present in the drug product at the proposed levels ([redacted]%) were not mutagenic/clastogenic. In conclusion, the total concentration of these epoxide impurites up to [redacted]% do not pose any significant mutagenic/clastogenic potential.

Thus, sponsor by providing additional tests (such as subjecting the [redacted] to the latest version of DEREK analysis), as well as by conducting two additional geno-toxicity assays (Ames and chromosome aberration assays with the atorvastatin drug product containing [redacted]) has qualified the impurities in their atorvastatin calcium drug product and these are acceptable.

Internal Recommendations:

From the pharmacology/toxicology point of view, the proposed levels of (b) (4) (b) (4) in the atorvastatin calcium drug product, as well as the cumulative effects of the multiple (b) (4) (up to (b) %) in the drug product can be considered qualified, based on submitted explanation and geno-toxicity studies.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/marchick/TranTrang/Leigh Ann Sears/Ripper, Li Haitao, Patankar Suhas,, Nagavelli Laxma
File name: ANDA 91226-0811-con (atorvastatin- Matrix)

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

/s/

INDRA ANTONIPILLAI
09/08/2011
Please see the Internal Pharmacology/Toxicology recommendations.

KAREN L DAVIS BRUNO
09/08/2011

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0552	
TO *(Division/Office)* DMEP - HFD-510 Thru: Leah Ripper, ODEII - HFD 102			FROM: Leigh Ann Sears/Haitao Li	
DATE: 8/26/2011	IND NO.	ANDA NO. 091226	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 5/26/2011,
NAME OF DRUG Atorvastatin Calcium		PRIORITY CONSIDERATION Expedited Review	CLASSIFICATION OF DRUG Lipid Lowering Agent	DESIRED COMPLETION DATE 9/10/2011
NAME OF FIRM Matrix Labs LTD				

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICIENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION
PROTOCOL-- BIOPHARMACEUTICS
IN--VIVO WAIVER REQUEST
DEFICIENCY LETTER RESPONSE
BIOAVAILABILITY STUDIES
PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
_SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review.(EXPEDITED REVIEW) "Impurities listed are higher than the RLD." Please evaluate the amendment ANDA in EDR Module 3 (see attached documents for reference). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.sears@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Pharm-Tox consults-ANDA 91226CR05, Amendment submitted May 26, 2011.

HFD-630/H. Li/CR/8/25/11
HFD-630/L. Nagavelli/TL/8/25/2011
HFD-617/L.A.Sears/PM/8/25/2011

The following deficiencies were sent to the firm per pharm-tox consult (#2011-0512) dated 4/22/2011 (DARRTS). The firm's response is included.

Deficiency:

(b) (4)

Firm's response:

(b) (4)

Deficiency:

(b) (4)

Firm's response:

(b) (4)

(b) (4)

In the previous submissions to this ANDA, Matrix has provided toxicological qualification studies involving individual epoxide impurities commensurate with their specification levels demonstrating lack of genotoxicity potential.
In consideration of all above, we believe that the lack of genotoxicity potential for structurally similar cumulative epoxide levels (b) (4) %) has been conclusively ascertained.

The documents supporting their claims are in EDR:
Location: Edr: 91226, May 26, 2011, m3 folder:
3.2.P.5.6 First DEREK Report on (b) (4) Impurity
Second DEREK Report on (b) (4) Impurity
(b) (4) TOX Studies (TOX 037-004 and TOX 037-005)
DEREK Report on (b) (4) Impurity
DEREK Report on (b) (4) Impurity
DEREK Report on (b) (4) Impurity

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

TRANG Q TRAN
08/29/2011

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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.

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/s/

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08/26/2011

LAXMA R NAGAVELLI
08/26/2011

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

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June 30, 2011

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

PATENT AMENDMENT

Dear Dr. Webber:

The purpose of this amendment is to notify the Agency that with respect to the above referenced ANDA, the parties in the underlying patent litigation filed a "Joint Motion to Dismiss" (attached) with the United States District Court for the District of Delaware on June 28, 2011. Matrix will notify FDA once the requested dismissal order has been entered by the court and provide a copy of the signed order. Upon entry of the dismissal order, Matrix's 30 month stay under 21 USC § 355(j)(5) will be lifted, making Matrix's ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg immediately eligible for approval upon completion of the regulatory review process.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep Rathod

Sandeep K. Rathod
Intellectual Property

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, and WARNER-LAMBERT COMPANY LLC,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 09-441-LPS Consolidated Action
MYLAN INC., MATRIX LABORATORIES LIMITED, and MATRIX LABORATORIES INC.,	)	
Defendants.	)	

JOINT MOTION TO DISMISS

WHEREAS, plaintiffs Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company and Warner-Lambert Company LLC ("Pfizer") and defendants Mylan Inc., Matrix Laboratories Limited, and Matrix Laboratories Inc. ("Mylan") are parties to a litigation relating to U.S. Patent No. 5,969,156 and its Re-examination Certificate, U.S. Patent No. 6,087,511 and U.S. Patent No. 6,274,740 ("the Action");

WHEREAS, Pfizer and Mylan have entered into an Agreement, dated as of January 24, 2011 ("Agreement"), pursuant to which the parties have resolved this action;

NOW THEREFORE, Pfizer and Mylan jointly move this Court pursuant to Fed. R. Civ. P. 41(a)(2) to enter the attached order providing that:

1. All claims and counterclaims in this action are dismissed without prejudice, each Party to bear its own costs, expenses and attorneys' fees in connection with this action;

2. This dismissal shall not act as an adjudication on the merits;

3. The Protective Order entered by the Court in this action shall remain in full force and effect notwithstanding the dismissal by the Court of this action;

4. The parties expressly waive any right of appeal from this Order; and

5. The Court reserves jurisdiction over this Order in the event of any dispute concerning it.

Dated: June 28, 2011

/s/ Rudolf E. Hutz
Rudolf E. Hutz (#484)
Jeffrey B. Bove (#998)
Mary W. Bourke (#2356)
Daniel C. Mulveny (#3984)
CONNOLLY BOVE LODGE & HUTZ LLP
1007 N. Orange Street
Wilmington, DE 19899
(302) 658-9141
rhutz@cblh.com

Attorneys for Plaintiffs

/s/ Neal C. Belgam
Neal C. Belgam (#2721)
Samuel T. Hirzel (#4415)
PROCTER HEYMAN LLP
300 Delaware Avenue, Suite 200
Wilmington, Delaware 19801
(302) 472-7300
nbelgam@proctorheyman.com

Attorneys for Defendants

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MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

June 30, 2011

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

PATENT AMENDMENT

Dear Dr. Webber:

Matrix Laboratories Limited ("Matrix") previously informed you, in a patent amendment to the above referenced ANDA, that the parties to the underlying patent litigation filed a joint motion to dismiss. The United States District Court for the District of Delaware entered the dismissal order today (attached), dismissing the suit without an adjudication on the merits. As a result, Matrix's 30 month stay under 21 U.S.C. § 355(j)(5) is no longer in effect. Accordingly, Matrix requests approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg immediately upon completion of the regulatory review process.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep Rathod

Sandeep K. Rathod
Intellectual Property

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, and WARNER-LAMBERT COMPANY LLC,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 09-441-LPS
	)	Consolidated Action
MYLAN INC., MATRIX LABORATORIES LIMITED, and MATRIX LABORATORIES INC.,	)	
Defendants.	)	

ORDER

The Court having considered the Joint Motion to Dismiss submitted by the Parties in the above-captioned matter pursuant to Fed. R. Civ. P. 41(a)(2), hereby orders as follows:

1. All claims and counterclaims in this action are dismissed without prejudice, each Party to bear its own costs, expenses and attorneys' fees in connection with this action;

2. This dismissal shall not act as an adjudication on the merits;

3. The Protective Order entered by the Court in this action shall remain in full force and effect notwithstanding the dismissal by the Court of this action;

4. The parties expressly waive any right of appeal from this Order; and

5. The Court reserves jurisdiction over this Order in the event of any dispute concerning it.

IT IS SO ORDERED this 30th day of June, 2011.

The Honorable Leonard P. Stark
United States District Judge

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MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
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Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
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Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

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On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

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Intellectual Property

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Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: June 28, 2011

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Gratuitous CMC Amendment

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Agency's telephone call received on June 24, 2011 from Leigh Ann Sears, of your Office, in which she requested clarification of the activities and responsibilities of each establishment registered in the ANDA.

An updated outside testing plan was submitted to this ANDA in a gratuitous CMC amendment on November 17, 2010 detailing function of each facility listed in this ANDA. Since November 2010, Matrix Nashik's QC unit is now equipped to perform some of the testing related to raw materials and all testing related to packaging materials that was previously proposed to be outsourced to contract testing facilities. Accordingly, a revised outside testing plan is provided in this amendment. In accordance with the revised outside testing plan, provided below are the functions performed by each of the establishments registered in the ANDA.

Establishment details	Function performed
Matrix Laboratories Ltd. (Nashik) Plot No. F-4 & F-12, Malegaon MIDC, Sinnar, Nashik-422 113, Maharashtra, INDIA Establishment Registration # 3005587313 Contact person : Mr. Pramod Kumar Singh Phone : +91.2551.230092 ; Fax : +91.2551.230924 E Mail : Pramodkumar.singh@matrixlabsindia.com	Testing, Manufacturing, Packaging, Release, stability (with exception of following testing from other group facilities or outside contract labs)
Matrix Laboratories Limited Unit 3 Plot No's 38 to 40, 49 to 51, Phase IV, IDA Jeedimetla, Hyderabad Andhra Pradesh, INDIA Establishment Registration # 3003937580 Contact person: Mr. Imtiyaz Basade Phone: +91.40.23097777, Fax: +91.40.23098572 E Mail : Imtiyaz.basade@matrixlabsindia.com	Atorvastatin Calcium 1. Identification test C by XRD

Establishment details	Function performed
(b) (4)	(b) (4)

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Wayne Talton at (304) 554-6551 or Shane Shupe at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

S. Wayne Talton for NB

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Shane Shupe
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

MATRIX

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Office of Generic Drugs, CDER, FDA
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RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
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Date: May 26, 2011

To:
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Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
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TELEPHONE AMENDMENT

Subject: **ANDA # 091226**,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to quality review comments dated May 12, 2011, during review of the subject ANDA of Matrix Laboratories Limited, India (Matrix). In this amendment we respond fully to all of the comments. For each item, we first restate the question **(in bold)** and then present our response. Considering that Matrix is submitting this response within 10 working days, we request the Agency to consider this as a Telephone amendment.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Shane Shupe at (304) 554-4148, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

for

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Shane Shupe
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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QUALITY DEFICIENCY - MINOR

ANDA 091226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Matrix Laboratories Limited

TEL: (304) 554-6551

ATTN: S. Wayne Talton

FAX: (304) 285-6407

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 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendments dated March 1, and March 7, 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 **4** 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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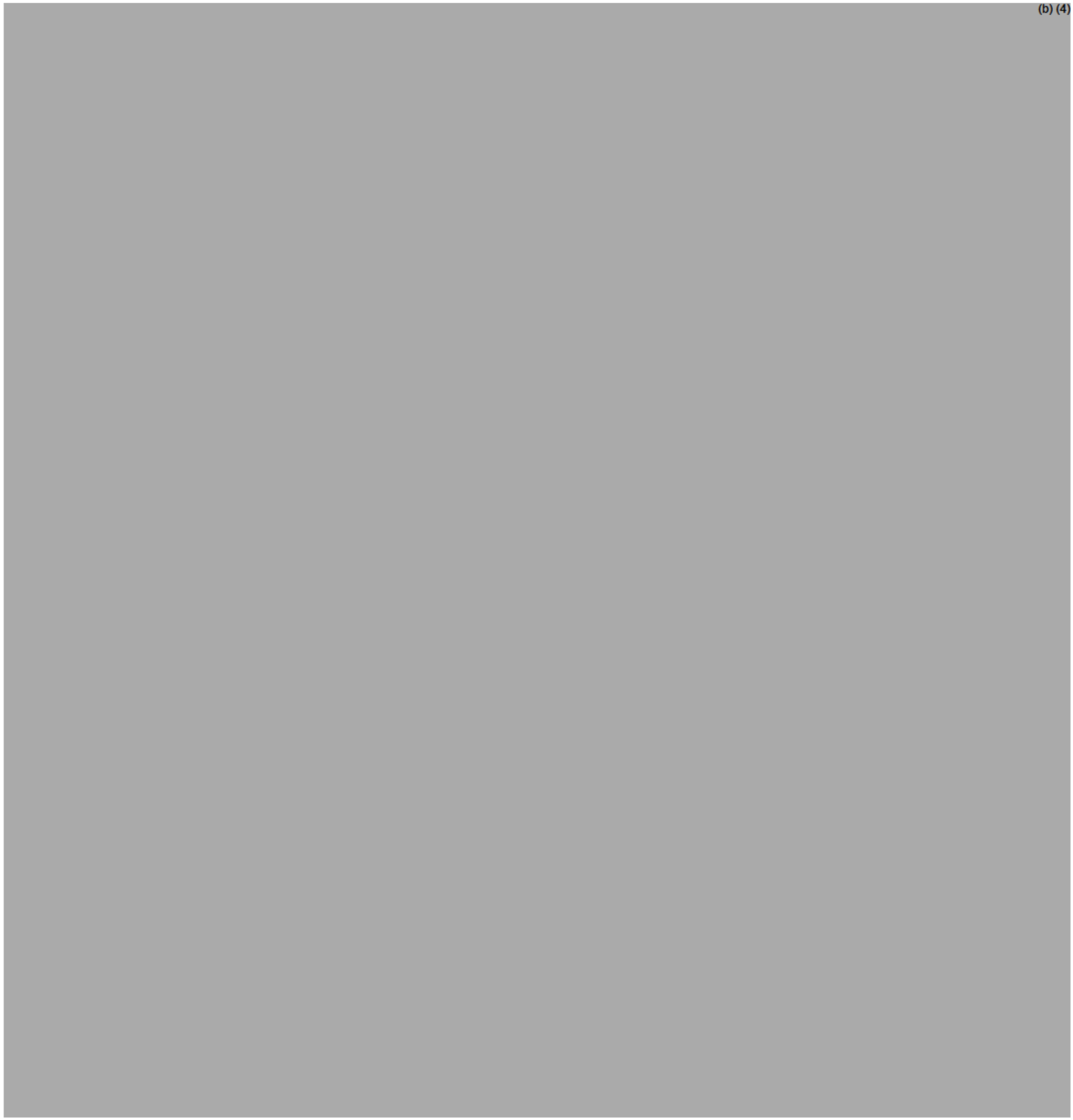
LIST OF DEFICIENCIES TO BE COMMUNICATED TO THE APPLICANT

ANDA: 091226 **APPLICANT:** Mylan/Matrix Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent Minor Deficiencies.

(b) (4)



(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

(b) (4)

b. Please provide all available long term stability data and revise the expiration dating to meet the established specification.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

LEIGH A SEARS
05/11/2011

MOHAMMED K AHMED
05/12/2011

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
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The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 5,273,995 and RE40667 and their associated pediatric exclusivities; prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156; 6,126,971 and their associated pediatric exclusivities; and prior to the expiration of U.S. Patent No. 7,790,197.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MEDICAL CONSULTATION

To:	Mark Gonitzke, Office of Generic Drugs (OGD)
ANDA:	ANDA 091226, Atorvastatin calcium, Matrix Labs Ltd
RLD:	Lipitor® (atorvastatin calcium), NDA 020702, Pfizer
Re:	L-arginine
Date of Review:	April 20, 2011
Medical Reviewer:	Linda Forsyth, M.D., Medical Officer, OGD
Through:	Dena Hixon, M.D., Associate Director for Medical Affairs, OGD
Issue:	*Clinical Team was requested to evaluate the safety of L-arginine in subjects with cardiovascular disease in generic atorvastatin.*

The Clinical Team received a medical consultation from Division of Chemistry, Office of Generic Drugs, regarding ANDA 091226. The generic version of atorvastatin calcium contains L-arginine as a (b) (4). This inactive ingredient is not contained in the reference listed drug. An 80 mg tablet contains (b) (4) of L-arginine and this exceeds the inactive ingredients database level. The Clinical Team was requested to evaluate the safety in subjects with cardiovascular disease.

The reference listed drug for atorvastatin calcium is Lipitor® (atorvastatin calcium), Pfizer (approved on December 17, 1996). Lipitor® is a lipid-altering agent. It is manufactured as a 10, 20, 40 and 80 mg tablet. The recommended starting dose of Lipitor® 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 Lipitor® is 10 to 80 mg once daily. Lipitor® can be administered as a single Lipitor® at any time of the day, with or without food. The starting dose and maintenance doses of Lipitor® should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of Lipitor®, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

L-arginine is a dietary supplement. It is a nonessential amino acid commonly promoted to play a role in the treatment of cardiovascular disease. This is purportedly due to antiatherogenic, antiischemic antiplatelet and antithrombotic properties. L-arginine is not recommended in patients following an acute myocardial infarction. It has been studied at oral doses of 6 to 30 g/day. It can be purchased as a dietary supplement, e.g. is sold as 1000 mg capsules, one to three capsules a day, advertised as an essential building block of nitric oxide.

Reference ID: 2939654

There were two studies with L-arginine in patients who experienced acute myocardial infarction. One study by Bednarz et al.[1] demonstrated oral L-arginine in myocardial infarction was well tolerated and there was a beneficial nonsignificant trend observed towards reduction of major clinical events. Patients with ST segment elevation were admitted within 24 hours after the onset of symptoms and received oral L-arginine 3 g three times a day or placebo for 30 days. The study was conducted in 792 patients. However, there was another subsequent study published by Schulman et al.[2] which concluded L-arginine added to standard postinfarction therapies did not improve vascular stiffness measurements or ejection fraction and may be associated with higher postinfarction mortality, and concluded it should not be recommended following acute myocardial infarction. This study similarly examined patients with first ST segment elevation myocardial infarction. There were 153 patients enrolled and randomly assigned to receive oral L-arginine 3 g three times a day or placebo for 6 months. There were six deaths which occurred during the 6-month study period and none in the placebo group. Due to safety concerns, the safety monitoring committee closed enrollment.

It is noteworthy, the excipient L-arginine has only been used in injection formulations and has not been used in products for oral use in CDER approved drugs.

The OGD medical officer reviewed the clinical literature summaries submitted to evaluate safety in subjects with cardiovascular disease. After reviewing the clinical studies and the limited available literature, it is the opinion of the OGD medical officer that the amount of the inactive ingredient L-arginine added to the proposed generic version of the atorvastatin appears reasonably safe.

The Office of New Drugs (OND), Division of Cardiovascular and Renal Products was consulted and on April 20, 2011 recommended the generic formulation of atorvastatin containing (b) (4) of L-arginine as an inactive ingredient is as safe as the reference listed drug. The OND medical officer did not believe there was any potential clinical benefit for this patient population from the addition of the amount of L-arginine in the generic formulation. A limitation of the review included reviewing clinical trials reported in literature with no raw data available to evaluate the integrity of the data or adverse event reporting.

RECOMMENDATIONS

The OGD Clinical Team has the following recommendation:

The available information supports a conclusion that the amount of L-arginine in the generic version of atorvastatin proposed under ANDA 91226 will not change the safety profile compared to that of the reference listed drug, including patients with

[1] Bednarz B, Jaxa-Chamiec T, Maciejewski P, Szpajer M, Janik K, Gnoit J, Kawka-Urbanek T, Drozdowska D, Gessek J, Laskowski H. Efficacy and safety of oral l-arginine in acute myocardial infarction. Results of the multicenter, randomized, double-blind, placebo-controlled ARAMI pilot trial. Kardiol Pol 2005; 62 (5):421-7.

[2] Schulman SP, Becker LC, Kass DA, Champion HC, Terrin ML, Forman S, Ernst KV, Kelemen MD, Townsend SN, Capriotti A, Hare JM, Gerstenblith G. L-arginine therapy in acute myocardial infarction:the vascular interaction with age in myocardial infarction (VINTAGE MI) randomized clinical trial. JAMA 2006; 295 (1):58-64.

Reference ID: 2939654

cardiovascular disease. Therefore, this formulation change should not preclude approval of the application.

Reference ID: 2939654

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

/s/

LINDA M FORSYTH
04/28/2011

DENA R HIXON
04/28/2011
I concur.

MATRIX

Matrix Laboratories Limited
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

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Sincerely,

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MATRIX

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Signed off in DARRTS on 4/22/2011

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 91-226

Date of submission: 3/7/2011.

Review Number: 3

Drug Names: Atorvastatin Calcium, 10, 20, 40, 80 mg tablets.

Consult #: 2011-0512

Consult from: Leigh Ann sears, and Trang Tran.

Request date: 4/6/2011. Desired completion date: 4/21/11

Generic drug name: Atorvastatin calcium tablets.

Drug class: Statins (generic atorvastatin). **Indication**: Lipid lowering.

Type of document: Electronic submission dated 3/7/2011.

Subject of Consult: OGD is requesting the pharmacology /toxicology consult on the impurities ((b) (4)) in the atorvastatin calcium drug product under ANDA 91-226. Previously two consults (including consult # 20009-0443 on this ANDA was signed off in DARRTS on 9/29/2010). They state that the sponsor has not qualified (b) (4) levels in the drug product. **The consult comments are stated below:**

> **OGD is requesting a Pharm/Tox Review. "Impurities listed are higher than the RLD." Please evaluate the need of qualifying the (b) (4) This consult is based on the consult # 20009-0443 which was done by Dr. Antonipillai. More information attached. (This ANDA is on EXPEDITED REVIEW)Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.sears@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.**

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.

Division: Division of Metabolic and Endocrinology products.

Review completion date: 4/21/11.

Introduction

OGD is concerned about the levels of (b) (4) impurity in the atorvastatin drug product. The chemist states that the sponsor does not want to qualify the high levels of (b) (4) in their drug product. The sponsor states that (b) (4) can be (b) (4) in the stomach to form (b) (4)% (b) (4) and (b) (4)% (b) (4). The proposed level of (b) (4) is NMT (b) (4)% in the drug product stability specification, and the highest observed levels of (b) (4) in the stability study at (b) (4) months are (b) (4)%.

The chemist states that they have observed up to (b) (4)% of these epoxide impurities in the drug product, based on the firm's stability data. They want to know if they need to worry about the potential cumulative genotoxic effect of these impurities?

The reviewing chemist further states that the firm performed (b) (4) study and observed that the (b) (4) (b) (4) breaks down to (b) (4) (b) (4) and (b) (4) which have been qualified. See the structures and reaction schemes, provided below.

Following Table was provided by Dr. Haitao Li (the reviewing chemist in OGD)

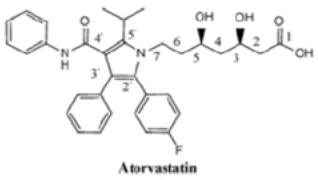
Name	Structure	Qualified Level
(b) (4)		

(b) (4)

6

(b) (4)

The following reaction scheme (b) (4) was provided to this reviewer by the OGD chemist



Atorvastatin

(b) (4)

The firm expects that (b) (4) will be (b) (4) to form (b) (4)% (b) (4) (b) (4) and (b) (4)% (b) (4). OGD is concerned that this compound is a (b) (4) (b) (4) the level of this compound is rather high in the drug product, and also it increases in stability samples. They think that the firm should qualify this impurity and want to know our opinion.

Following table was provided by the chemist in OGD:

Structure/Soures (PI or DI) USP/PF 35(1) name and limit	Structures	Lipitor (NDA 20-702) limits	DMF 21477 limit	ANDA 91226 DP (release/stability)
(b) (4)				
(b) (4)				

Structure/Soures (PI or DI) USP/PF 35(1) name and limit	Structures	Lipitor (NDA 20-702) limits	DMF 21477	ANDA 91226 DP (release/stability)
[redacted]				

(b) (4)

Note that in the previous qualification study, the firm spiked atorvastatin calcium with (b) (4)% (b) (4) and (b) (4)% (b) (4) and demonstrated that these levels do not cause genotoxicity. The firm also spiked atorvastatin calcium with (b) (4)% (b) (4) and demonstrated that this level did not cause genotoxicity (see the review in DARRTS, signed off on 9/29/2010).

In summary, previously sponsor by providing 2-week toxicity study in one species (rats) with impurities (spiked with (b) (4) and (b) (4) in the atorvastatin calcium drug product, as well as with (b) (4) impurity), as well as by conducting two geno-toxicity studies (Ames and chromosome aberration assay) has qualified the impurities in their atorvastatin calcium, and these were considered acceptable from the pharmacology/toxicity point of view.

The highest dose of atorvastatin calcium that will be marketed under this ANDA is 80 mg/day. The sponsor has proposed NMT (b) (4)% of (b) (4) in the drug product, and the highest observed (b) (4) in the drug product has been (b) (4)%. Assuming the worse case scenario of (b) (4)% (b) (4) present in the drug product, its concentration in the drug product will be (b) (4) (or (b) (4)) for chronic use.

Epoxides are a class of alkylating agents. Epoxides and hydroperoxides are highly reactive. Epoxide-containing substances from both natural and man-made sources, are ubiquitous in the environment and food supply, as well as being generated endogenously. Epoxides are electrophilic, this property being related to the chemical reactivity of the strained epoxide ring. The reactivity of the epoxide and hydroperoxide groups makes them particularly useful as alkylating reagents. Short chain aliphatic epoxides, in particular, are commonly used in synthetic processes, e.g., ethylene oxide, propylene oxide, epoxybutane, styrene oxide, and epichlorohydrin. A consequence of this chemical reactivity is that many aliphatic and aromatic epoxides are mutagenic. Oxidation is a common degradation pathway in liquid and solid formulations. Peroxyl radicals can add to alkenes either intra- or inter-molecularly, leading to the formation of hydroperoxides.

The impurities stated above, including (b) (4) have the genotoxic potential.

In general, the exposure level of genotoxic impurity of 1.5 ug /person/day, as proposed by the EMEA and PhRMA, is considered a reasonable threshold, below which further qualification for genotoxicity or carcinogenicity concerns would not be required to support a marketing application (McGovern, Jacobson-Kram, “Trends in Analytical Chemistry’ 25: No.8, 790, 2006). This threshold is an estimate of daily exposure

expected to result in an upper bound lifetime risk of cancer of less than 10^{-6}, a risk level that is thought to pose negligible safety concerns. An additional analysis of subsets of highly potent carcinogens have suggested that a threshold of 0.15 ug per day, corresponding to a 10^{-6} lifetime risk of cancer may be more appropriate for chemicals with structural alerts for potential genotoxicity (published draft Guidance for Industry, Genotoxic and Carcinogenic impurities in Drug substance and products: Recommended Approaches, December 2008).

As indicated earlier in the atorvastatin drug product, as much as (b) (4) of (b) (4) impurity could be present. According to guidance, this limit is significantly higher than the exposure level of genotoxic impurity of 1.5 ug /person/day (published draft Guidance for Industry, Genotoxic and Carcinogenic impurities in Drug substance and products: Recommended Approaches, December 2008).

Therefore (b) (4) of (b) (4) impurity is a concern, even though it is (b) (4) to the other products (e.g. (b) (4), and (b) (4)). The concern exist that not only high level of this impurity is present in the drug product, but also the potential carryover of the (b) (4) into API, although sponsor has (b) (4) these epoxides and they expect that (b) (4) will be (b) (4) in stomach to form (b) (4)% (b) (4) and (b) (4)% (b) (4), the concern remains that if it is not fully (b) (4), than any (b) (4) epoxides may pose a concern. Additionally, sponsor has not provided any data that (b) (4) can be converted to form (b) (4)% (b) (4) and (b) (4)% (b) (4) in the stomach. Note that the current product is for chronic use.

Also chemist in OGD has an additional concern, they state that as much as (b) (4)% of these epoxide impurities could be present in the drug product, based on the firm's stability data. They are concerned about the potential cumulative genotoxic effect of all these epoxide impurities.

As stated earlier sponsor has added the impurities to the drug, and conducted the genotoxicity assays and 2-week toxicity studies, however these studies have limited value, based on Guidance below ((published draft Guidance for Industry, Genotoxic and Carcinogenic impurities in Drug substance and products: Recommended Approaches, December 2008).

"It should be noted, however, that allowing genotoxicity assessment of the impurity as it is present with the drug substance, rather than in isolation, renders the genotoxicity assessments much less sensitive. For example, the potent mutagens that are typically used as positive controls in the bacterial mutation assay, such as 9-aminoanthracene and methyl methanesulfonate, when present with a noncytotoxic drug substance at the minimal level for qualification, would not be detected by these genotoxicity assays because the maximum concentration of the impurity at the limit concentration of the drug substance would not be sufficient to produce a genotoxic response in the assays. If the drug substance is cytotoxic, this approach of assessing the impurity as it is present with the drug substance would be even more insensitive, since the drug's toxicity would further limit the level at which the impurity could be tested."

The above Guidance states that "Assays conducted with the impurity in isolation are recommended. However, studies with the drug substance containing, or spiked with,

the impurity can be considered in cases where it can be demonstrated that synthesizing sufficient amounts of the impurity is infeasible".

We do not know if the sponsor has had difficulty in synthesizing sufficient amounts of the impurities. Also we do not know if the sponsor has tried any structure activity relationship (SAR) assessment of the known carcinogens (such as the epoxides stated above)

The Guidance also states that "As part of this threshold approach, applicants can conduct and provide to the FDA an SAR assessment to identify structural similarities to known carcinogens. In cases where significant structural similarities to a known carcinogen are identified".

In general, an exposure level of 1.5 µg per person per day for each impurity can be considered an acceptable qualification threshold for supporting a marketing application. The level of (b) (4) impurity in the current drug product is significantly higher. The above threshold is an estimate of daily exposure expected to result in an upper bound lifetime risk of cancer of less than 10-6 (one in a million), a risk level that is thought to pose negligible safety concerns. The threshold was based on an analysis of the carcinogenic potencies of 477 chemicals and was derived from the probability distribution of carcinogenic potencies of those compounds.

However, in cases where a class or family of structurally similar impurities is identified and is expected to have similar mechanisms resulting in their genotoxic or carcinogenic potential, the total daily exposure to the related compounds should be evaluated, relative to the recommended threshold exposure.

Summary:

The proposed level of (b) (4) impurity in the drug product is NMT (b) (4)% (and the levels from stability studies have shown levels up to (b) (4)%). The sponsor claims that this impurity is converted at (b) (4) to (b) (4)% (b) (4) (b) (4) impurity and (b) (4)% (b) (4) impurity. Data to support this conversion have not been provided and are likely needed because these 2 impurities have been qualified by 2-week toxicity and geno-toxicity assays, at levels of (b) (4) of (b) (4)% and (b) (4)% for (b) (4). Therefore if the sponsor can demonstrate conversion of (b) (4) (b) (4) into (b) (4)% (b) (4) impurity and (b) (4)% (b) (4) impurity, resulting levels of the (b) (4) and (b) (4) at the levels already qualified (i.e. (b) (4)% and (b) (4)% respectively), then further qualification of (b) (4) may not be necessary.

Alternatively the sponsor could qualify the (b) (4) impurity using 2-week toxicity (spiking the impurity {e.g. (b) (4)%} into the atorvastatin calcium) and in vitro geno-toxicity studies, as they have for the prior impurities qualification at the levels of concern. This assumes that the (b) (4) is present at levels that exceed the RLD. Another option would be to reduce the levels of (b) (4) to less than 1.5 mcg/day, or to the levels in the RLD if this was technically feasible.

The other question brought up by OGD is the potential of cumulative geno-toxicity of these impurities. The draft guidance indicates that 1.5 mcg/day is the threshold for

toxicity concern based on a one in a 100,000 lifetime risk of cancer and levels of any impurity above this threshold require safety qualification. The guidance does indicate that where structurally similar impurities are identified that are expected to have a similar mechanism resulting in their geno-toxicity or carcinogenic potential (i.e epoxides in this case), the total daily exposure should be evaluated relative to the recommended threshold exposure. Based on the identified atorvastatin [redacted]: [redacted] (not qualified), [redacted] (NMT [redacted]%), [redacted] (NMT [redacted]%), [redacted] (NMT [redacted]%) and their qualified individual levels, it appears that the cumulative effect of [redacted] and [redacted] were tested together, whereas the [redacted] was tested separately from these 2 impurities and the [redacted] has not yet been tested for geno-toxicity.

Therefore, a cumulative effect of these impurities has not been assessed based on the information reviewed. The chemist indicated that epoxide impurities that have been structurally identified (n=[redacted]) may reach [redacted]% (or [redacted]) of the atorvastatin dose (80 mg/day) which exceeds the RLD, where the cumulative epoxide levels are [redacted]% of the atorvastatin dose (individual epoxide impurity specs are [redacted]%). It seems that even with the individual qualification of epoxide impurities, the cumulative effects have not been addressed. This seems a valid safety concern for a potential interchangeable, generic, chronic use drug.

Internal Recommendations:

From the pharmacology/toxicologyy point of view, although the proposed levels of [redacted] and [redacted] impurities, as well as [redacted] impurity in the atorvastatin calcium drug product were qualified, based on submitted toxicity studies earlier, the concern remains over the combined or cumulative effects of all these genotoxic impurities in the current atorvastatin drug product. The sponsor should be asked to provide safety for the cumulative effects of these genotoxic epoxides present in their drug product and address the total daily exposure to the related compounds, relative to the recommended threshold exposure of concern for genotoxic impurities based on the draft guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdfhttp://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf

The Guidance states that “in cases where a class or family of structurally similar impurities is identified and is expected to have similar mechanisms resulting in their genotoxic or carcinogenic potential, the total daily exposure to the related compounds should be evaluated, relative to the recommended threshold exposure” (published draft Guidance for Industry, Genotoxic and Carcinogenic impurities in Drug substance and products: Recommended Approaches, December 2008). Alternatively the sponsor Can reduce the levels of these epoxide impurities to levels present below those in the listed drug or below those of the threshold for toxicologic concern (1.5 mcg/day)

As far as the safety of [redacted] is concerned, the sponsor claims that this impurity is converted at [redacted]) to [redacted]% [redacted]

(b) (4) impurity and (b) (4)% (b) (4) impurity, and therefore will not qualify it. The sponsor will have to demonstrate conversion of (b) (4) into (b) (4)% (b) (4) impurity and (b) (4)% (b) (4) impurity, and demonstrate that the resulting levels of the (b) (4) and (b) (4) at the levels already qualified i.e. (b) (4)% and (b) (4)% respectively, then further qualification of (b) (4) may not be necessary.

Alternatively, the sponsor could qualify the (b) (4) impurity using 2 week toxicity (spiking the impurity {e.g. (b) (4)%} into the atorvastatin calcium) and in vitro geno-toxicity studies, as they have for the prior impurities qualification at the levels of concern. This assumes that the (b) (4) is present at levels that exceed the RLD. Another option would be to reduce the levels of (b) (4) to less than 1.5 mcg/day, or to the levels in the RLD if this was technically feasible.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/marchik/TranTrang/Leigh Ann Sears/Ripper, L
File name: ANDA 91226-11-OGD consult (atorvastatin- Matrix)

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

/s/

INDRA ANTONIPILLAI
04/22/2011
Please see the internal pharmacology/toxicology recommendations.

KAREN L DAVIS BRUNO
04/22/2011

MATRIX

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95, Matrix certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 5,273,995 and RE40667 and their associated pediatric exclusivities; prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156; 6,126,971 and their associated pediatric exclusivities; and prior to the expiration of U.S. Patent No. 7,790,197.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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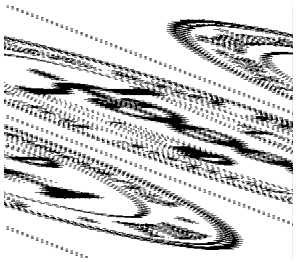
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Intellectual Property



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Through: Thomas Marciniak, MD, Team Leader, DCaRP/ODE I/OND/CDER
Norman Stockbridge, PhD, MD, Director, DCaRP/ODE I/OND/CDER

To: Linda Mary Forsyth, MD, Medical Officer, OGD
Cc: Dena R. Hixon, MD, Associate Director for Medical Affairs, OGD
Mark A. Gonitzke, Project Manager, DC4 TM 43, OGD

ANDA #:	091-226	**Sponsor**:	Matrix Laboratories, Inc.
Drug Name:	Atorvastatin calcium tablets	**Reference drug:**	Liptor® (atorvastatin calcium)
Drug Class:	Statins – lipid lowering drugs	**Indication**:	Lipid lowering
Consult Date:	31-Mar-2011	**Date received:**	31-Mar-2011
Date assigned:	01-Apr-2011	**Date completed**:	20-Apr-2011

CONSULTATION

The Clinical Team in the Office of Generic Drugs (OGD) states that they received a request from the OGD Chemistry Division III regarding evaluation of the safety of ANDA 091-226 (atorvastatin calcium) in patients with cardiovascular disease. This generic product atorvastatin calcium contains an inactive ingredient, L-arginine, as a (b) (4) ((b) (4) L-arginine in a 80 mg tablet of atorvastatin); L-arginine is not contained in the reference listed drug (Liptor®).

Documents provided with the consultation include:
(i) the pharm/tox review performed by the Division of Metabolism and Endocrine Products, in which the pharm/tox reviewer was unable to evaluate the safety of L-Arginine in patients with cardiovascular (CV) disease,
(ii) OGD medical reviewer's comments and
(iii) the sponsor's justification with literature references.

OGD requests DCRP to address the following question: *We request your assessment of the safety considerations for adding L-arginine to atorvastatin calcium in amounts up to* (b) (4) *for the 80 mg highest strength, given that this product will be used on a chronic basis in patients with cardiac disease or risk factors for cardiac disease. Do you consider this generic product be as safe as the reference listed drug with the addition of L-arginine to the formulation? Is there any potential clinical benefit for this population?*

BACKGROUND

The concern for safety of L-arginine in patients with cardiovascular (CV) disease appears to have arisen from the clinical outcome findings of two placebo-controlled double-blind clinical trials of oral L-arginine:

(i) The VINTAGE IM trial[1] at John's Hopkins enrolled 153 post-myocardial infarction patients 60 years or older who were treated with 3 g L-arginine three times a day (TID). The Data Safety and Monitoring committee closed enrolled after 6 months because there was an *increased* mortality in patients who received L-arginine (6 deaths (8.6%) vs. none in placebo group, P=0.01) with no effect in clinical outcomes, left ventricular ejection fraction (LVEF) or non-invasive measures of vascular stiffness. The 6-month

[1] Schulman SP, Becker LC, Kass DA, Champion HC, Terrin ML, Forman S, et al. L-Arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* 2006; 295: 58-64.

clinical endpoint events (death, MI, heart failure hospitalization) occurred in 12 (16.7%) in L-arginine group and 7 (10.1%) in placebo group. Five of the patients who died were 60 years or older (15.5%, P=0.02), the causes being myocardial rupture (1), death at home without symptoms (2) and presumed sepsis (2).

(ii) The ARAMI pilot trial[2] in 792 patients (mean age 64 years) with acute ST-elevation myocardial infarction (STEMI) admitted within 24 hours after onset of symptoms were randomized to receive 3 g L-arginine 3 times/day for 30 days (394 patients) or placebo. In 774 patients who were eligible for analysis, the event rates of major clinical events (30-day CV death, reinfarction, successful resuscitation, shock, pulmonary edema or recurrent myocardial ischemia) were 24% in L-arginine group and 27% in placebo group (Odds ratio 0.63; 95% CI 0.39-1.02; p=0.06). In this study, withdrawals due to adverse events (AEs) occurred in 9 patients (7= gastrointestinal upset, 2= hypotension) in L-arginine group and 10 in placebo group.

In CDER approved drugs, L-arginine is used as an excipient in injection formulations. For example, L-arginine is approved by FDA in injectable antibiotics as an aid to solubilize the drug (at doses up to of 780 mg/g of aztreonam (Azacatam) or 725 mg/g of Maxipime (cefepime) with exposure to L-arginine ranging from (b) (4) to (b) (4) which is (b) (4) times that in a tablet of generic atorvastatin calcium ((b) (4) of L-arginine). However, these antibacterial drugs are not for prolonged chronic use or for oral use.

I agree with the pharm/tox reviewer that nonclinical studies may not address or establish the safety risks in patients with CV disease because these nonclinical studies are performed in healthy animals. It is unclear which CV models are most relevant to the situation of humans with chronic or acute coronary artery disease.

With this background, I reviewed the literature related to L-arginine, including its oral use as a nutritional supplement and the information in clinical trials in which L-arginine is administered to patients with CV disease or risk factors for CV events.

REVIEW FINDINGS

L-arginine is a "non-essential" amino acid. In healthy adults with adequate protein intakes, endogenous synthesis of L-arginine is sufficient to meet physiologic needs. Following oral consumption, L-arginine is absorbed in the bowel by an active transport system, but is partly metabolized by enterocytes, and partly during its passage through the liver. Peak concentration after oral administration is reached after 1 – 2 hours. The usual range of L-arginine plasma levels are 81.6 ± 7.3 µmol/L in young men and 113.7 ± 19.8 µmol/L in elderly men, and 72.4 ± 6.7 µmol/L in young women and 88.0 ± 7.8 µmol/L in elderly women.[3]

The World Health Organization considered L-arginine to be a macronutrient and a normal component of protein with no safety concern at current levels of intake when used as a flavouring agent.[4]

In the US, L-arginine is generally recognized as safe (GRAS) per 21 CFR §582.5145 for use as a nutrient and/or dietary supplement. It is listed as an approved food additive permitted for direct addition to food for human consumption (21 CFR § 172.320) at levels up to 6.6% (percent by weight of total protein of the finished food). L-arginine is also approved as an active ingredient

[2] Bednarz B, Jaxa-Chamiec T, Maciejewski P, Szpajer M, Janik K, Gniot J, Kawka-Urbanek T, Drozdowska D, Gessek J, Laskowski H. Efficacy and safety of oral L-Arginine in acute myocardial infarction. Results of multicenter, randomized, double-blind, placebo-controlled ARAMI pilot trial. *Kardiologia Polska* 2005; 62(5): 421-427.

[3] Böger, Rainer H. (2007) The Pharmacodynamics of L-Arginine. *J Nutr* 2007; 137 (6, Suppl 2):1650S-1655S.

[4] Joint FAO/WHO Expert Committee on Food Additives (2004 Report TRS 928-JECFA 63/98 and Tox Monograph FAS 54-JECFA 63/435).

in over-the-counter (OTC) drug products (21 CFR § 310.545(20) Weight control drug products).

Arginine is contained in relatively high amounts in some foods (Table 1). There is no data available on the recommended daily amount (RDA) of L-arginine; it is believed to be about 2000 mg/day. Most people consume between 1 – 2 grams of L-arginine daily through the foods they eat. It is estimated that the mean dietary intake of L-arginine in industrialized countries is about 3 – 6 g/day, and that about 5 g of L-arginine is ingested each day in a normal Western diet.[3]

Table 1 Foods High in Arginine

Food	Serving Size (gm)	Free Arginine (mg)
Sesame flour	100	4,465
Soy protein isolate (K type)	100	4,156
Gelatins (dry powder)	100	3,951
Crustaceans (Alaska King)	100	3,805
Sesame Seeds	150	3,750
Dungeness, cooked	100	3,538
Shrimp, raw	100	3,349
Pumpkin Seeds	140	3,040
Poultry (turkey), raw	100	2,866
Almonds	145	2,600
Brazil Nuts	140	2,595
Pork chops	100	2,348
Walnuts	100	2,055
Hazelnuts	135	2,020
Pistachios	130	1,160
Pine Nuts	30	1,075
Pecans	110	875
Snails	85	850
Macadamia Nuts	135	770
Squash, winter	205	690
Wheat Germ	180	460
Peanut Butter	15	437
Shredded Coconut	80	320
Bran Flakes	50	140

A risk assessment study[5] suggested that L-arginine at oral intakes up to **20 g/day** is not associated with adverse effects (observable safe level – OSL). This OSL from the risk assessment study is used as the basis for a recent GRAS notification for L-arginine submitted to FDA in 2008 May for its use as a food additive.[6]

This OSL of 20 g/d is (b) (4) times the amount of L-arginine (b) (4) contained in the generic formulation of a 80 mg atorvastatin calcium tablet.

The sponsor submitted literature on several clinical trials, some small (about 5 patients), some of very short duration, some were open label, some uncontrolled, and some used intravenous infusion of arginine. I focused my review on the safety information reported in clinical trials where the ***oral*** form of L-arginine was administered to patients with CV diseases or risk of CV events.

As presented in the background, two randomized, double-blind, placebo-controlled clinical trials in patients with myocardial infarction (Table 2) showed an important safety finding of *increased* mortality (6 deaths in L-arginine group vs. none in placebo group) in patients in the VINTAGE IM trial who received L-arginine 3 g TID for 6 months. This safety issue was not observed in the shorter ARAMI trial in which patients received L-arginine 3 g TID for 30 days only.

[5] Sha, A, Hathcock, JN. Risk Assessment for safety of arginine when added to the diet. *The amino acids taurine, L-glutamine, and L-Arginine,* Regulatory Toxicology and Pharmacology, 50(2008):376-399.

[6] Hibbert, RG. (2008) GRAS Notice 000290: L-Arginine.

Table 2 Studies of patients with myocardial infarction (MI) who were administered L-arginine orally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
STEMI – within 24 h after symptoms (ARAMI pilot trial)	792	R, DB, PC, MC	3 g TID x **30 days** (n=394)	Endpoint events (30-day CV death, reinfarction, successful resus, shock, pulmonary edema or recurrent myocardial ischemia) occurred in 24% in L-arginine group and 27% in placebo group	Withdrawals due to AEs in 9 pts (2 hypotension, 7 GI) in L-arginine vs. 10 in placebo group	Bednarz, 2005
MI (VINTAGE IM Trial)	153	R, DB, PC	3 g TID x **6 months** vs placebo	No improvement in clinical outcomes, LVEF or non-invasive measures of vascular stiffness. Endpoint events (death, MI, HF hosp) in 12 (16.7%) in L-arginine gr vs. 7 (10.1%) in placebo group	6 (8.6%) in L-arginine group died vs. none in placebo (P<0.01)	Schulman, 2006

R= randomized; DB= double blind, PC= placebo-controlled; MC= multicenter; MI= myocardial infarction; STEMI= ST elevation MI; LVEF= left ventricular ejection fraction

In seven randomized, placebo-controlled clinical trials in patients with heart failure (Table 3) who were treated with oral L-arginine doses varying from 4.6 g/day to 20 g/day for treatment durations from 7 days to 28 days, there was no signal of serious adverse events apart from one patient who reported unstable angina (a condition to be expected in this patient population).

Table 3 Studies of patients with heart failure (HF) who were administered L-arginine orally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
Mild to Moderate CHF (NYHA II-III)	21	R, DB, PC, CO	9 g/day x 7 days	Sig. increased exercise duration (P<0.05)	No AEs reported	Bednarz, 2004
Severe heart failure	20	R, DB, PC	20 g/day x 28 days	No effect on endothelial function	1 pt= UA; 3= diarrhea	Chin-Dusting, 1996
Chronic heart failure	40	R, PC, inpatient	8 g/day x 4 weeks	Improved endothelium-dependent vascular dilatation	No AEs reported	Hambrecht, 2000
Heart failure	5	R, DB, PC, CO	4.6 g/day x 6 weeks vs. placebo	Non significant increased mean response to FBF and nitroprusside	No AEs reported	Kubo, 1994
Heart failure	18	R, DB, PC, CO	20 g x 14 days vs. placebo; 14- day WO	Sustained elevation of plasma L-arginine (x4)	No AEs reported.	Prior, 2000
Heart failure	17	R, DB, PC, CO	5.6 – 12.6 g/ day x 6 weeks	Significantly increased exercise forearm blood blow	1 pt= diarrhea 2= acute gout	Rector, 1996
Congestive heart failure (men)	50	R, DB, PC	6 g/day x 1 week vs. placebo	Increased exercise duration, forearm blood flow decreased exercise-induced constriction	No AEs reported	Yousuffuddin, 2001

R= randomized; DB= double blind, PC= placebo-controlled; CO= crossover; CHF= congestive heart failure; UA= unstable angina

Table 4 Studies of patients with cardiac procedures who were administered L-arginine orally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
Young orthotopic heart transplant patients	8 (+15 controls)	R, DB, PC, CO	6 g/day x 2 week, 2 week WO	Significantly decreased MAP and increased FMD no effect on LV function	1 placebo= sudden death	Lim, 2001 and 2004
Coronary angio-graphy for recurrent chest pain	26	R, DB, PC	3 g TID x **6 months**	Sig. increased coronary blood blow (P<0.05) in response to acetylcholine	1 in each gr discontinued due to GI	Lerman, 1998
Cardiopathic non-diabetics after Aorto-coronary bypass	26	R, DB, PC	6.4 g/day x **6 months** vs. placebo	Decr asymmetric dimethyl-arginine levels (P<0.01), endothelial dysfunction and incr cGMP (P<0.01)	No AEs reported	Lucotti, 2009
Stent Implantation subjects	60	R, DB, PC	200mg/kg **IV** infusion x 4 h at 12 & 3 h before PCI; 500mg IVx 10 min pre- stent implantation, then **oral** 6 g/dayx 14 d	No effect on quantitative coronary angiography and intracoronary ultrasonography (ICUS)	No AEs reported.	Dudek, 2002; Dudek, 2004

R= randomized; DB= double blind, PC= placebo-controlled; CO= crossover; WO= washout; MAP= mean arterial pressure; LV= left ventricle; FMD= ??????

In 4 randomized, double-blind, placebo-controlled clinical trials of L-arginine in patients who had undergone cardiac procedures such as coronary angiography, stent implantation, aorto-coronary bypass and heart transplant (Table 4), no AEs were reported. In the patients who underwent coronary angiography or aorto-coronary bypass, L-arginine was given in doses ranging from 6.4 g/day to 9 g/day over a duration of 6 months, without the finding of an increase in deaths reported in the VINTAGE MI trial.

In eleven clinical trials in patients with hypertension (7 placebo-controlled, 2 open-label, and 2 unknown design), L-arginine was administered orally in a wide variety of doses (Table 5). There were no AEs reported by patients who received high loading doses of 3 g/hour for 10 hours or by those who received 1200 mg/day (with N-acetylcysteine 600 mg BID) for six months. It is reassuring that all seven pregnant patients who received oral doses of 1.5 to 2.5 g/day of L-arginine from the 13th week of pregnancy did not report AEs, and all delivered healthy children.

Table 5 Studies of patients with Hypertension who were administered L-arginine orally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
Hypertension	10	Not available	2 g TID x 4 weeks	Decreased resting systolic BP	No AEs reported	Fragasso, 2001
Mild hypertension & Type 2 Diabetes	6	CO	Oral 3 g/h x 10 h	Reduced systolic and diastolic BP	No AEs reported	Huynh, 2002
Essential hypertension	35 (+17 controls)	R, DB, PC	6 gm vs. placebo	Improved endothelium dependent vasodilation	No AEs reported	Lekakis, 2001 and 2002
Essential HTN	12	R, DB, PC, CO	2 g TID	Significant decrease in BP	No AEs reported	Pagnotta, 1997
Grade 2-3 HTN	13	R, DB, PC, CO	2 g TID x 4 wks	Significant improvement in angina class, systolic BP at rest, QOL	No AEs reported	Palloshi, 2001, 2004
Essential HTN	20	R, PC	2 g TID x 6 wk vs placebo	Reduced SBP (14 mmHg) and DBP (8 mmHg); P<0.05	No AEs reported.	Pezza, 1998
Obese HTN patients	20	PC	3 g/d or placebo x 4 wk	Decreased TNF-α (not significant)	No AEs reported.	Pupek-Musialik 2002
Type 2 Diabetics with mild HTN	6	R, PC	3 g/h 4 am till 2 pm on d 2 or 3	Reduced BP (13 mmHg)	No AEs reported	Tayak, 1999
HTN	10	Open label	14-21 g/d x 3 m	Plasma L-arginine/ADMA ratios restored to normal	No AEs reported	Chan, 2000
HTN and Type 2 diabetes (men)	24	R, DB, PC	1200 mg/d + N-acetylcysteine 600mg BID x **6 months**	Improved endothelial function by incr NO production and improved NO bioavailability via reduced oxidative stress	No AEs reported	Martina, 2008
Pregnant HTN subjects	7	Open label	1.5 – 2.5 g/d from 13th week of pregnancy	BP reduced >15 mmHg in 3 subjects. All subjects delivered healthy children	No AEs reported	Zdebski, 1995 and 1995

R= randomized; DB= double blind, PC= placebo-controlled; CO= crossover; HTN=hypertension; SBP= systolic BP; DBP= diastolic BP; NO= nitric oxide; QOL= quality of life.

Table 6 shows 18 relatively small clinical trials in patients with a wide spectrum of coronary artery disease or cardiovascular risk factors in which L-arginine was administered orally at doses ranging from 21 g/day for 3 days, to 14 g/day for 7 days, 9 g/day for 1 month, 6 to 9 g/day for 3 months, or 6 g/day for 6 months. In two placebo-controlled clinical trials in patients with the clinical syndrome of mitochondrial encephalopathy, lactic acidosis and stroke (MELAS), 4 to 24 g/day of L-arginine was administered orally for 18 to 24 months. No signal of cardiovascular toxicity was reported with "high dose short duration" or "low to high dose long duration" regimens in these clinical trials in patients with coronary artery disease or risk factors for cardiovascular events.

Table 6 Studies of patients with different types of CV disease administered L-arginine orally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
CAD (Men)	10	R, DB, PC, CO	Oral 7g TID x3 days+ 10d WO	Improved endothelium-dependent dilatation of brachial artery	No AEs reported	Adams, 1997
CAD	25	R, DB, PC, CO	Oral 6g/d x 3 days+ 3d WO	Sig. increased exercise duration (P<0.03); no effect on ST-segment depression	No AEs reported	Bednarz, 2000
Microvascular angina	10	R, DB, PC, CO	7 g BID x 4 wk	Increased exercise tolerance	No AEs reported.	Bellamy, 1996
Chronic Stable CAD	18	R, DB, PC, CO	9 g/d x 1 month + 1 month WO	Increased L-Arginine levels, no improvement in NO-dependent vascular function	No AEs reported	Blum, 1999
CAD	35	R, DB, PC, CO	9 g/d x 1 month + 1 month WO	Increased L-Arginine levels; no improvement in NO bioavailability	No AEs reported	Blum, 2000
CAD and atherosclerosis	7 + 8	Open label	100 mg/kg oral single dose	No changes in mean BP or heart rate	No AEs reported	Bokelman, 1995
CAD + stable angina pectoris	22	R, DB, PC	2 g TID oral x 3d	Increased time to ST-depression max (P<0.04) during exercise	No AEs reported	Ceremuzynski, 1997
CAD	119	R, PC, DB	Oral 9 g/d, vs. placebo vs. creatinine 21g/d vs. both x 4d	2 to 2.5-fold increased plasma L-arginine; no benefit on vascular function	No AEs reported	Jahangir, 2009
CAD and Class II or III angina	36	R, DB, CO	3.3 g BID vs. placebo x 1 wk, 1 month WO	Better brachial artery endothelial function, greater exercise duration on treadmill, high QOL scores	AEs = bowel habit change, flatulence, headache, & chest/leg pain	Maxwell 2002
Stable angina pectoris	14	R, PC, CO	700 mg 4x/d vs placebo x5-10d	Increased treadmill walking time at 4 h and 24 h	No AEs reported.	Parker, 2002
Stable angina	40	R, DB, PC	15 g/d x 2 wk vs. placebo	Endothelin dependent vaso-dilation, oxidative stress or exercise performance = no improvement	UA in 1 pt on L-arginine, hospitalized for PCI	Walker, 2001
Stable CAD	31	OL, CO, R (active control)	10 g/d or 500 mg vitamin C x4 wk; 2 wk WO	Improved endothelial function and reduced LDL oxidation. One patient on L-arginine reported atypical chest pain.	Diarrhea (5), stomach pain (1), incr blood glucose (1); 1 pt on vit C = muscle sprain	Yin, 2005
CAD with intractable angina	10	Case controlled	9 g/d x **3 months**	7 improved from angina IV to II	No AEs reported	Blum, 1999
Severe diffuse CAD	19	R, PC	6 g/d x **3 m** (+ 200μg VEGF)	Improved post-surg anterior wall perfusion & contractility	No AEs reported	Chan, 2007
Severe diffuse CAD	19	R, PC	6 g/d x 3 months vs. placebo	Improved anterior wall perfusion on PET, smaller perfusion defects, better anterior wall contractility	No AEs reported	Ruel, 2008
Multiple risk factors or vascular disease	45	R, DB,PC	6 g/d x **6 months**	Sig decr in SBP (p< 0.007); sig incr in large artery elasticity LAEI (P<0.0001)	No AEs reported	Gutman 2005, Shargorodsky 2006
MELAS Syndrome	24 (+72 controls)	PC	4 – 24 g/d x **18 months**	Improved stroke-like symptoms	No AEs reported	Koga 2005 and 2007
MELAS Syndrome	15 (+20 controls)	PC	4 – 24 g/d x **24 months**	Decreased frequency and severity of stroke symptoms	No AEs reported	Koga, 2006

R= randomized; DB= double blind; PC= placebo-controlled; CAD= coronary artery disease; CO= crossover; WO= washout; OL= open label; UA= unstable angina; PCI = percutaneous coronary intervention; NO= nitric oxide; QOL= quality of life; MELAS= mitochondrial encephalopathy, lactic acidosis and stroke syndrome.

In four small clinical trials in patients with pulmonary hypertension (Table 7), there were no AEs reported following oral administration of L-arginine for short durations (5 days to one week).

Table 7 Studies of patients with Pulmonary Hypertension who were administered L-arginine orally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
Sickle cell disease with pulmonary HTN	4	OL	0.1 g/kg TID x 5 days orally	Decreased pulmonary artery pressure and platelet aggregation	No AEs reported	Morris, 2000
Sickle cell disease with pulmonary HTN	10	OL	0.1 g/kg TID x 5 days orally	15.2% reduction in pulmonary artery systolic pressure	No AEs reported	Morris, 2003
Pulmonary HTN	17	R, DB, PC	1.5 g/10kg/d oral vs placebo x 1 wk	Decreased PAP (11%) and total pulmonary resistance	No AEs reported	Nagaya, 2000
Precapillary pulmonary HTN	19	R, DB, PC	1.5 g/10kg/d oral vs placebo x 1 wk	Improved hemodynamics and exercise	No AEs reported	Nagaya, 2001

R= randomized; DB= double blind; PC= placebo-controlled; HTN=hypertension;

Table 8 Studies of patients with different types of CV disease administered L-arginine parenterally

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
CHF	7	Open label	500 mg/kg IV infusion	No effect on contractility; negative chronotropic effect.	2= hypotension; one with RBBB & Chaga's disease= transitory complete AV block	Bocchi, 2000
Heart failure secondary to CAD	9	OL	Losartan 50 mg qdx 2 d; then L-arginine 20g IV after losartan on day 2	"Superior" effects on hemodynamic variables and endothelium dependent vasodilatation	No AEs reported	Koifman, 2006
CAD and stable angina	24	Open label	Intracoronary infusion 50 and 150 µmol/min x 8 min) vs. saline	Larger proportion of complex than smooth stenosis dilated by >10% (P<0.01)	No AEs reported	Tousoulis, 2001
Angina pectoris	8	OL	50 mg/min IV infusion x 10 min	Increased coronary blood flow responses to acetylcholine	No AEs reported	Egashira, 1996
Stable CAD with exercise-induced ST depression	22	DB, CO	5 mg/kg/min x 20 min	Significantly incr forearm blood flow (P<0.001) and acetylcholine-mediated forearm vasodilatation (P<0.0001)	No AEs reported.	Quyyumi, 1998
Angina pectoris	12	R, PC, CO	2.5 mmol/kg IV x30 min	Prolonged exercise time (improved myocardial perfusion)	Decreased SBP, DBP and HR, and thirst	Fujita, 2000
Obese hypertensive	10	Open label	500 mg/kg IV infusion (30 min)	Significant reductions in systolic and diastolic BP	No AEs reported	Castejon, 2000
Hypertension + Type 2 Diabetes	23	Open label	100 mg/kg IV infusion (30min)	No effect on renal hemodynamics	No AEs reported.	Delles, 2003
Mild to Moderate essential hypertension	39	Open label	500 mg/kg IV infusion (30 min)	Reduced mean BP and renal vascular resistance, no effect on GFR	2 subjects= pain at the catheter insertion site	Higashi, 1999
Essential+ secondary hypertension	8	Open label	500 mg/kg infusion (30 min)	Hypotension & tachycardia (due to decreased peripheral resistance)	No AEs reported	Hishikawa, 1992
Essential+ secondary hypertension	16	Open label	500 mg/kg infusion (30 min)	Hypotension & tachycardia (due to decreased peripheral resistance)	No AEs reported	Hishikawa, 1993
HTN	14 (+12 control)	SB, PC	Brachial infusion (10, 20, 40, 80 & 160 µmol	No sig change in basal blood flow or vascular resistance	No AEs reported.	Panza, 1993
Pulmonary HTN, heart failure and controls	10 5 10	PC	500 mg/kg IV infusion (30 min)	Reduced PAP & pulmonary vascular resistance	No AEs reported	Mehta, 1995
Cardiac Syndrome X	9 (+14 control)	R, PC	IV 0.125 g/min x 120 min vs saline	Incr basal forearm blood flow, forearm cGMP release, nitrite and nitrate, and decr endothelin-1	No AEs reported.	Piatti, 2003

R= randomized; DB= double blind, SB= single blind; PC= placebo-controlled; CAD= coronary artery disease; MI= myocardial infarction; HTN=hypertension; CHF= congestive heart failure

In 14 clinical trials (Table 8), L-arginine administered parenterally (intravenous infusion or

intracoronary or brachial infusion) to a broad spectrum of patient with cardiovascular diseases (hypertension, angina, pulmonary hypertension and heart failure) was not associated with cardiovascular toxic effects apart from pain at the catheter insertion site or decreased blood pressure and, in an open-label study in patients with congestive heart failure, two patients experienced hypotension and one patient with right bundle branch block and Chaga's disease experienced transitory complete AV block (a condition that can be expected in this disease).

Impaired renal function did not increase AEs despite elevated plasma L-arginine levels observed in children with chronic renal failure (Table 9) after administration of oral L-arginine.

Table 9 Studies of patients with renal disease administered L-arginine

Study Population	Number studied	Study Design	L-Arginine dose	Endpoint studied	AEs	Sponsor's Source
Chronic Renal failure and endothelial dysfunction (children)	21	R, DB, PC, CO	2.5 g/m^2 or 5g/m^2 x 4 wk + 4 wk WO	Elevated plasma levels. No improvement in endothelial function	No AEs reported	Bennett-Richards, 2002

In all of the above clinical trials in patients with different types of cardiovascular conditions, I find no signal that taking L-arginine orally worsened the existing cardiovascular condition. There were no reports of serous adverse events, even when L-arginine was administered at relatively higher doses for relatively long durations (up to 24 months).

LIMITATIONS OF THIS REVIEW

This review is limited to the clinical trials reported in the literature; no raw data is available so no evaluation of the integrity of data or AE reporting can be made. Most of the clinical trials are of small size and short duration, and studied pharmacodynamic or hemodynamic parameters. Only the two clinical trials in post-MI patients studied clinical outcome events as primary efficacy parameters, albeit in a relatively small number of patients (153 in VINTAGE MI trial, 792 patients in ARAMI trial) for a relatively short duration (6 months in VINTAGE MI trial, 1 month in ARAMI trial). That no AEs were reported in these clinical trials should not instill a false sense of security because none of them was designed to evaluate safety, cardiovascular or otherwise.

REVIEWER'S COMMENTS AND RECOMMENDATIONS

There is no evidence from available clinical literature that exposure to (b) (4) of L-arginine (contained in a tablet of generic formulation of atorvastatin calcium) – which is at (b) (4) to (b) (4) of the daily dietary consumption (2 – 5 g/day) and (b) (4) of the observable safe level (b) (4) – can cause an increased risk of cardiovascular or other serious adverse effects in patients with cardiovascular disease or risk factors for cardiovascular events. This clinical reviewer's recommendation is that the generic formulation of atorvastatin calcium containing (b) (4) (b) (4) of L-arginine as an inactive ingredient is as safe as the reference listed drug. I do not think that any potential clinical benefit can be expected for this patient population from the addition of this small amount of L-arginine in the generic formulation.

Thank you for requesting our input into the development of this product under ANDA 091-226. We welcome more discussion with you now and in the future.

Khin Maung U, MBBS, MMedSc, MD (NSW, Australia), MD, FACP
Medical Officer, DCaRP, ODE I, OND, CDER, FDA

cc: orig.
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OGD / Linda Mary Forsyth / Dena R. Hixon / Mark A. Gonitzke

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/s/

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RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
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Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2011

FROM: Robert L. West, Deputy Director
Office of Generic Drugs

THROUGH: Keith O. Webber, Ph.D., Deputy Director
Office of Pharmaceutical Science

SUBJECT: Expedited Review of Certain Atorvastatin ANDAs

TO: ANDA 077575 - Sandoz Inc.; ANDA 078773 - Teva Pharmaceuticals USA; ANDA 090548 - Apotex Inc.; ANDA 091226 - Matrix Laboratories/Mylan Pharmaceuticals

THIS DOCUMENT CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION

Pfizer's Lipitor (atorvastatin calcium) is a cholesterol-lowering agent that has been very widely prescribed for many years. The purpose of this memorandum is to document the agency's basis for expediting the review of certain atorvastatin ANDAs.[1] The actual decision to expedite the review of eligible atorvastatin ANDAs was made in late February 2011; reviewers were notified of this decision at that time.

Ranbaxy submitted its atorvastatin ANDA in 2002. It was the first generic applicant to submit an ANDA for atorvastatin. Ranbaxy challenged all the patents listed by Pfizer as covering Lipitor. By challenging the patents, under the FD&C Act Ranbaxy became eligible for 180 days of generic drug exclusivity. As a pre-MMA ANDA, the Ranbaxy ANDA is not subject to the forfeiture provisions now found in the 180-day exclusivity provisions of the Act.

[1] It is acknowledged that the circumstances here do not fit squarely under OGD's MaPP 5240.3, which among other things describes circumstances under which an ANDA will be given expedited review. However, the circumstances here (e.g., the existence and complexity of the questions related to the Ranbaxy AIP and ANDA reliability, the highly uncertain date upon which ANDAs may be eligible for final approval, the review issues posed by the applications, and the size of the market demand for this drug product) are of such an unusual nature that they could not have been anticipated. Review of these applications on an expedited basis is, however, consistent with OGD's long-term goal of reviewing pending ANDAs in such a manner that, by the time patent and exclusivity barriers to approval have expired, appropriate reviews will have been completed. With first generic ANDAs that have been found scientifically approvable, OGD has a long history of approving these as promptly as permitted under the statutory provisions pertaining to patents, patent litigation, and exclusivity. Prompt review of ANDAs does not, of course, guarantee that any application will be ready for final approval as of a specific date. To be approved, an application must meet the requirements under section 505(j) of the FD&C Act and applicable regulations.

In a letter dated February 25, 2009, CDER informed Ranbaxy that CDER was applying its Application Integrity Policy (AIP) to the applications CDER identified as originating from Ranbaxy's Paonta Sahib site in India. CDER concluded that there was:

> "a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications … developed at the Ranbaxy Laboratories, Paonta Sahib site."

Certain "subsequent applicants" (i.e., those applicants whose ANDAs would not be approved prior to or during Ranbaxy's 180-day exclusivity period) have written the agency and stated that the agency should declare Ranbaxy ineligible for 180-day exclusivity (in short, because of the AIP). Mylan recently brought suit against the agency on this point. No decision has been made, at this time, about the status of Ranbaxy's eligibility for 180-day exclusivity. Issues related to Ranbaxy's eligibility for exclusivity and the review of the Ranbaxy ANDA are not addressed in this memorandum.

November 30, 2011, is the earliest date Ranbaxy could market under its 2008 settlement agreement with Pfizer. If Ranbaxy were to obtain approval of its ANDA and market promptly after that date, approval of subsequent ANDAs could be blocked until the end of May, 2012. [2] However, June 28, 2011, is the expiration date of the pediatric exclusivities attaching to two key Lipitor patents. If Ranbaxy loses its eligibility for 180-day exclusivity, the ANDAs identified in this memorandum could become eligible for approval on June 28, 2011.[3]

In managing the workload in OGD, we must take into account these unusual circumstances and the possibility that Ranbaxy may lose its claim for exclusivity either by relinquishing it or by an agency determination that Ranbaxy is not eligible for exclusivity, e.g., because Ranbaxy's ANDA was not "substantially complete" at the time of its submission. If this were to happen, the agency has concluded that it is in the public interest to have completed its scientific reviews of any atorvastatin ANDA that otherwise could be approved and marketed to the American public as early as June 28, 2011. To date, no atorvastatin ANDA has been tentatively approved.

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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

MATRIX

Matrix Laboratories Limited
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RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0512	
TO *(Division/Office)* DMEP - HFD-510 Thru: Leah Ripper, ODEII - HFD 102			FROM: Leigh Ann Sears	
DATE: 4/6/2011	IND NO.	ANDA NO. 091226	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 3/7/2011,
NAME OF DRUG Atorvastatin Calcium		PRIORITY CONSIDERATION EXPEDITED REVIEW	CLASSIFICATION OF DRUG Lipid Lowering Agent	DESIRED COMPLETION DATE 4/21/2011
NAME OF FIRM Matrix Laboratories Limited				

REASON FOR REQUEST

I. GENERAL

- Γ NEW PROTOCOL
- Γ PROGRESS REPORT
- Γ NEW CORRESPONDENCE
- Γ DRUG ADVERTISING
- Γ ADVERSE REACTION REPORT
- Γ MANUFACTURING CHANGE/ADDITION
- Γ MEETING PLANNED BY _____
- Γ PRE NDA MEETING
- Γ END OF PHASE II MEETING
- Γ RESUBMISSION
- Γ SAFETY/EFFICACY
- Γ PAPER NDA
- Γ CONTROL SUPPLEMENT
- Γ RESPONSE TO DEFICPENCY LETTER
- Γ FINAL PRINTED LABELING
- Γ LABELING REVISION
- Γ ORIGINAL NEW CORRESPONDENCE
- Γ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

- DISSOLUTION
- PROTOCOL-- BIOPHARMACEUTICS
- IN--VIVO WAIVER REQUEST
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

IV.DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- _SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review. "Impurities listed are higher than the RLD." Please evaluate the need of qualifying the (b) (4). This consult is based on the consult # 20009-0443 which was done by Dr. Antonipillai. More information attached. (This ANDA is on EXPEDITED REVIEW)Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.sears@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER Leigh Ann Sears	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

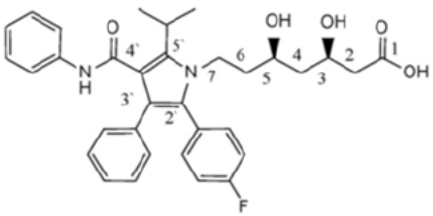
Pharm-Tox consults-ANDA 91226

HFD-630/Haitao. Li/CR/
HFD-630/L. Nagavelli/TL
HFD-617/L.A.Bradford/PM

The firm is trying to justify not qualifying the high level of (b) (4) in the drug product. They proposed NMT (b) (4)% in the drug product stability specification and the highest observed (b) (4) data in the stability study is (b) (4)%.

Name	Structure	Qualified Level
(b) (4)		

The firm performed hydrolysis study and observed that the (b) (4) under (b) (4) breaks down to (b) (4) and (b) (4) which have been qualified (see structures above and reaction scheme below). They expect (b) (4) can (b) (4) in stomach to form (b) (4)% (b) (4) and (b) (4)% (b) (4). Our concern is that this compound is a (b) (4), the level is rather high in the drug product, and also it is increasing in stability samples. We think the firm should qualify this impurity. What is your opinion?



Atorvastatin

(b) (4)

Also in the previous qualification study, the firm spiked atorvastatin calcium with (b) (4)% (b) (4) and (b) (4)% (b) (4) and demonstrated the level does not cause genotoxicity. The firm also spiked atorvastatin calcium with (b) (4)% (b) (4) and demonstrated the level does not cause genotoxicity.

We observed up to (b) (4)% of these epoxides in total based on the firm's stability data. Do we need to worry about the potential cumulative genotoxic effect of these impurities?

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
04/06/2011

TRANG Q TRAN
04/06/2011

MATRIX

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Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95, Matrix certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 5,273,995 and RE40667 and their associated pediatric exclusivities; prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156; 6,126,971 and their associated pediatric exclusivities; and prior to the expiration of U.S. Patent No. 7,790,197.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95, Matrix certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 5,273,995 and RE40667 and their associated pediatric exclusivities; prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156; 6,126,971 and their associated pediatric exclusivities; and prior to the expiration of U.S. Patent No. 7,790,197.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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 1, 2011

FROM: Keith O. Webber, Ph.D.
Acting Director, OGD

SUBJECT: Status of ANDA Review

TO: ANDA 091226 - Atorvastatin Calcium Tablets
Matrix Laboratories LTD

In light of the ongoing activity involving this application, we are documenting the current status of the reviews. This ANDA was submitted to FDA on December 31, 2008. Since that date, OGD has been in regular communication with the ANDA sponsor, Matrix Laboratories (a Mylan subsidiary), regarding our review. The current status of the application is as follows:

Bioequivalence: Acceptable on February 17, 2011

Labeling: Acceptable on December 29, 2010

EES (assessment of whether facilities have acceptable cGMPs for the product for which approval is being sought): Acceptable on March 1, 2011

CMC Review:

Most recently, on February 23 (via e-mail) and February 25, 2011, OGD sent descriptions of chemistry deficiencies in the application to Matrix. The deficiencies included requests for information regarding the address and contact name for certain facilities, a comparison of impurity levels to Lipitor, information regarding a newly identified impurity, drug product release and stability specifications, and information regarding drug substance and excipient compatibility. Matrix responded to the February 23, 2011 deficiencies on March 1, 2011, and to the February 25, 2011 chemistry deficiencies on March 7, 2011. The February 23 deficiencies (sent via e-mail) are incorporated in the Sponsor's March 1 response attached. Copies of the February 25, 2011 deficiency letter and the Sponsor's response are also attached. The responses will be reviewed according to OGD procedures.

Among the CMC issues identified is the proposed level of L-arginine in the proposed product. L-arginine is an inactive ingredient in Matrix's product and is present at a level of (b) (4) in the 80 mg strength tablet. L-arginine has only been used in approved injectable drug products (that are not for chronic use) and has never been used in oral products before. Matrix did not conduct standard pharm/tox studies and only provided literature data. This issue has been consulted to the pharm/tox staff. Their conclusion on the acceptability of L-arginine was not definitive. Matrix's data package was submitted to OGD's Clinical Staff. They are consulting the Office of New Drugs' Division of Cardiovascular and Renal Products regarding the safety of adding L-arginine to the proposed generic atorvastatin calcium in ANDA 091226.

Note that in July 2005, Pfizer submitted a petition asking FDA to carefully scrutinize applications seeking approval for products that include certain polymorphic forms of atorvastatin. They are concerned that certain forms of the active ingredient may be more susceptible to impurities, degrade more quickly than Lipitor, and thus have inferior stability. We are assessing the issues raised in the petition as we consider atorvastatin ANDAs. Matrix's proposed drug product contains an (b) (4) form of the atorvastatin drug substance while Pfizer's product contains a crystalline form.

DMF Review: DMF 21477, Matrix Laboratories Ltd.

The DMF was reviewed on February 17, 2011 and found to be deficient (3 deficiencies). The deficiencies were faxed to the DMF holder on February 17, 2011. The deficiencies included a request to include a quantitative test for calcium (and establish limits for the calcium range), and to provide all stability data collected to date, and the DMF holder was informed that their drug substance did not comply with the current USP monograph for (b) (4) limit. The DMF holder responded to the deficiencies on March 9, 2011. This response will be reviewed according to OGD procedures.

OGD's staff intends to review Matrix's ANDA and all other atorvastatin ANDAs in a timely manner so that FDA review time will not delay approval. 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.

Attachments

10 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

QUALITY DEFICIENCY - MINOR

ANDA 091226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Matrix Laboratories Limited

TEL: (304) 554-5899

ATTN: Keith Giunta

FAX: (304) 285-6407

FROM: Mark Gonitzke

FDA CONTACT PHONE: (240) 276-8422

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendments dated November 18 and December 14, 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 ____ 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*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

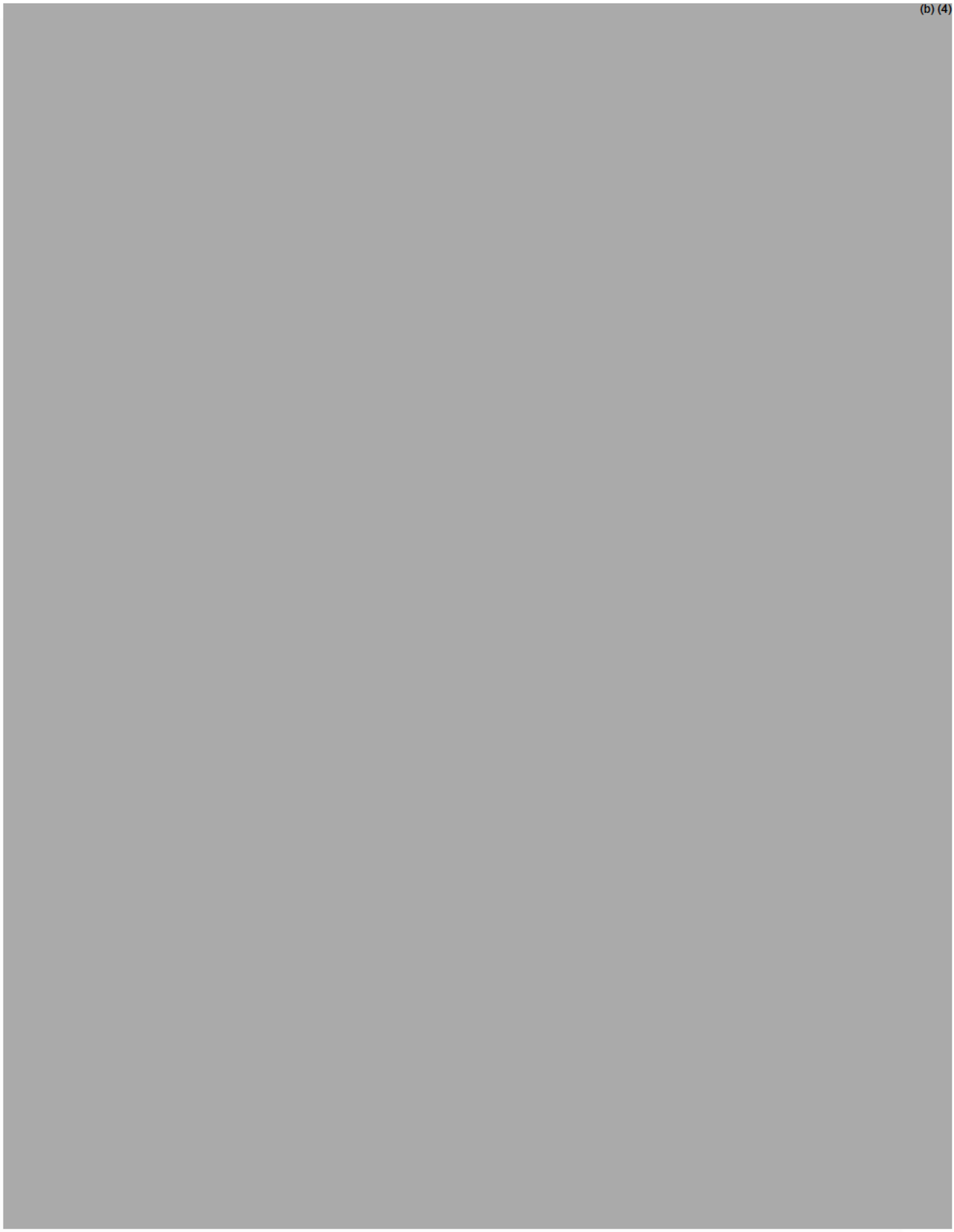
ANDA: 091226 **APPLICANT:** Matrix Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

[redacted]


(b) (4)



B. Please acknowledge and respond to the following comments:

1. Please provide up to date long-term stability data for drug product.

2. The Pharm/Tox consult for L-arginine in this product was not definitive. Based on comments from the Pharm/Tox reviewer, we have submitted your data package to our Clinical Staff for an opinion. We await the outcome of this consult.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

SUSAN ZUK
02/25/2011

MATRIX

ANDA # 91-226, Atorvastatin Calcium Tablets, 10mg, 20mg, 40mg and 80mg
Response to MINOR Quality Deficiencies dated Feb 25, 2011

RESPONSE: MINOR QUALITY COMMENTS DATED FEBRUARY 25, 2011

ANDA # : 91-226
APPLICANT : Matrix Laboratories Limited
DRUG PRODUCT : Atorvastatin Calcium Tablets, 10mg, 20mg, 40mg and 80mg
FDA CONTACT : Mark Gonitzke

A. The deficiencies presented below represent MINOR deficiencies

Comment # 1

(b) (4)

Response:

(b) (4)

Comment # 2

(b) (4)

Response:

(b) (4)

16 pages have been withheld immediately following this page as b4 (CCI/TS)

(b) (4)

[redacted]

B. Please acknowledge and respond to the following comments:

1. **Please provide up to date long-term stability data for drug product.**

   Response:
   As requested, available (b) (4) LT data has been provided under **section 3.2.P.8.3** in accordance with revised specifications.

   ---

2. **The Pharm/Tox consult for L-arginine in this product was not definitive. Based on comments from the Pharm/Tox reviewer, we have submitted your data package to our Clinical Staff for an opinion. We await the outcome of this consult.**

   Response:
   We acknowledge the Agency's comment.

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
04/01/2011

KEITH O WEBBER
04/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: *(Division/Office)* Norman Stockbridge, M.D., Division of Cardiovascular and Renal Products

FROM: Linda Forsyth, M.D., Office of Generic Drugs (OGD) through Dena R. Hixon, M.D., Associate Director for Medical Affairs, OGD

DATE:	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 31, 2011	-	ANDA 091226	Consult Request	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atorvastatin Calcium	Expedited review	Statins Lipid lowering drugs	April 29, 2011

NAME OF FIRM Matrix Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE 11 MEETING
- ☐ RESUBMISSION SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(Specify Below)* Clinical Safety Issue

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL-- BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL ☐ PRECLINICAL

COMMENTS

(b) (4)

(b) (4)

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

CC: ANDA

Reference ID: 2926976

REQUEST FOR CONSULTATION

To:	Norman Stockbridge, M.D. Division Director Division of Cardiovascular and Renal Products
From:	Linda Mary Forsyth, M.D. Medical Officer Office of Generic Drugs
Through:	Dena R. Hixon, M.D. Associate Director for Medical Affairs Office of Generic Drugs
RE:	Request for advice on the safety of L-arginine in generic atorvastatin calcium in patients with cardiovascular disease, ANDA 091226
Date of Request:	March 31, 2011
Date Response Requested:	April 29, 2011

The Clinical Team in the Office of Generic Drugs (OGD) received a medical consultation from Division of Chemistry III, OGD, regarding ANDA 091226. The generic version of atorvastin calcium contains L-arginine as a (b) (4) and this inactive ingredient is not contained in the reference listed drug or any other oral drug product. An 80 mg tablet contains (b) (4) of L-arginine. The Inactive Ingredients database shows this ingredient only in approved parenteral drug products. The Clinical Team was requested to evaluate the safety in subjects with cardiovascular disease.

The reference listed drug for atorvastatin calcium is Lipitor® (atorvastin calcium), Pfizer (approved on December 17, 1996). Lipitor® (atorvastatin calcium) is a lipid-altering agent. It is manufactured as 10, 20, 40 and 80 mg tablets. The recommended starting dose of Lipitor® is 10 or 20 mg once daily.

A pharmacology/toxicology review was performed by the Division of Metabolism and Endocrine Products and is included in DARRTS 9/29/2011 and the sponsor's justification for adding L-arginine in their product is submitted in DARRTS 4/8/2010, 3.2, P.1.2. The pharmacology/toxicology reviewer was unable to evaluate the safety of L-arginine in patients with cardiovascular disease.

The OGD medical officer reviewed the clinical trial summaries contained in the sponsor's justification of safety in subjects with cardiovascular disease. L-arginine as been given to a variety of patients with cardiovascular disease in doses <30 g and it has

Reference ID: 2926976

been well tolerated. An article published by Bednarz B, et al.[1] in 2005 examined the effects of L-arginine given to patients with acute myocardial infarction. Patients with ST segment elevation were admitted within 24 hours after the onset of symptoms and received oral L-arginine 3 g three times a day or placebo for 30 days. The study was conducted in 792 patients and showed oral L-arginine supplementation was well tolerated and a nonsignificant beneficial trend was observed towards reduction of major clinical events. However, another study published in 2006, by Schulman SP et al.[2] similarly examined patients with first ST segment elevation myocardial infarction. There were 153 patients enrolled and randomly assigned to receive oral L-arginine 3 g three times a day or placebo for 6 months. Six patients receiving L-arginine died during the 6 month study and none in the placebo group, so the data and safety monitoring committee closed enrollment. The study noted there was no significant change from baseline to 6 months in the vascular stiffness measurements or left ventricular ejection fraction. This study concluded that L-arginine should not be recommended following acute myocardial infarction.

In CDER approved drugs, the excipient, L-arginine, has only been used in injection formulations and has not been used in products for oral use.

L-arginine is available as a dietary supplement and is promoted to help maintains blood vessel tone. For example, 1 g capsules are available as an "essential building block of nitric oxide" taken one to three capsules daily.

OGD has the following questions for the Division of Cardiovascular and Renal Products:

Question for Division of Cardiovascular and Renal Products:

> We request your assessment of the safety considerations for adding L-arginine to atorvastatin calcium in amounts up to (b) (4) for the 80 mg highest strength, given that this product will be used on a chronic basis in patients with cardiac disease or risk factors for cardiac disease. Do you consider this generic product be as safe as the reference listed drug with the addition of L-arginine to the formulation? Is there any potential clinical benefit for this population?

We appreciate input on this matter from your Division regarding appropriate safety considerations for the generic version of this drug. If you have any questions, I can be reached directly at 240-276-8702.

---

[1] Bednarz B, Jaxa-Chamiec T, Maciejewski P, Szpajer M, Janik K, Gnoit J, Kawka-Urbanek T, Drozdowska D, Gessek J, Laskowski H. Efficacy and safety of oral l-arginine in acute myocardial infarction. Results of the multicenter, randomized, double-blind, placebo-controlled ARAMI pilot trial. Kardio Pol. 2005; 62(5):421-7.

[2] Schulman SP, Becker LC, Kass DA, Champion HC, Terrin ML, Forman S, Ernst KV, Kelemen MD, Townsend SN, Capriotti A, Hare JM, Gerstenblith G. L-arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. JAMA 2006; 295(1): 58-64. Comment: JAMA 2006; 295(18): 2138-9.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Consult No: 2011-0499

TO: *(Division/Office)*	FROM:
OGD/Medical Officer	Mark Gonitzke/Leigh Ann Sears/Susan Zuk

DATE:	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/28/2011		091226	Amendment	9/29/2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atorvastatin Calcium	30 days	Lipid Lowering	3/30//2011

NAME OF FIRM Matrix Labs LTD

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE 11 MEETING
- ☐ RESUBMISSION SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(Specify Below)* Impurity Medical Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL BIOPHARMACEUTICS
- ☐ IN VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS

The Division of Chemistry is requesting a consult for Atorvastatin (generic version of Lipitor). The product contains (b) (4) of L-aginine per tablet as a (b) (4). Since this ingredient exceeds the IIG level and is not found in the RLD, we sent a Pharm/Tox consult to OND toxicologists to receive an opinion on the safety of the ingredient at the level proposed. Pharm/tox was not able to evaluate the safety of the clinical literature summaries in subjects with Cardiovascular disease and advised to seek medical consult. The Tox review is in DARRTs (9/29/2010 submit date) and the firm's response is also in DARRTS (Quality Response 4/8/2010, see TOC link 3.2, P.1.2). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when checked into DARRTs.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY (Check one)
Mark Gonitzke	☒ MAIL e-mail ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

Reference ID: 2911454

CC: ANDA

Reference ID: 2926976

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
02/28/2011

Reference ID: 2926976

Signed off in DARRTS on 9/29/10

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 91-226

Date of submission: 4/8/10. OGD is requesting the pharmacology /toxicology consult on the impurities in the atorvastatin calcium drug product under ANDA 91-226.

Review Number: 2 (Previous consult on this ANDA wa signed off in DARRTS on 6/16/2009

Drug Names: Atorvastatin Calcium, 10, 20, 40, 80 mg tablets.

Consult #: 20009-0443 for atorvastatin calcium tablets.

Consult from: Leigh Ann Bradford, and Trang Tran.
Request date: 8/10/2010

Generic drug name: Atorvastatin calcium tablets.
Drug class: Statins (generic atorvastatin). **Indication**: Lipid lowering.

Type of document: Electronic submission dated 4/8/10.

Subject of Consult: OGD is requesting a pharmacology/toxicology consult because the impurities listed are higher than the RLD (see submission 8/4/10 in EDR, module 3). Sponsor has provided number of toxicity studies to qualify the impurities in the drug product. Additionally, they have provided justification for use of the inactive ingredient L-Arginine, in the current drug product. L-Arginine is present at doses of (b) (4) in the sponsor's 80 mg dosage form atorvastatin calcium tablets. Note that in the previous consult review (see DARRTs), we recommended that the sponsor establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), which may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use here ((b) (4)).

The consult comments are stated below:

OGD is requesting a Pharm/Tox Review. "Impurities listed are higher than the RLD." Please evaluate the amendment ANDA in EDR Module 3 (see attached documents for reference). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Bradford, HFD-617 (Leigh.bradford@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.

Division: Division of Metabolic and Endocrinology products.

Review completion date: 9/17/10.

Introduction

OGD wants us to review the proposed levels of impurities in the drug product which are higher than RLD in the abbreviated NDA (ANDA) 91-226 (Matrix laboratories, Inc). OGD wants us to review the completed studies submitted in the support of higher impurities in the drug product and to provide information if they are acceptable.

Following information is provided on the impurities in the drug substance and the drug product

Impurities information:

(b) (4)

(b) (4)

Impurities control in Drug Substance ATORVASTATIN CALCIUM

TEST	RESULTS		SPECIFICATION
	AC0090408 (DS Manufacturer)	1004608 (DP Manufacturer)	
Related Substances (by HPLC)			

(b) (4)

Impurities control in Drug Product

Impurities limit in Finished Product Specification- Atorvastatin Calcium Tablets, 10 mg, 20, 40 and 80 mg.

Test	Specification	
	Release	Shelf life
Related Substances (by HPLC)		

(b) (4)

Chemical names of the impurities:

(b) (4)

The firm submits 3 reports for (b) (4) impurity for DP specification (b) (4)% for release and (b) (4)% for stability).

1. Bacterial Reverse Mutation Test Report (b) (4) impurity (93 page)
2. In Vitro Mammalian Chromosome Aberration Test Report (b) (4) impurity (93 page)
3. 14-Day repeated dose oral toxicity study by Gavage in wistar rats- (b) (4) impurity (373 page)

The firm submits 2 reports for (b) (4) and (b) (4) Impurities for DS and DP specification (see attached for specification).

1. Baterial Reverse Mutation Assay for Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) (b) (4) and (b) (4)% (b) (4) Impurities of Atrovastatin (89 page)
2. In Vitro Mammalian Chromosome Aberration Test Report for Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atrovastatin (129 page)

The firm submits 1 report for L-Arginie Safety Assessment.

1. L-Arginine Safety Assessment (47 page).

Additionally, sponsor has submitted a 2-week toxicity study of atorvastatin calcium drug product containing (b) (4) and (b) (4) impurities.

Following toxicity studies have been conducted to support the impurity (b) (4) and (b) (4) (b) (4) impurities in the atorvastatin calcium drug product.

1. A 2-Week Oral Toxicity Study of atorvastatin calcium containing atorvastatin (b) (4) (b) (4) impurity in Rats (Study No. Tox 037-003)

The purpose of this study was to qualify atorvastatin (b) (4) and atorvastatin (b) (4) (b) (4) impurities in the atorvastatin drug product at the (b) (4) and (b) (4)% level, respectively. The study

Study no: Tox 037-003
Volume #, and page #: eCTD submission dated 8/4/10

Conducting laboratory and location: (b) (4)

Date of study initiation: 8/28/09
GLP compliance: Yes
QA report: yes (X) no ( )

Drug lot #, and % purity:

Drug without impurity

6.1.1. Test Articles

Identification	Atorvastatin Calcium
Lot Number	AC0160708
Assigned Testing Facility ID	09001E
Purity	(b) (4)%
Receipt Date	21-Jul-2009
Expiration Date	31-Oct-2009

Drug with impurity: The impurities present were atorvastatin (b) (4) and (b) (4) impurities; the lot numbers were similar for both products, but receipt dates were different. It is not clear how these two were different; analytical description is provided below. Note that the sponsor states that the atorvastatin (b) (4) impurity is present at concentration of (b) (4)% and atorvastatin (b) (4) impurity is present at concentration of (b)% (relative to atorvastatin calcium drug product), see the foot note below in the Experimental design Table.

Identification	(b) (4) impurity
Lot Number	ADL/941(149)/1008
Assigned Testing Facility ID	09001F
Purity	(b) (4)%
Receipt Date	21-Jul-2009
Expiration Date	None provided

Identification	(b) (4) impurity
Lot Number	ADL/941(149)/1008
Assigned Testing Facility ID	090037
Purity	(b) (4)%
Receipt Date	28-Aug-2009
Expiration Date	None provided

ANALYTICAL DESCRIPTION

PRODUCT: (b) (4) Impurity	CONTROL NUMBER: ADL/941(149)/1008

(b) (4)

PRODUCT: (b) (4) Impurity	CONTROL NUMBER: ATC/IMP/918/118

(b) (4)

Methods (unique aspects):

Doses in administered units: 0, 40, 80 mg/kg/day with and without impurities were administered to rats (male and female Sprague Dawley Crl:CD{SD}, 9 weeks of age, BWs of males were 325-379 g; females were 207-256 g).

Groups 3 and 5: The Atorvastatin Calcium and [redacted] impurity were combined at ratios of [redacted] impurity to Atorvastatin Calcium). Since this ratio already provided an approximate [redacted] impurity concentration of [redacted]% relative to Atorvastatin Calcium, additiona [redacted] impurity was not required to be added to the preparation.

The dose levels were selected based on information found in the summary basis of approval for atorvastatin calcium (Lipitor®; NDA 20-702) in an attempt to produce graded responses to the test article while preserving large multiples of the human daily exposure potential. The high-dose level was expected to produce some toxic effects, but not excessive lethality that would prevent meaningful evaluation and represents approximately [redacted] the maximum human dosage on a body surface area basis (mg/m^2). The low-dose level was expected to produce no observable indications of toxicity.

Experimental design Table below

Experimental Design

Group No.	No. of Toxicity Animals		Test Material	Atorvastatin Dose Level (mg/kg/day)	Atorvastatin Dose Concentration (mg/mL)	Atorvastatin Dose Volume (mL/kg)	Atorvastatin Adjusted Dose Concentration[a] (mg/g^b)
	Male	Female					
1	10	10	[redacted]% CMC	0	0	10	0
2	10	10	Atorvastatin Calcium	40	4	10	4.136
3	10	10	Atorvastatin Calcium + impurities[c,d]	40	4	10	4.136
4	10	10	Atorvastatin Calcium	80	8	10	8.272
5	10	10	Atorvastatin Calcium + impurities[c,d]	80	8	10	8.272

[a]Expressed as [redacted] concentration. Correction factor o [redacted] applied (based on [redacted]
[b]The dose concentrations were based on an approximate density of 1 g/mL.
[c]The [redacted] impurity was adjusted by [redacted] for purity.
[d]The Atorvastatin Calcium and [redacted] impurity was combined at a ratio o [redacted]% concentration of [redacted] impurity relative to Atorvastatin Calcium). This provided an approximate [redacted] impurity concentration o [redacted]% relative to Atorvastatin Calcium.

Formulation/vehicle: 1% carboxymethylcellulose in reverse osmosis deionized water. Dosing volume was 10 ml/kg.

Methods and results are described below.

The following variables and end points were evaluated in this study: clinical signs, body weights, body weight changes, food consumption, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), gross necropsy findings, organ weights, and histopathologic examinations.

Gross pathology: At sacrifice.
Organs weighed: Following organs were weighed as shown in the Table below.

Adrenal gland[a]	Prostate gland
Brain	Salivary gland[a]
Epididymis[a]	Seminal vesicle[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	Uterus
Pituitary gland	
[a]Paired organ weight.	

Histopathology: This was performed at sacrifice in control and high dosed animals in organs listed in histopathology Table below.

Tissue Collection and Preservation

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic[b]
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland[c]
Bone marrow smear[a]	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (inguinal)
Harderian gland (paired)	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (nonglandular and glandular)
Intestine, colon	Testis (paired)[d]
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses
Lymph node, mesenteric	

[a]Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.
[d]Preserved in modified Davidson's fixative and then transferred to 10% neutral buffered formalin.

Results:

Mortality: No treatment related mortality was observed.

Clinical signs: No drug related effects were observed.

Body weights: Body weight gains were higher in females with both products on days 8-14 with impurities (4,10, 9 g at 0, 40, 80 mg/kg/day respectively) and without impurities (4, 10, 8 g respectively). Since the sponsor did not include the RLD in this study, it is not clear if this is unique to the current drug product. Sponsor states the following on BW changes:

A single statistically significant decrease in mean body weight changes was noted in the 40 mg/kg/day atorvastatin calcium (with impurities)-treated males during the Day 8 to 14 body weight interval; however, in the absence of a dose response, this change was not considered toxicologically meaningful.

A 14-DAY TOXICITY STUDY ADMINISTERED BY ORAL GAVAGE TO RATS

(b) (4)



A 14-DAY TOXICITY STUDY ADMINISTERED BY ORAL GAVAGE TO RATS

(b) (4)



Food consumption: Food consumption (FC) was not affected

Hematology: Hematological parameters such as hemoglobin was increased at a high dose in males with the drug without impurities (14.7, 15.3, 15.9* g/dl at 0, 40, 80 mg/kg/day respectively, *p<0.05) and at all doses with impurities (14.7, 15.4*,15.6* g/dl respectively, *p<0.05). Similar observation were noted for hematocrit values. Since the sponsor did not include the RLD in this study, it is not clear if this is unique to the current drug product.

Sponsor below states that basically similar hematological findings were noted with both products, (the drug with or without impurities).

Atorvastatin calcium and atorvastatin calcium (with impurities)-related changes were observed in mean red cell mass, platelets, and white blood cell counts in males when compared to the controls. There were no test article-related changes noted in females.

Slight, dose-dependent increases in erythrocytes, hemoglobin, and hematocrit were noted across all test article-treated males. The atorvastatin calcium (with impurities)-treated groups were less affected than the atorvastatin calcium only groups; increases in red cell mass up to 7% and 9% were observed in atorvastatin calcium (with impurities)-treated males and atorvastatin calcium only males, respectively. In addition, slight increases in platelets were evident at 80 mg/kg/day in both atorvastatin calcium-treated groups (with and without impurities); increases up to 16% and 17% were noted, respectively.

Increases in mean leukocytes (49%), lymphocytes (49%), monocytes (78%), and basophils (4-fold) were evident in 80 mg/kg/day males treated with atorvastatin calcium only. The increases observed were approximately 2-fold greater than the 80 mg/kg/day atorvastatin calcium with impurities group.

Statistically Significant Differences in Hematology and Coagulation Parameters

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	Erythrocytes	Group 2 ↑	8.24	7.84	7.040-9.660
			Group 4 ↑	8.54		
			Group 5 ↑	8.42		
		Hemoglobin	Group 3 ↑	15.4	14.7	13.40-17.70
			Group 4 ↑	15.9		
			Group 5 ↑	15.6		
		Hematocrit	Group 2 ↑	45.1	42.9	37.80-48.10
			Group 3 ↑	44.9		
			Group 4 ↑	46.3		
			Group 5 ↑	45.0		
		Platelets	Group 4 ↑	1273	1085	737.0-1403.0
			Group 5 ↑	1262		
		Leukocytes	Group 4 ↑	13.79	9.27	4.80-17.72
		Lymphocytes	Group 4 ↑	11.05	7.40	3.53-13.99
		Monocytes	Group 4 ↑	0.66	0.37	0.10-0.89
		Basophils	Group 4 ↑	0.04	0.01	0.00-0.10
Females	15	Hemoglobin	Group 3 ↑	14.8	14.1	12.90-16.90
Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4)) Group 4 (80 mg/kg/day) Group 5 (80 mg/kg/day, (b) (4))						

(b) (4)

SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

(b) (4)

(b) (4)

SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

(b) (4)

(b) (4)

SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

(b) (4)

(b) (4)

SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

(b) (4)

Clinical chemistry: In general similar drug related effects were observed on clinical chemistry parameters. For example ALT was increased in males at all doses with both drugs (without impurities, the values were 27, 53*,177* IU/L at 0, 40, 80 mg/kg/day respectively, *p<0.05); with impurities the values were 27, 62*, 89* IU/L at 0, 40, 80 mg/kg/day respectively, as seen below

Atorvastatin calcium and atorvastatin calcium (with impurities)-related changes were observed in mean AST, ALT, alkaline phosphatase, serum GGT (males only), total bilirubin, total protein, and globulin. Males appear to be affected more than females.

Dose-dependent increases in ALT were observed in the 40 and 80 mg/kg/day groups. Increases up to 3-fold and 6-fold were noted in the atorvastatin calcium only and atorvastatin calcium with impurities groups, respectively. Increases in mean AST, alkaline phosphatase, and total bilirubin were noted in both groups treated at 80 mg/kg/day; greater differences from control were evident in the atorvastatin calcium only group (up to 4-fold) compared to the atorvastatin calcium with impurities group (up to 2-fold) and were more pronounced in males. ALT, AST, alkaline phosphatase, and total protein are consistent with previous studies conducted in rats with atorvastatin. Increases (up to 10-fold) were noted in mean serum GGT in 40 and 80 mg/kg/day males treated with atorvastatin calcium only and were noted to be within the Testing Facility's historical control range.

Decreases in mean total protein and globulin were evident in males in both groups treated at 80 mg/kg/day (atorvastatin calcium alone or in combination with two impurities) and in 80 mg/kg/day females treated with atorvastatin only. For males, the differences from control were comparable between the groups (up to 7 % and 9% in atorvastatin calcium only and atorvastatin calcium with impurities-treated groups, respectively). Correlating increases (up to 9%) in A/G ratio were noted.

SUMMARY OF CLINICAL CHEMISTRY DATA (b) (4)

(b) (4)



SUMMARY OF CLINICAL CHEMISTRY DATA (b) (4)



Statistically Significant Differences in Clinical Chemistry Parameters

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	AST	Group 4 ↑	368	87	50.0-126.0
			Group 5 ↑	198		
		ALT	Group 2 ↑	53	27	18.0-41.0
			Group 3 ↑	62		
			Group 4 ↑	177		
			Group 5 ↑	89		
		ALK Phosphatase	Group 4 ↑	197	138	49.0-196.0
			Group 5 ↑	226		
		GGT, Serum	Group 4 ↑	0.29	0.03	0.000-0.470
		Total Bilirubin	Group 4 ↑	0.18	0.11	0.090-0.190
			Group 5 ↑	0.15		
		Cholesterol	Group 4 ↑	54	38	33.0-95.0
		Triglyceride	Group 3 ↓	39	42	30.0-119.0
			Group 5 ↓	30		
		Total Protein	Group 5 ↓	5.21	5.49	5.190-6.460
		Globulin	Group 5 ↓	2.40	2.64	2.340-3.360
Females	15	ALT	Group 4 ↑	81	24	15.0-97.0
			Group 5 ↑	72		
		Globulin	Group 4 ↓	2.58	2.86	2.280-3.350
		A/G Ratio	Group 4 ↑	1.17	1.09	0.980-1.440
		Phosphorus	Group 3 ↓	7.14	7.76	3.950-7.870

Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4)) Group 4 (80 mg/kg/day)
Group 5 (80 mg/kg/day, (b) (4))

Urinalysis: No drug related effects were observed.

Organ weights: In female rats, liver weights were increased at 80 mg/kg/day with impurities (8.3* vs 7.6 g g in control, *p<0.5, by 8%), not seen with the drug without impurities (7.9 vs 7.6 g in controls)

Statistically Significant Differences in Organ Weights

Sex	Day	Organ	Absolute Weight	Relative to Body Weight	Relative to Brain Weight
Males	Day 15	Liver	--	Group 2 ↓	--
		Kidneys	--	Group 3 ↑	--
		Epididymides	--	Group 4 ↑	--
Females	Day 15	Liver	--	Group 5 ↑	--
Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4) Group 4 (80 mg/kg/day) Group 5 (80 mg/kg/day, (b) (4)					

Gross pathology: The findings in general were similar with both products as shown below in the Table.

Gross (Internal) Necropsy Findings for Main Study Animals

Sex	Day	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	15	Kidney – dilated pelvis	--	--	--	--	1/10
		Kidney – discoloration pale	--	--	1/10	--	--
		Kidney cortex, roughened surface	--	--	1/10	--	--
		Mandibular lymph node, enlarged	--	--	1/10	--	1/10
		Nonglandular stomach, thickened	--	--	1/10	--	--
		Thymus – discoloration dark	1/10	--	--	1/10	--
		Thymus – foci dark	1/10	--	--	--	--
Females	15	Kidney – discoloration pale	--	--	1/10	--	--
		Mandibular lymph node, discoloration dark	--	--	--	1/10	--
		Ovary – periovarian cyst(s)	--	--	--	--	1/10
		Thymus – foci dark	--	--	--	1/10	--
		Thyroid – small	--	1/10	--	--	--
Group 1 (0 mg/kg/day) Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4) Group 4 (80 mg/kg/day) Group 5 (80 mg/kg/day, (b) (4)							

Histopathology: Histopathology findings in the liver were generally comparable with the drug without and with impurities, as seen below.

	Placebo	Without Impurity		With Impurity	
Doses (mg/kg/day)	Zero	40 m/k/d	80 m/k/d	40 m/k/d	80 m/k/d
Liver, single cell necrosis: **Males**	M=0/10	3/10	10/10	3/10	10/10
Liver, single cell necrosis: **Females**	F=0/10	1/10	5/10	0/10	2/10

Minimal to mild necrosis of individual hepatocytes (single cell necrosis) was noted in the livers of all 80 mg/kg/day atorvastatin calcium and atorvastatin calcium (with impurities)-treated males, five 80 mg/kg/day atorvastatin calcium-treated females, and two 80 mg/kg/day atorvastatin calcium (with impurities)-treated females. This liver change was also present in three males each in 40 mg/kg/day atorvastatin calcium and atorvastatin calcium (with impurities)-treated groups and in one 40 mg/kg/day atorvastatin calcium female, but was not present in 40 mg/kg/day atorvastatin calcium (with impurities) females. These liver changes are consistent with previous studies conduct in rats with atorvastatin[8].

A 14-DAY TOXICITY STUDY OF ATORVASTATIN CALCIUM ADMINISTERED BY ORAL GAVAGE TO RATS
Incidence of Histopathologic Findings for All Study Animals (continued)

Table: 1

PROJECT NUMBER: FMA46A SPECIES: RAT

Tissue/ Diagnosis/ Modifier(s)	Group 1		Group 2		Group 3		Group 4		Group 5	
	M	F	M	F	M	F	M	F	M	F
KIDNEY (continued)										
DEGENERATION/REGENERATION, TUBULAR	5	3	0	0	0	0	1	1	2	3
UNILATERAL, MINIMAL	4	3	0	0	0	0	1	1	2	2
BILATERAL, MINIMAL	1	0	0	0	0	0	0	0	0	1
DILATATION, PELVIS	0	0	0	0	0	0	0	0	1	0
UNILATERAL, MINIMAL	0	0	0	0	0	0	0	0	1	0
NEPHROPATHY, CHRONIC PROGRESSIVE	0	0	0	0	1	0	0	0	0	0
BILATERAL, SEVERE	0	0	0	0	1	0	0	0	0	0
WITHIN NORMAL LIMITS	5	7	0	0	0	1	9	9	7	7
LIVER	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NECROSIS, SINGLE CELL	0	0	3	1	3	0	10	5	10	2
HEPATOCELLULAR, MINIMAL	0	0	3	1	3	0	7	4	8	2
HEPATOCELLULAR, MILD	0	0	0	0	0	0	3	1	2	0
TENSION LIPIDOSIS	0	0	0	0	1	1	0	0	0	0
MINIMAL	0	0	0	0	1	1	0	0	0	0
WITHIN NORMAL LIMITS	10	10	7	9	6	9	0	5	0	8
LUNG	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
INFLAMMATION, CHRONIC	0	0	0	0	0	0	0	0	1	0
FOCAL, MINIMAL	0	0	0	0	0	0	0	0	1	0
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	9	10
LYMPH NODE, MANDIBULAR	(9)	(10)	(0)	(0)	(1)	(0)	(10)	(10)	(10)	(10)
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS	0	0	0	0	0	0	0	1	0	0
SINUSAL, MILD	0	0	0	0	0	0	0	1	0	0
HYPERPLASIA, LYMPHOID	0	0	0	0	0	0	0	0	1	0
MILD	0	0	0	0	0	0	0	0	1	0
WITHIN NORMAL LIMITS	9	10	0	0	1	0	10	9	9	10
LYMPH NODE, MESENTERIC	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
MAMMARY GLAND	(10)	(10)	(0)	(0)	(0)	(0)	(9)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	9	10	10	10
NERVE, SCIATIC	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
OVARY	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(10)
WITHIN NORMAL LIMITS	0	10	0	0	0	0	0	10	0	10
PANCREAS	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
PARATHYROID	(7)	(7)	(0)	(0)	(0)	(0)	(7)	(10)	(4)	(8)
WITHIN NORMAL LIMITS	7	7	0	0	0	0	7	10	4	8
PITUITARY	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
PROSTATE	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(10)	(0)
INFLAMMATION, CHRONIC	3	0	0	0	0	0	2	0	2	0
MINIMAL	3	0	0	0	0	0	0	0	1	0

Titles:
Group 1 0 MG/KG/DAY
Group 2 40 MG/KG/DAY
Group 3 40 MG/KG/DAY (b) (4)
Group 4 80 MG/KG/DAY
Group 5 80 MG/KG/DAY (b) (4)

() = Number Of Animals Examined For This Tissue

Toxicokinetics: No TK studies were conducted.

Following is sponsor's conclusions of the above study

> Administration of atorvastatin calcium (alone and in combination with two impurities) by once daily oral gavage for a minimum of 14 days did not result in mortality, but was associated with minimal to mild necrosis of individual hepatocytes (single cell necrosis) in the liver. The liver changes were observed across all groups treated with atorvastatin calcium and atorvastatin calcium with impurities, except for females administered 40 mg/kg/day atorvastatin calcium with impurities. Based on these results, the no-observed-adverse-effect level (NOAEL) for atorvastatin calcium alone could not be identified under the conditions of this study. The no-observed-adverse-effect level (NOAEL) for atorvastatin calcium (with two impurities) was considered to be 40 mg/kg/day for females and could not be identified for males. Taken together, the findings demonstrated that following repeated oral administration to rats, the presence of the two impurities had no differential or novel toxicity when compared to the toxicity profile of atorvastatin alone.

In summary: In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurities to rats. The impurities were (b) (4) (b) (4) (at concentration of (b) (4) %) and (b) (4) (at concentration of (b) (4) %, both relative to atorvastatin calcium drug product). The TK parameters of the drug (such as Cmax and AUC values) were not measured in this study. The drug had no effects on clinical signs, BWs and food consumption with and without the impurities. Hematological parameters, such as hemoglobin and hematocrit were increased at all doses of the drug (with impurities) and at a HD without the impurities. In clinical chemistry parameters, similar effects were observed on liver enzymes, etc. with or without impurities (see the Table in the results section), since the RLD was not used, it is hard to know if these toxicities were unique to the current drug product. The histopathological changes in the liver were also in general similar in the presence or absence of impurities in the drug product. No NOAEL could be established in this study as even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one. They also did not determine the exposures of the drug with and without impurities.

Genetic toxicology studies

Following gene-toxicity studies have been conducted with the (b) (4) (at concentration of (b) (4) %) and (b) (4) (at concentration of (b) (4) %, both relative to atorvastatin calcium drug product) to qualify these impurities.

1) AMES test was conducted with atorvastatin calcium with and without impurities. As seen below, atorvastatin calcium was negative in the AMES test at doses up to 5000 ug/plate in the presence and absence of impurities (report # TOXICITY 037-001).

The study was conducted at (b) (4) at (b) (4) on 8/18/2009.

Methods: these are described below:

[redacted] Code Number	Test Article / Impurity ID	Batch No.	Purity (per protocol)	Test Article Description	Storage Conditions
AC27KV	Atorvastatin Calcium	AC0160708	[redacted]%	White powder	-15 to -40°C, stored in the dark with desiccant
AC27KW	[redacted] Impurity of Atorvastatin	ADL/941(149)/1008	[redacted]%	[redacted]	
AC27KX	[redacted] Impurity of Atorvastatin	ATC/Imp/918/118	[redacted]%		

The test articles, Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted]% [redacted] and [redacted]% [redacted] Impurities of Atorvastatin (referred to as Atorvastatin Calcium with impurities), were tested in the Bacterial Reverse Mutation Assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A in the presence and absence of Aroclor-induced rat liver S9. The assay was performed in two phases, using the plate incorporation method. The first phase, the initial toxicity-mutation assay, was used to establish the dose-range for the confirmatory mutagenicity assay and to provide a preliminary mutagenicity evaluation. The second phase, the confirmatory mutagenicity assay, was used to evaluate and confirm the mutagenic potential of the test article.

[redacted] was selected as the solvent of choice based on the request of the Sponsor, solubility of Atorvastatin Calcium and [redacted] After sonication at 32°C for 20 minutes in the solubility test, Atorvastatin Calcium formed a soluble and clear solution at approximately 500 mg/mL, the maximum concentration tested.

Results

Initial Toxicity-Mutation Assay

The results of the initial toxicity-mutation assay with Atorvastatin Calcium with impurities are presented in Tables 5 and 6. These data were generated in Experiment B1. In the initial toxicity-mutation assay, the maximum dose tested was 5000 µg per plate; this dose was achieved using a concentration of 50 mg/mL and a 100 µL plating aliquot. The dose levels tested were 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate. [redacted] was observed at 5000 µg per plate. Toxicity was observed at 5000 µg per plate with tester strain TA100 only. Based on the findings of the initial toxicity-mutation assay, the maximum dose plated in the confirmatory mutagenicity assay was 5000 µg per plate.

In Experiment B1 (Initial Toxicity-Mutation Assay), no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.

Confirmatory Mutagenicity Assay

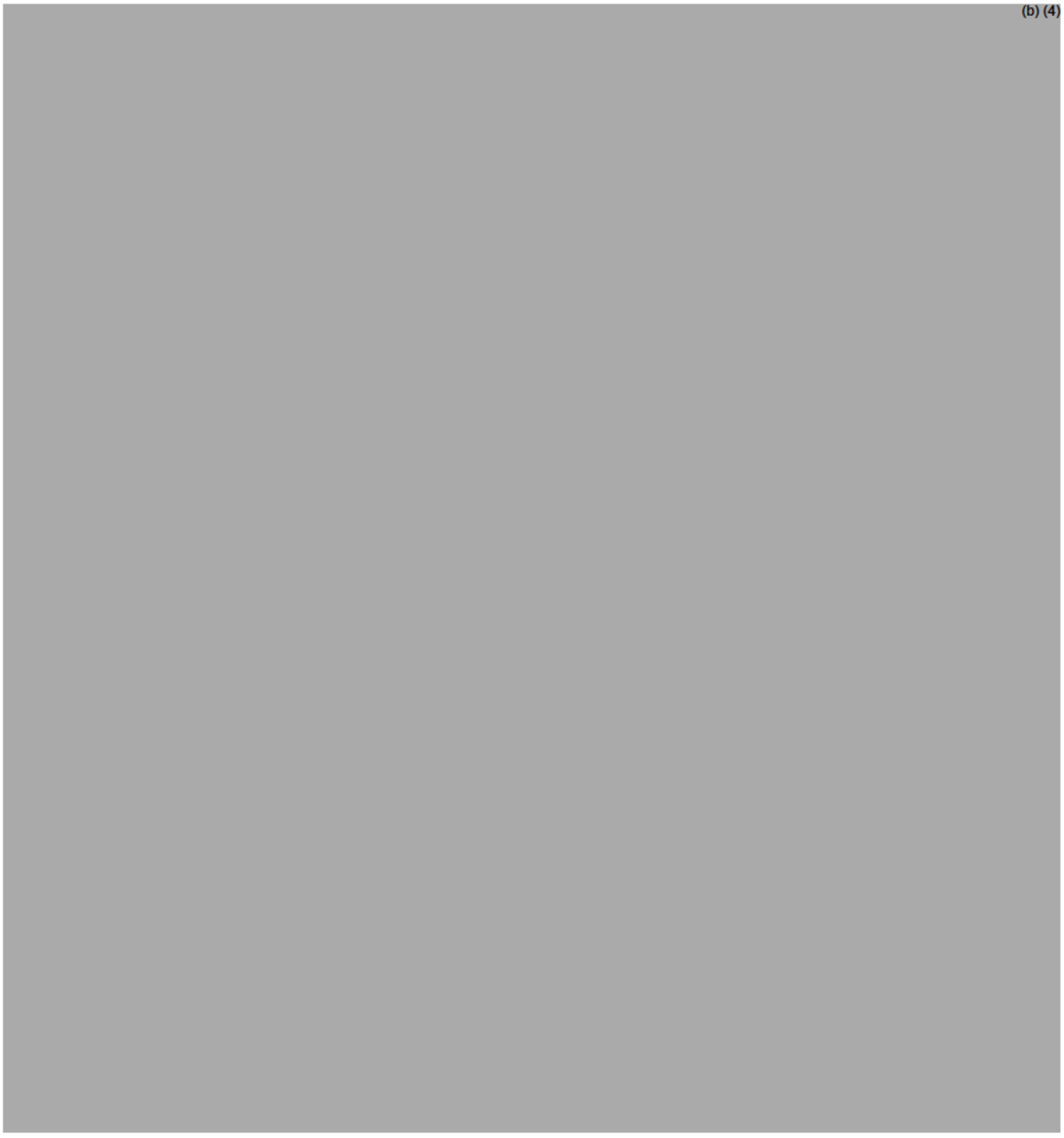
The results of the confirmatory mutagenicity assay with Atorvastatin Calcium with impurities are presented in Tables 7 and 8. These data were generated in Experiment B2. The dose levels

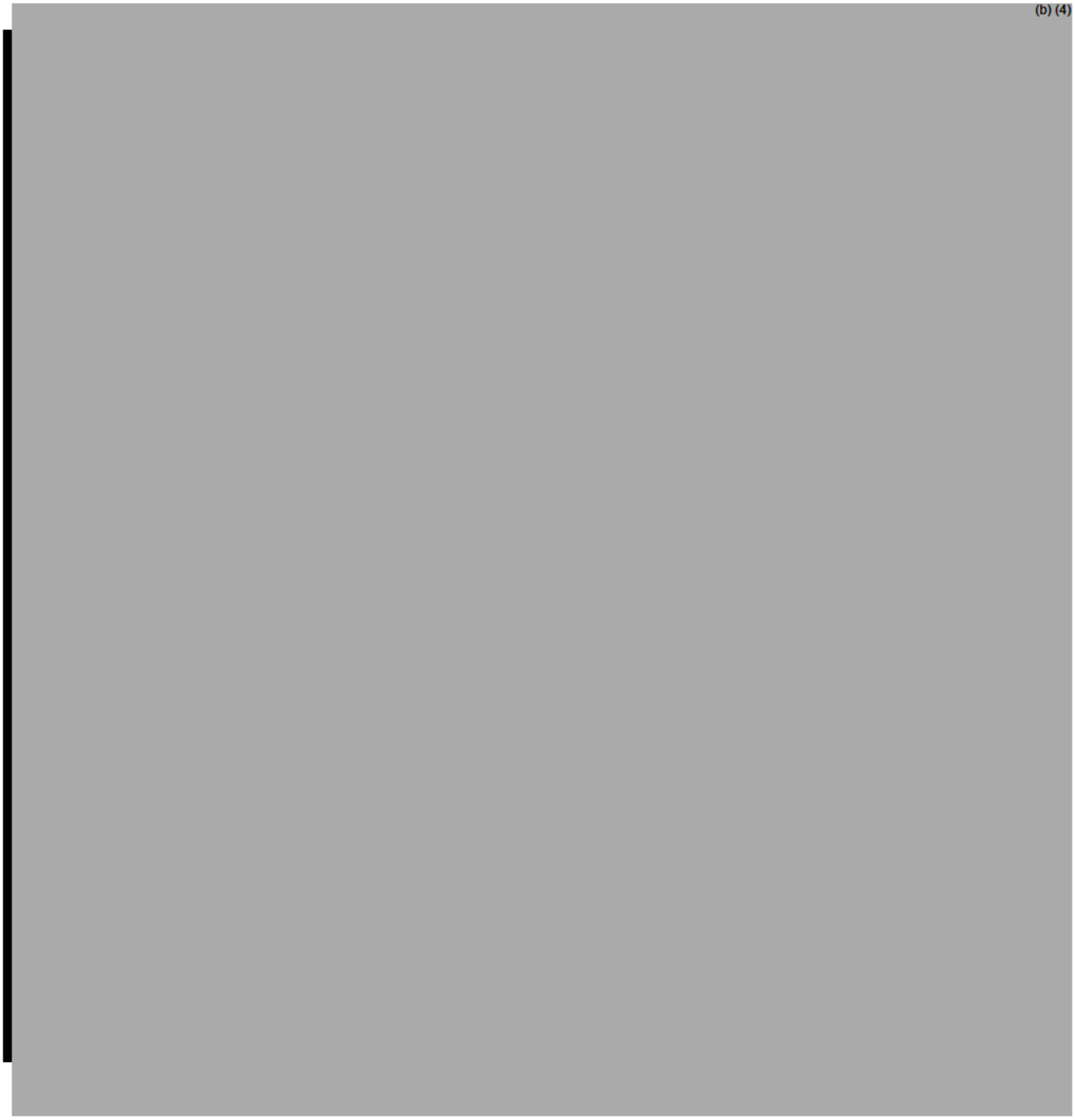
tested were 50, 150, 500, 1500 and 5000 µg per plate. [redacted] was observed at 5000 µg per plate with several test conditions. Toxicity was observed at 5000 µg per plate with tester strains TA98 and TA100 only.

In Experiment B2 (Confirmatory Mutagenicity Assay), no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.

Drug with impurities: Without S-9 activation

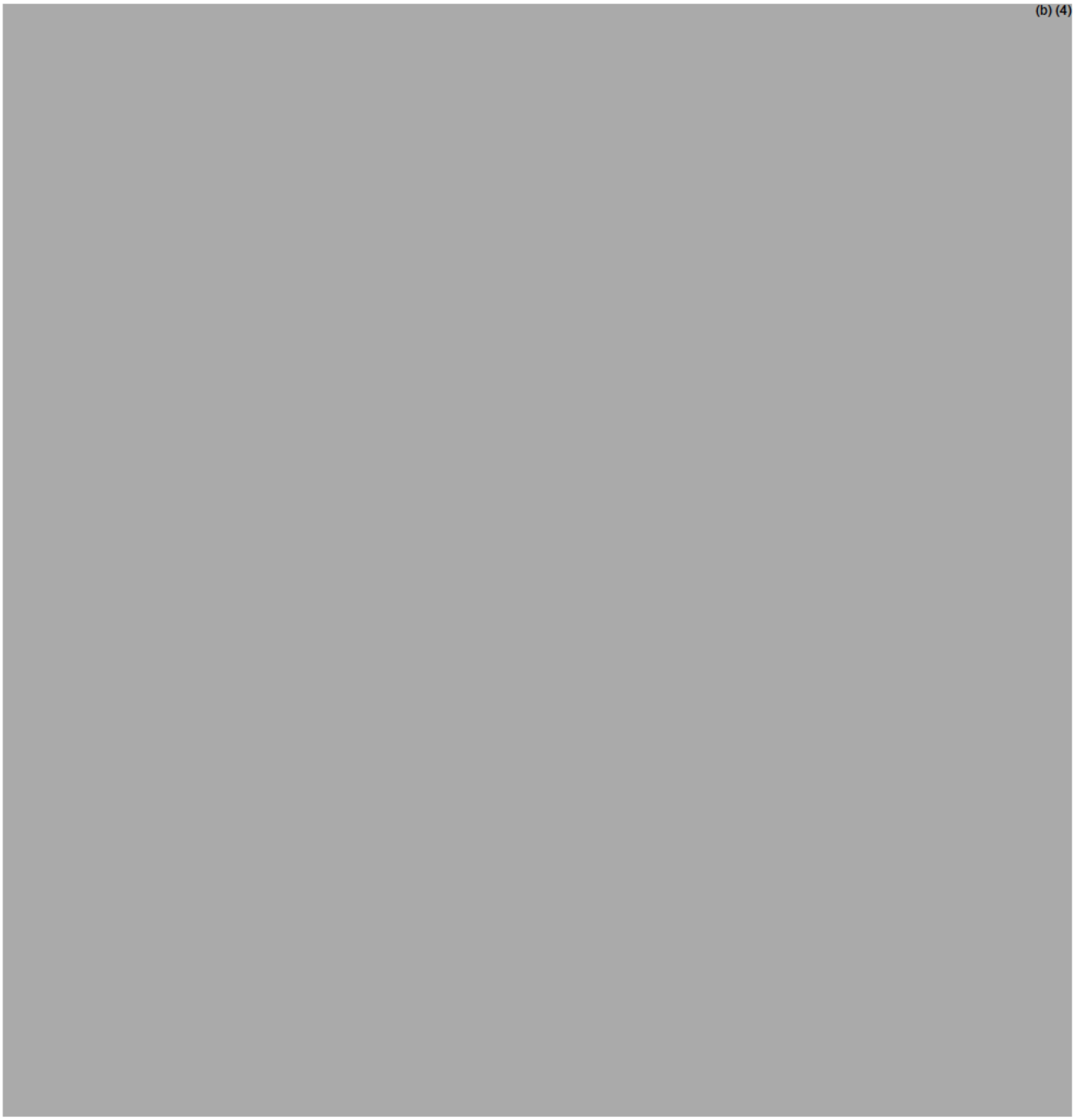
(b) (4)

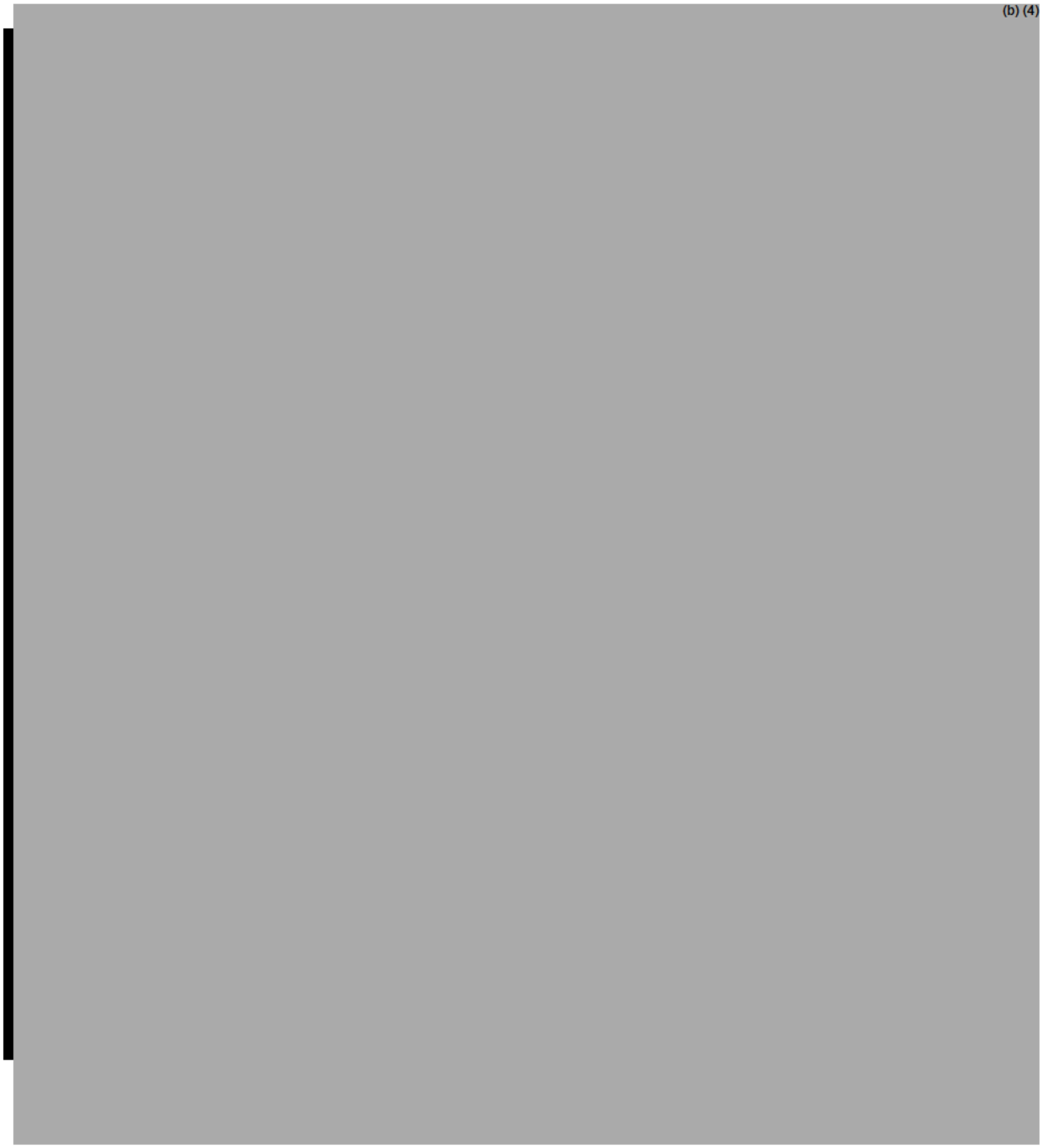



(b) (4)

Drug with impurities: With S-9 activation




(b) (4)


(b) (4)



Similar observations were made in the confirmatory assay.

Sponsor's conclusions are provided below:

All criteria for a valid study were met as described in the protocol. The results of the Bacterial Reverse Mutation Assay indicate that, under the conditions of this study, neither **Atorvastatin Calcium** nor **Atorvastatin Calcium spiked with** (b) (4)% (b) (4) **and** (b) (4)% (b) (4) (b) (4) **Impurities of Atorvastatin** did not cause a positive mutagenic response with any of the tester strains in either the presence or absence of Aroclor-induced rat liver S9.

2. In vitro chromosomal aberration test in Peripheral blood lymphocytes:. Atorvastatin calcium spiked with impurities (with (b) (4)% (b) (4) and (b) (4)% (b) (4)) was tested in an 'in vitro mammalian chromosome aberration' test. The drug was negative in the above assay with and without impurities (study # TOX 037-002). This assay was conducted a (b) (4) in (b) (4)

Methods: These are described below

The test articles, Atorvastatin Calcium (AC27KV) and Atorvastatin Calcium spiked with [redacted] were tested in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes (HPBL) in both the absence and presence of an Aroclor-induced S9 activation system. A preliminary toxicity test was performed to establish the dose range for testing in the cytogenetic test. The chromosome aberration assays were used to evaluate the clastogenic potential of the test articles.

***In Vitro* Mammalian Chromosome Aberration Test with Atorvastatin Calcium (AC27KV)**

In the preliminary toxicity assay using Atorvastatin Calcium, the maximum dose tested was 5000 µg/mL. Human peripheral blood lymphocytes were treated in the absence and presence of an Aroclor-induced S9 activation system for 4 hours, and continuously for 20 hours in the absence of S9 activation. The dosing solutions were adjusted for the purity of Atorvastatin Calcium using a correction factor of [redacted] Atorvastatin Calcium was soluble in [redacted] at all concentrations tested. Visible [redacted] was observed in treatment medium at dose levels ≥ 1500 µg/mL and dose levels ≤ 500 µg/mL were soluble in treatment medium at the beginning and conclusion of the treatment period. At the conclusion of the treatment period, hemolysis was observed at dose levels ≥ 1500 µg/mL in the non-activated and S9-activated 4-hour exposure groups and at dose levels ≥ 500 µg/mL in the non-activated 20-hour exposure group.

Selection of dose levels for the chromosome aberration assay was based on a reduction in the mitotic index relative to the solvent control. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was observed at dose levels ≥ 500 µg/mL in all three treatment groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 10 to 450 µg/mL for all three treatment groups.

In the chromosome aberration assay using Atorvastatin Calcium, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. Atorvastatin Calcium was soluble in [redacted] and in the treatment medium at all concentrations tested at the beginning and conclusion of the treatment period.

Selection of doses for microscopic analysis was based on mitotic inhibition (the lowest dose with at least 50% reduction in mitotic index, relative to the solvent control) in all harvests. The dose levels selected for analysis were 300 µg/mL in the non-activated 4-hour exposure group, 250 µg/mL in the S9-activated 4-hour exposure group and 150 µg/mL in the non-activated 20-hour exposure group.

The percentage of cells with structural or numerical aberrations in the Atorvastatin Calcium-treated groups was not increased relative to solvent control at any dose level ($p>0.05$, Fisher's Exact test).

The results of the assay using Atorvastatin Calcium are summarized in the following table:

Treatment Time (hours)	Recovery Time (hours)	Harvest Time (hours)	S9	Mitotic Index Reduction[1] at dose scored (µg/mL)	LED[2] for Structural Aberrations (µg/mL)	LED[2] for Numerical Aberrations (µg/mL)
4	16	20	-			
20	0	20	-			
4	16	20	+			

[1] relative to the solvent control at high dose evaluated for chromosome aberrations
[2] LED = lowest effective dose level

***In Vitro* Mammalian Chromosome Aberration Test with Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin (b) (4)**

One of the impurities provided by the Sponsor for use in this study was originally named (b) (4) impurity of Atorvastatin with a potency of (b) (4)%, as indicated in the protocol and Technical Data Sheet provided with the original sample. The original potency of the impurity sample ((b) (4)%) was used to determine the correction factor for adjustment of the dosing formulation samples. Subsequently, the Sponsor provided a second Technical Data Sheet with an updated impurity name and potency ((b) (4)%). The updated name for the impurity is (b) (4) impurity of Atorvastatin and will be used throughout the report. The discrepancy between the potencies listed on the Technical Data Sheets is due to the instability of the compound. Since the potency of the impurity decreased by (b) (4)% and the results of the formulation analysis from the confirmatory assay were 100% of target for this impurity, the actual concentration of the (b) (4) impurity was still within (b) (4)% of target, even taking into account the change in potency. Therefore, the Study Director has concluded that the discrepancy between the potency values did not adversely impact the integrity of the data or the validity of the study conclusion.

In the preliminary toxicity assay using Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin, the maximum dose tested was 5000 µg/mL. Human peripheral blood lymphocytes were treated in the absence and presence of an Aroclor-induced S9 activation system for 4 hours, and continuously for 20 hours in the absence of S9 activation. The dosing solutions were adjusted for the purity of Atorvastatin Calcium using a correction factor of (b) (4) for the purity of (b) (4) using a correction factor of (b) (4) and for the purity of (b) (4) using a correction factor of (b) (4) The amount of each spiking agent weighed was also adjusted to compensate for the presence of the (b) (4) impurity in the (b) (4) impurity, as determined during the analytical validation. Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin was soluble in (b) (4) at all concentrations tested. Visible (b) (4) was observed in treatment medium at dose levels ≥ 500 µg/mL and dose levels ≤ 150 µg/mL were soluble in treatment medium at the beginning and conclusion of the

treatment period. At the conclusion of the treatment period, hemolysis was observed at dose levels ≥ 500 µg/mL in all three treatment groups.

Selection of dose levels for the chromosome aberration assay was based on a reduction in the mitotic index relative to the solvent control. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was observed at dose levels ≥ 150 µg/mL in all three treatment groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 5 to 125 µg/mL for the non-activated 4 and 20-hour treatment groups, and from 5 to 150 µg/mL for the S9-activated 4-hour exposure group.

Results

In the chromosome aberration assay using Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin was soluble in [redacted] and in the treatment medium at all concentrations tested at the beginning and conclusion of the treatment period.

Selection of doses for microscopic analysis was based on mitotic inhibition (the lowest dose with at least 50% reduction in mitotic index, relative to the solvent control) in all harvests. The dose levels selected for analysis were 25, 75 and 125 µg/mL in the non-activated 4-hour exposure group, 10, 50 and 150 µg/mL in the S9-activated 4-hour exposure group and 25, 50 and 100 µg/mL in the non-activated 20-hour exposure group.

The percentage of cells with structural or numerical aberrations in the Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin-treated groups was not increased relative to solvent control at any dose level ($p>0.05$, Fisher's Exact test).

The results of the assay using Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin are summarized in the following table:

Treatment Time (hours)	Recovery Time (hours)	Harvest Time (hours)	S9	Mitotic Index Reduction[1] at dose scored (µg/mL)	LED[2] for Structural Aberrations (µg/mL)	LED[2] for Numerical Aberrations (µg/mL)
4	16	20	-	[redacted]		
20	0	20	-			
4	16	20	+			

[1] relative to the solvent control at high dose evaluated for chromosome aberrations
[2] LED = lowest effective dose level

Based on the findings of this study, Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin were concluded to be negative for the induction of structural and numerical chromosome aberrations in both non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

Table 7. Atorvastatin calcium was tested in the absence of impurities in the chromosome aberration test.

(b) (4)

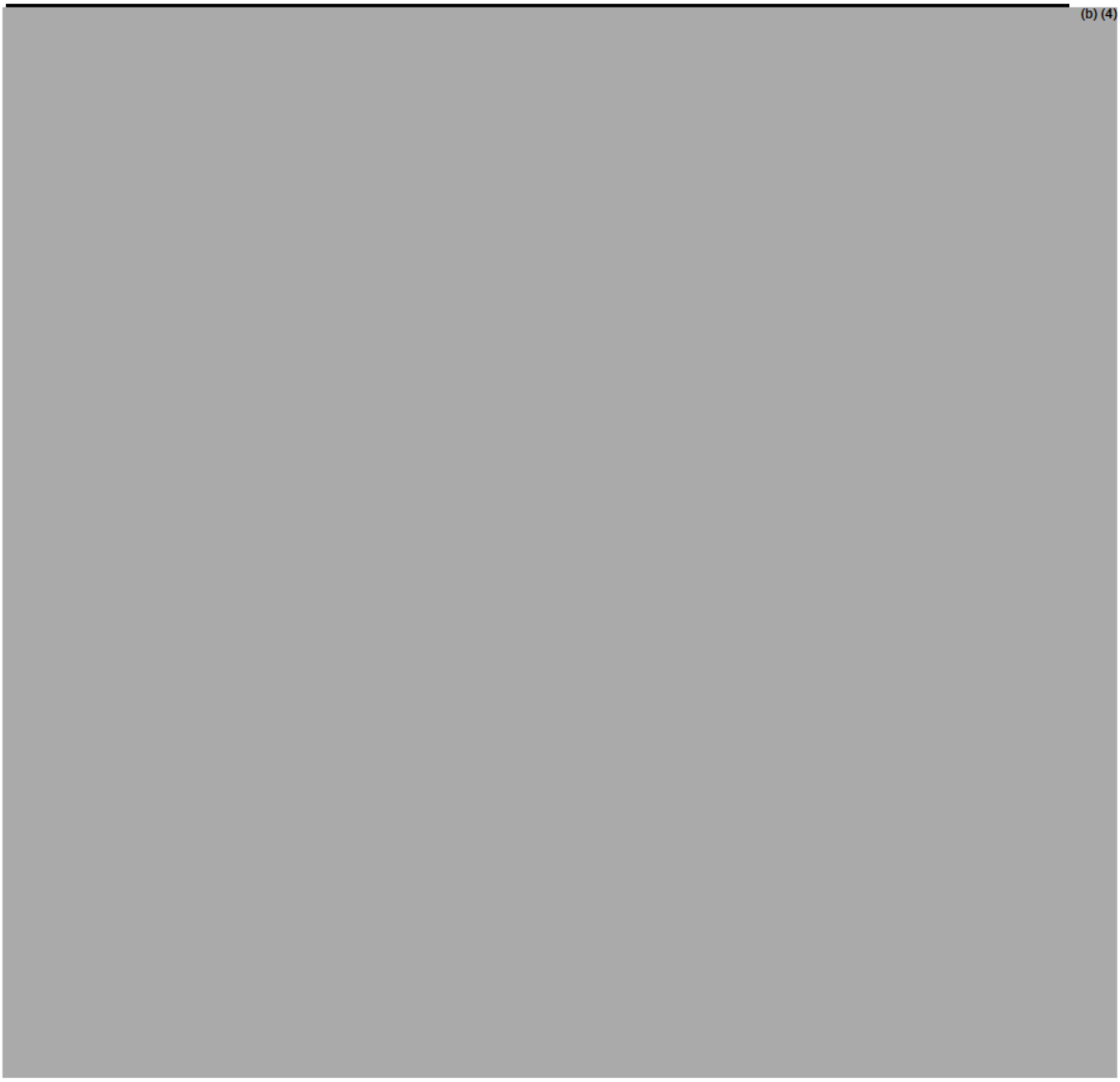
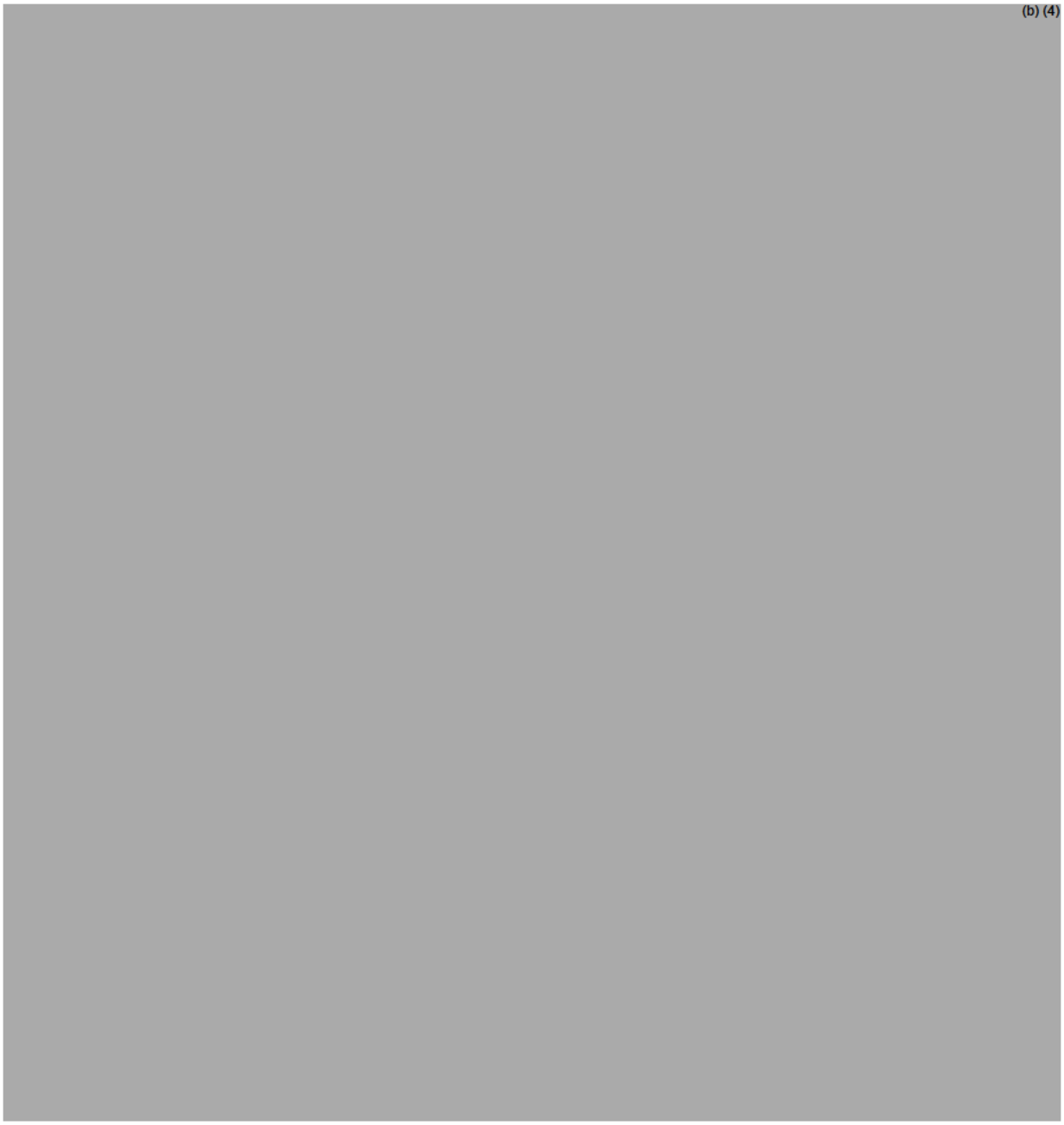


Table 14. Atorvastatin calcium was tested in the presence of impurities in the chromosome aberration test.



Conclusions:

Under the conditions of the assay described in this report, Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin were concluded to be negative for the induction of structural and numerical chromosome aberrations in both non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

In summary, Sponsor by providing a 2-week toxicity study in rats with the atorvastatin with impurities (spiked with [redacted] and [redacted] in the atorvastatin calcium drug product) vs without impurities, as well as by conducting two geno-toxicity studies (Ames and chromosome aberration assay) has qualified the impurities in atorvastatin calcium, and these are acceptable. Thus from the pharmacology/toxicity point of view, the proposed levels of [redacted] and [redacted] impurities in the atorvastatin calcium drug product are qualified based on toxicity studies.

Following toxicity studies have been conducted to support the [redacted] impurity in the atorvastatin calcium drug product

A 2-Week Oral Toxicity Study of atorvastatin calcium containing [redacted]% of [redacted] impurity in Rats (Study No. G7008)

The purpose of this repeated dose 14 day toxicity study in Wistar rats was to assess the toxic potential of test item (Atorvastatin Calcium) without impurities and with impurities [redacted] Impurity) when administered daily by oral gavage. This study is intended to provide information on major toxic effects on target organs and an estimate of a "No Observed Effect Level (NOEL)"

Study no: G7008
Volume #, and page #: eCTD submission dated 8/4/10

Conducting laboratory and location [redacted]
Date of study initiation: 12/23/2009
GLP compliance: Yes
QA report: yes (X) no ( )

Drug lot #, and % purity:
Atorvastatin (without impurities) batch # ACO160708, manufactured by Matrix Laboratories in India on 11/07; purity was [redacted]%

Atorvastatin (with impurities) batch # ATC-ARL (A-489) 51B, manufactured by Matrix Laboratories Ltd. on 11/09; purity was [redacted]%. Following COA was provided on the drug with impurity, the percentage of impurity present in the drug was [redacted]% as stated in Table 1 below.

APPENDIX 11 contd. Certificate of Analysis / Technical Data Sheet

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

TECHNICAL DATA SHEET

(b) (4)

[redacted]

Formulation/vehicle:. 1% sodium carboxy methyl cellulose (NaCMC-low viscosity). Dosing volume was 10 ml/kg.

Methods (unique aspects):

Male and female Wistar rats were assigned to five groups and each group comprised 10 rats /sex. Each treatment group was administered with respective dose formulation (40 and 80 mg / kg Bwt) at the dose volume of 10 mL/kg Bwt. Animals in the vehicle control group were administered with the vehicle [1.0 % sodium salt of carboxy methylcellulose(low viscosity) in Milli Q water] at the dose volume of 10 mL/kg Bwt. The test items were prepared as two separate dose suspensions, without impurities (Atorvastatin Calcium) and with impurity [redacted] Impurity).

Two dose levels of 40 (G2a) and 80 (G3a) mg/kg of test item without impurity (Atorvastatin Calcium) have been selected. In additions, the two dose levels of 40 (G2b) and 80 (G3b) mg/kg of test item with impurity [redacted] Impurity) has been selected.

Required quantities of each of the test item were calculated as below:

a) API calculation (for G2a and G3a groups):

$$\text{Amount of Atorvastatin calcium (mg)} = \frac{\text{Required concentration (mg/mL)} \times \text{Total volume (mL)} \times 100}{\text{\% Purity of Atorvastatin Calcium}}$$

b) API calculation (for G2b and G3b groups):

$$\text{Amount of Atorvastatin calcium (mg)} = \frac{\text{Required concentration (mg/mL)} \times \text{Total volume (mL)} \times 99.00}{\text{\% Purity of Atorvastatin Calcium}}$$

c) Impurity caluculation (for G2b and G3b groups):

$$\text{Amount of [redacted] Impurity (mg)} = \frac{\text{Required concentration (mg/mL)} \times \text{Total volume (mL)} \times 1.00}{\text{\% Purity of [redacted] Impurity}}$$

Doses in administered units: 0, 40, 80 mg/kg/day with and without impurities were administered to rats (8 weeks of age, BW males 243-248 g /females 170-171 g) by gavage orally for 14 consecutive days.

Table 1.

Groups	G1	G2a	G3a	G2b	G3b
Doses (mg/kg Bwt / day)	0	40	80	40	80
Total test item required (mg)-API	0	401.7	803.2	397.7	795.3
Total impurity added@ (mg)	0	-	-	[redacted]	
Premix volume(mL)	-	20	20	20	20
Total volume made up with vehicle (mL)	100	100	100	100	100
Stirring Time(Min)	15	15	15	15	15
Concentration(mg/mL)	0	4	8	4	8

@[redacted]% of total API

Experimental design and parameters measured are shown in the Table below:

TABLE 1. Details of Experimental Design, Treatment regime, Clinical Pathology Investigations, Pathology and Sacrifice Schedule

Group No.	Dose (mg/kg Bwt/day)	No. of rats per group		Treatment Period-oral gavage (Days)		Clinical Pathology investigations			Pathology		Sacrifice schedule	
		M	F	M	F	Haematology	Clinical chemistry	Urinalysis	Gross pathology	Histopathology	M	F
G1	0	10	10	14	14	+	+	+	+	+	Day 15	Day 15
G2a	40	10	10	14	14	+	+	+	+	a	Day 15	Day 15
G3a	80	10	10	14	14	+	+	+	+	+	Day 15	Day 15
G2b	40	10	10	14	14	+	+	+	+	a	Day 15	Day 15
G3b	80	10	10	14	14	+	+	+	+	+	Day 15	Day 15

+: Yes, a: Liver only

Each animal in the experiment was observed for clinical signs, mortality, ocular abnormalities, neurological effects and changes in the body weights and food intake. The laboratory investigations such as haematology, clinical chemistry and urinanalysis were performed at the end of the treatment period.

Gross pathology: At sacrifice.

Organs weighed: Following organs were weighed as shown in the Table below.

Histopathology: This was performed at sacrifice in control and high dosed animals in organs listed in histopathology Table below.

Histopathological examination was carried out on the preserved organs of vehicle control (G1), high dose without impurities (G3a) and high dose with impurity (G3b) group rats. In addition, all gross lesions from all the animals were examined microscopically. As Liver was showing test item related histopathological changes in high dose groups (G3a and G3b), it was examined in respective the low dose group rats (G2a and G2b).

b. Tissue collection

The following organs and tissues (indicated as X) were collected from all rats and preserved in 10% Neutral Buffered Formalin (NBF):

Sl. No.	Tissue	Organ Weights	Collection Preservation	Microscopic Examination
1	Adrenal glands	X	X	X
2	Aorta		X	X
3	Bone marrow smear		X	X

Sl. No.	Tissue	Organ Weights	Collection Preservation	Microscopic Examination
4	Brain including medulla/pons, cerebellum and cerebrum	X	X	X
5	Cecum		X	X
6	Colon		X	X
7	Duodenum		X	X
8	Epididymides	X	X	X
9	Esophagus		X	X
10	Eyes with optic nerve*		X	X
11	Mammary gland		X	X
12	Femur bone with joint**		X	X
13	Heart	X	X	X
14	Ileum with Peyer's patches		X	X
15	Jejunum		X	X
16	Kidneys	X	X	X
17	Lacrimal glands		X	X
18	Larynx		X	X
19	Liver	X	X	X
20	Lungs (with bronchi and bronchioles) #	X	X	X
21	Mesenteric lymph nodes		X	X
22	Mandibular lymph nodes		X	X
23	Ovaries	X	X	X
24	Oviducts		X	X
25	Pancreas		X	X
26	Pituitary		X	X
27	Prostate$	X	X	X
28	Rectum		X	X
29	Salivary glands		X	X
30	Sciatic nerves		X	X
31	Seminal vesicles and coagulating glands $	X	X	X
32	Skin		X	X
33	Skeletal muscle		X	X
34	Spinal cord at 3 levels - cervical, mid thoracic and lumbar.		X	X
35	Spleen	X	X	X
36	Sternum with marrow**		X	X
37	Stomach		X	X
38	Testes@	X	X	X
39	Thymus	X	X	X
40	Thyroid with Parathyroids***	X	X	X
41	Tongue		X	X
42	Trachea		X	X
43	Urinary bladder		X	X
44	Ureters		X	X
45	Uterus with Cervix	X	X	X
46	Vagina		X	X

#: Lungs inflated with 10%NBF before fixation
*: Collected in Davidson's fluid.
@: Collected in modified Davidson's fluid.
X: Activity carried out.
**: Decalcified prior to sectioning

Results:

Mortality: No treatment related mortality was observed.

Clinical signs: No drug related effects were observed.

Functional observation Battery (FOB): Significant findings were noted with atorvastatin vs the control in some FOB tests as seen below, but no significant drug related effects were observed between atorvastatin with or without impurities. The RLD was not used in this study to know if these effects were unique to this drug product.

Neuromuscular observations:

Grip Strength: At 80 mg / kg Bwt / day, hindlimbs grip strength was significantly higher in G3a males and G3b males whereas in G3b females, fore limbs grip strength were significantly higher and were considered to be incidental as the observed changes are marginal (3 to 8%).

Motor Activity: At 80 mg / kg Bwt / day, significantly higher horizontal and total activity scores were seen in G3a males and horizontal, vertical and total activity scores in G3b males whereas in females, significantly higher vertical activity scores were observed in G3a group animals.

At 80 mg / kg Bwt / day, significantly higher rectal body temperature was observed in G3b females as compared to the vehicle control group. The change seen in rectal body temperatures was considered to be incidental as the observed change is marginal(less than 1%).

TABLE 4 contd. Summary of Functional Observation Battery

Group No. Dose (mg/kg)		Neuromuscular observations						Refer Appendices 3 & 4 Physiological Observation
		Grip strength (kg)			Motor activity score			
		Forelimbs Average	Hindlimbs Average	Hindlimb footsplay (cms) Average	Horizontal score	Vertical score	Total score	Body temperature (°F)
Males								
G1	Mean	0.989	0.495	5.36	776.20	606.50	1382.70	98.59
0	SD	0.02	0.03	1.22	344.23	248.21	586.18	0.79
	N	10	10	10	10	10	10	10
			+		+		+	
G3a	Mean	1.002	0.527	5.19	1074.00	756.60	1830.60	98.73
80	SD	0.03	0.02	0.72	160.43	94.29	238.16	0.38
	N	10	10	10	10	10	10	10
Females								
G1	Mean	0.826	0.439	5.41	1295.10	762.00	2057.10	100.01
0	SD	0.02	0.03	0.94	159.05	129.54	276.99	0.46
	N	10	10	10	10	10	10	10
						+		
G3a	Mean	0.844	0.442	5.06	1246.00	905.00	2151.00	99.92
80	SD	0.02	0.03	0.82	94.04	163.10	179.20	0.40
	N	10	10	10	10	10	10	10

N: No. of observations
+ : Significantly higher (+) than the vehicle control group

TABLE 4 contd. Summary of Functional Observation Battery

Refer Appendices 3 & 4

Group No. Dose (mg/kg)		Neuromuscular observations						Physiological Observation
		Grip strength (kg)			Motor activity score			
		Forelimbs Average	Hindlimbs Average	Hindlimb footsplay (cms) Average	Horizontal score	Vertical score	Total score	Body temperature (°F)
Males								
G1	Mean	0.989	0.495	5.36	776.20	606.50	1382.70	98.59
0	SD	0.02	0.03	1.22	344.23	248.21	586.18	0.79
	N	10	10	10	10	10	10	10
			+		+	+	+	
G3b	Mean	0.994	0.535	5.31	1079.30	804.20	1883.50	98.41
80	SD	0.03	0.02	0.66	165.91	134.21	287.47	0.60
	N	10	10	10	10	10	10	10
Females								
G1	Mean	0.826	0.439	5.41	1295.10	762.00	2057.10	100.01
0	SD	0.02	0.03	0.94	159.05	129.54	276.99	0.46
	N	10	10	10	10	10	10	10
		+						+
G3b	Mean	0.858	0.462	5.35	1218.90	767.00	1985.90	100.58
80	SD	0.03	0.03	0.74	87.00	156.30	216.11	0.48
	N	10	10	10	10	10	10	10

N: No. of observations
+ : Significantly higher (+) than the vehicle control group

Body weights: In males, body weight gains were higher with the impurity at a HD (15.3, 18.9, 19.4* at 0, 40, 80 mg/kg/day, *p<0.05), while these were not higher without impurities (15.3, 18.9, 17.6 respectively).

Table 7 shows the body weight gains in males without impurities.

TABLE 7. Summary of Cumulative Net Body Weight Gains (g) – Males

Refer Appendix: 7

G1 vs G2a & G3a

Body Weight Gain (g)

				Days					
		Base Weight Day						Abs Gain	% Gain
			From:	1	4	8	11	1	1
Group	Sex	1	To:	4*	8*	11	14	14	14
G1	M	248.208	Mean	5.765	12.590	12.663	6.848	37.866	15.26
		14.056	S.D.	3.656	3.859	3.449	3.661	6.056	2.34
		10	N	10	10	10	10	10	10
G2a	M	245.241	Mean	9.072	18.508*	9.542	9.074	46.196	18.85
		15.991	S.D.	2.455	3.973	4.103	2.248	5.693	2.21
		10	N	10	10	10	10	10	10
G3a	M	243.356	Mean	10.918*	13.147	10.757	8.088	42.910	17.61
		16.239	S.D.	4.409	4.639	3.362	3.365	7.254	2.60
		10	N	10	10	10	10	10	10

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level;

Abs Gain = absolute bodyweight gain between base period and end of the analysis period
% Gain = percentage bodyweight gain between base period and end of the analysis period

Group G1 - G1 0 Group G2a - G2a 40 Group G3a - G3a 80

G1 vs G2b & G3b

Table below shows the body weight gains in males with impurities.

Body Weight Gain (g)

Group	Sex	Base Weight Day 1		Days From: 1	4	8	11	Abs Gain 1	% Gain 1
				To: 4*	8*	11	14	14	14
G1	M	248.208	Mean	5.765	12.590	12.663	6.848	37.866	15.26
		14.056	S.D.	3.656	3.859	3.449	3.661	6.056	2.34
		10	N	10	10	10	10	10	10
G2b	M	245.702	Mean	11.040*	15.557	9.916	9.822	46.335	18.85
		16.526	S.D.	3.461	7.920	3.480	4.252	11.047	4.32
		10	N	10	10	10	10	10	10
G3b	M	243.957	Mean	10.367*	16.709	10.552	9.528	47.156*	19.41*
		15.846	S.D.	2.150	3.477	5.741	3.209	8.125	3.63
		10	N	10	10	10	10	10	10

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level;

Abs Gain = absolute bodyweight gain between base period and end of the analysis period
% Gain = percentage bodyweight gain between base period and end of the analysis period

Group G1 - G1 0 Group G2b - G2b 40 Group G3b - G3b 80

Food consumption: Food consumption (FC) was not significantly altered

Ophthalmoscopy: No drug related effects were observed.

Hematology: Some subtle differences were observed between two products, for example all doses of the drug with impurities decreased prothrombin (PT) time in rats (16.6, 15.1*, 15.4* seconds at 0, 40, 80 mg/kg/day respectively) vs this was noted only at a HD without impurities (16.6, 16.4, 14.5* sec respectively).

Sponsor states following changes in the hematological parameters. Basically they state that similar findings were observed with both products.

Increase in Mean Corpuscular Haemoglobin Concentration (5%) in high dose (G3b) males was considered insignificant as the percent change was minimal and was within the physiological variations.

Minimal increase in haematocrit values (7%) and decrease in Mean Corpuscular Haemoglobin Concentration (3%) in high dose (G3a) females were also considered insignificant as the percent changes were within physiological variation.

- Decrease in Prothrombin Time in high dose (G3a:-12%) females
- Decrease in Prothrombin Time in high and low dose (G2b:-9 % G3b:-17%) females

TABLE 1. Summary of Haematological Values at Termination – Males

Refer Appendix 1

Group No. Dose (mg/kg)		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV f/l	MCH pg	MCHC g/l	Plat G/l	P.T. s	APTT s	Neut %	Lymp %	Mono %	Eosi %	Baso %	Retic %
G1	Mean	8.40	8.59	158.20	0.495	57.72	18.40	318.40	1200.30	16.78	11.73	19.61	74.54	2.67	1.78	0.21	3.29
0	SD	2.48	0.43	14.32	0.017	1.76	1.42	20.95	191.20	1.89	2.47	14.02	17.43	0.59	3.46	0.09	0.41
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
G2a	Mean	7.47	8.58	159.50	0.492	57.48	18.62	324.30	1271.30	17.08	11.93	23.48	69.34	3.56	2.11	0.24	3.46
40	SD	1.48	0.47	5.66	0.025	2.99	0.77	11.46	75.90	0.69	2.37	6.08	7.64	1.08	2.12	0.12	0.46
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
G3a	Mean	9.53	8.88	163.70	0.504	56.73	18.43	325.00	1325.90	15.87	10.88	21.54	71.58	3.41	1.98	0.28	3.45
80	SD	1.85	0.42	8.90	0.031	1.34	0.29	8.96	98.73	1.30	2.47	7.07	8.20	1.21	2.11	0.08	0.48
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
G2b	Mean	9.54	8.32	157.70	0.474	57.00	18.96	332.60	1277.50	15.44	11.32	22.00	72.77	2.97	1.11	0.21	3.46
40	SD	2.21	0.32	6.67	0.019	1.72	0.79	8.49	152.23	1.18	1.75	4.26	4.48	0.49	1.03	0.09	0.42
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
								* (+5)									
G3b	Mean	8.58	8.80	164.70	0.493	56.06	18.73	333.90	1385.40	16.73	11.31	19.14	75.39	3.16	1.11	0.23	3.41
80	SD	2.21	0.47	11.51	0.034	1.48	0.66	8.60	155.82	1.03	1.52	4.54	4.78	1.15	0.43	0.05	0.69
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

*: Significantly higher than the vehicle control group
Values in parenthesis indicate % change

TABLE 2. Summary of Haematological Values at Termination – Females

Refer Appendix 2

Group No. Dose (mg/kg)		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV f/l	MCH pg	MCHC g/l	Plat G/l	P.T. s	APTT s	Neut %	Lymp %	Mono %	Eosi %	Baso %	Retic %
G1	Mean	5.54	8.12	151.90	0.459	56.56	18.71	330.90	1293.20	16.62	13.56	16.44	78.67	2.80	0.97	0.17	3.43
0	SD	0.76	0.25	6.87	0.020	1.77	0.81	7.99	90.70	0.51	2.03	4.37	5.26	0.77	0.41	0.07	0.54
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
											* (-25)						
G2a	Mean	6.37	8.31	153.10	0.469	56.47	18.47	326.70	1348.30	16.43	10.14	15.34	79.58	2.25	1.57	0.21	3.80
40	SD	1.63	0.30	7.19	0.018	2.13	0.80	7.45	75.87	0.68	1.79	4.35	4.45	0.44	1.17	0.12	0.82
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
					* (+7)			* (-3)		* (-12)							
G3a	Mean	6.53	8.43	157.40	0.491	58.22	18.68	320.80	1309.90	14.55	11.23	20.69	72.12	2.45	3.67	0.22	3.49
80	SD	2.39	0.37	6.06	0.021	1.37	0.50	8.38	154.63	0.71	3.01	9.01	11.68	0.96	3.78	0.09	0.59
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
										* (-9)							
G2b	Mean	6.24	8.31	152.90	0.463	55.75	18.40	330.30	1216.80	15.14	10.37	14.46	80.75	2.55	1.09	0.21	3.65
40	SD	1.63	0.32	6.08	0.015	1.65	0.42	9.45	133.98	0.83	2.86	3.96	4.50	0.43	0.86	0.07	0.52
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
										* (-17)							
G3b	Mean	7.76	8.43	156.60	0.470	55.81	18.59	333.30	1360.30	15.43	12.26	15.88	76.70	3.48	2.48	0.23	3.86
80	SD	2.61	0.38	7.14	0.026	1.83	0.62	9.64	136.78	1.19	3.40	4.31	8.91	1.09	5.04	0.11	0.79
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

*: Significantly higher / lower than the vehicle control group
Values in parenthesis indicate % change

Clinical chemistry: ALP levels in females were higher with all doses of the drug with impurities in rats (71, 98*, 98* U/L at 0, 40, 80 mg/kg/day respectively), not so without impurities. (71, 81, 89

U/L sec respectively). LDH and serum sodium levels were similarly higher with impurities in females than without it, see below. The following changes were observed on clinical chemistry parameters.

Males

TABLE 3. Summary of Clinical Chemistry Values at Termination – Males

Refer Appendix 3

Group No. Dose (mg/kg)		Glu mmol/l	BUN mmol/l	T.Pro g/l	AST U/l	ALT U/l	ALP U/l	GGT^ U/l	T-Bil# µmol/l	Creat# µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	T.Chol mmol/l
G1	Mean	6.58	5.81	62.03	92.70	36.40	140.90	-	1.96	25.33	41.09	2.56	2.75	1.50
0	SD	1.16	0.75	2.22	21.88	7.85	33.52		0.21	2.60	1.21	0.22	0.16	0.15
	n	10	10	10	10	10	10		5	9	10	10	10	10
					* (+177)	* (+349)					* (+6)		* (-7)	* (+27)
G2a	Mean	5.69	5.97	61.97	256.80	163.60	166.80	-	2.53	24.40	43.61	2.67	2.56	1.91
40	SD	0.50	0.62	3.26	143.87	120.98	38.02		0.48	3.24	1.20	0.42	0.09	0.41
	n	10	10	10	10	10	10		9	10	10	10	10	10
			* (+21)		* (+268)	* (+375)	* (+58)				* (+7)		* (-13)	* (+29)
G3a	Mean	5.95	7.01	61.57	341.20	173.00	222.70	-	2.31	26.40	44.10	2.39	2.39	1.93
80	SD	1.54	1.14	3.04	252.11	122.90	73.52		0.51	4.53	1.81	0.16	0.14	0.47
	n	10	10	10	10	10	10		7	10	10	10	10	10
					* (+104)	* (+187)				* (-12)	* (+5)		* (-14)	
G2b	Mean	6.40	5.80	62.69	188.90	104.40	146.60	-	1.92	22.40	43.28	2.38	2.37	1.99
40	SD	0.53	0.94	2.08	142.31	97.73	31.43		-	2.46	1.39	0.21	0.17	0.22
	n	10	10	10	10	10	10		1	10	10	10	10	10
			* (+15)		* (+203)	* (+278)	* (+53)				* (+9)	* (-11)	* (-18)	
G3b	Mean	5.94	6.69	61.41	281.10	137.70	216.20	-	2.05	23.80	44.81	2.29	2.26	1.93
80	SD	0.83	0.77	2.08	127.22	66.88	43.20		0.24	1.99	1.26	0.18	0.10	0.78
	n	10	10	10	10	10	10		7	10	10	10	10	10

^: GGT: Lower Limit of Quantification (LLOQ): 3U/l and this parameter not analysed.
#: T Bil: Lower Limit of Quantification (LLOQ): 1.71µmol/l. Creat: Lower Limit of Quantification: 18µmol/l. Values below LLOQ were not considered for Statistical analysis. Values in parenthesis indicate % change.
*: Significantly higher / lower than the vehicle control group.

TABLE 3 contd. Summary of Clinical Chemistry Values at Termination – Males

Refer Appendix 3

Group No. Dose (mg/kg)		Glob g/l	A/G -	Trig mmol/l	CK U/l	LDH U/l	Na mEq/l	K mEq/l	Cl mEq/l
G1	Mean	20.94	1.97	0.50	425.50	245.10	142.03	3.84	91.33
0	SD	1.21	0.08	0.07	205.57	187.53	4.17	0.41	3.12
	n	10	10	10	10	10	10	10	10
		* (-12)	* (+23)	* (-20)			* (+3)		* (+4)
G2a	Mean	18.36	2.42	0.40	307.50	194.10	146.58	3.66	95.37
40	SD	2.77	0.36	0.04	115.54	49.60	3.09	0.67	1.80
	n	10	10	10	10	10	10	10	10
		* (-17)	* (+30)	* (-24)			* (+4)		* (+7)
G3a	Mean	17.47	2.57	0.38	356.10	235.80	147.24	3.90	97.57
80	SD	2.35	0.40	0.07	89.37	91.34	1.66	0.60	2.88
	n	10	10	10	10	10	10	10	10
			* (+14)	* (-14)	* (-37)		* (+4)		* (+6)
G2b	Mean	19.41	2.24	0.43	267.30	176.70	147.04	3.65	96.70
40	SD	1.62	0.20	0.05	73.12	39.61	1.83	0.25	2.20
	n	10	10	10	10	10	10	10	10
		* (-21)	* (+39)	* (-22)	* (-46)		* (+4)		* (+8)
G3b	Mean	16.60	2.73	0.39	228.90	189.40	147.12	3.66	98.55
80	SD	1.82	0.29	0.04	64.32	23.26	6.29	0.50	4.12
	n	10	10	10	10	10	10	10	10

+/-: Significantly higher/lower than the vehicle control group.
Values in parenthesis indicate % change.

Females

TABLE 4. Summary of Clinical Chemistry Values at Termination – Females

Refer Appendix 4

Group No. Dose (mg/kg)		Glu mmol/l	BUN mmol/l	T.Pro g/l	AST U/l	ALT U/l	ALP U/l	GGT^ U/l	T-Bil# µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	T.Chol mmol/l
G1	Mean	6.28	6.23	63.32	79.70	29.30	70.80	-	2.31	26.20	44.82	2.24	2.71	1.53
0	SD	0.45	0.82	1.70	8.04	6.06	18.15		0.43	2.30	2.22	0.28	0.09	0.24
	n	10	10	10	10	10	10		9	10	10	10	10	10
G2a	Mean	6.12	6.23	63.35	90.60	35.60	80.70	-	2.09	25.50	45.29	2.17	2.58	1.76
40	SD	0.60	1.11	2.75	14.79	14.33	18.74		0.25	2.92	1.64	0.22	0.14	0.35
	n	10	10	10	10	10	10		7	10	10	10	10	10
				* (+4)	* (+40)	* (+67)					* (+6)		* (-10)	* (+31)
G3a	Mean	5.73	6.58	65.99	111.50	48.80	89.10	-	2.17	25.50	47.38	2.25	2.43	2.01
80	SD	0.75	1.20	2.71	29.09	10.08	27.74		0.28	2.55	1.73	0.24	0.16	0.40
	n	10	10	10	10	10	10		8	10	10	10	10	10
				* (+5)	* (+18)		* (+38)				* (+6)		* (-12)	
G2b	Mean	6.34	6.79	66.32	93.70	33.80	97.70	-	2.22	28.70	47.37	2.12	2.38	1.83
40	SD	0.40	1.27	1.92	8.55	4.24	17.90		0.30	5.17	1.95	0.37	0.15	0.34
	n	10	10	10	10	10	10		5	10	10	10	10	10
				* (+7)	* (+66)	* (+152)	* (+38)				* (+8)		* (-14)	* (+40)
G3b	Mean	5.94	7.29	67.77	132.00	73.70	97.70	-	2.64	29.00	48.16	2.13	2.32	2.14
80	SD	0.93	0.87	1.29	25.95	20.52	23.13		0.41	3.06	1.64	0.17	0.12	0.52
	n	10	10	10	10	10	10		6	10	10	10	10	10

^: GGT: Lower Limit of Quantification (LLOQ): 3U/l and this parameter not analysed.
#: T Bil: Lower Limit of Quantification (LLOQ): 1.71µmol/l. Values below LLOQ were not considered for Statistical analysis.
Values in parenthesis indicate % change. *: Significantly higher / lower than the vehicle control group.

TABLE 4 contd. Summary of Clinical Chemistry Values at Termination – Females

Refer Appendix 4

Group No. Dose (mg/kg)		Glob g/l	A/G -	Trig mmol/l	CK U/l	LDH U/l	Na mEq/l	K mEq/l	Cl mEq/l
G1	Mean	18.50	2.45	0.39	335.20	148.10	142.40	3.72	93.13
0	SD	1.54	0.31	0.03	140.37	22.03	5.39	0.68	4.11
	n	10	10	10	10	10	10	10	10
G2a	Mean	18.06	2.53	0.37	358.90	159.50	143.00	3.65	94.58
40	SD	1.70	0.23	0.03	130.47	48.15	2.78	0.61	1.96
	n	10	10	10	10	10	10	10	10
				* (-10)					* (+6)
G3a	Mean	18.61	2.56	0.35	418.80	279.70	147.20	3.64	98.43
80	SD	1.67	0.21	0.03	259.23	275.02	6.40	0.74	2.61
	n	10	10	10	10	10	10	10	10
							* (+5)		* (+8)
G2b	Mean	18.95	2.51	0.38	282.00	222.30	149.30	3.55	100.65
40	SD	1.32	0.23	0.02	73.53	72.23	4.40	0.72	3.96
	n	10	10	10	10	10	10	10	10
						* (+143)	* (+6)		* (+8)
G3b	Mean	19.61	2.47	0.39	313.40	360.50	150.84	3.85	100.88
80	SD	1.12	0.20	0.06	93.99	253.02	5.01	0.64	4.31
	n	10	10	10	10	10	10	10	10

Values in parenthesis indicate % change.
+/-: Significantly higher/lower than the vehicle control group.

The following significant changes in clinical chemistry parameters were considered test-item related changes.

	MALES				FEMALES			
Analyte	ATORVASTATIN CALCIUM		(b) (4) IMPURITY		ATORVASTATIN CALCIUM		(b) (4) IMPURITY	
	G2a	G3a	G2b	G3b	G2a	G3a	G2b	G3b
	40 mg/kg	80 mg/kg	40 mg/kg	80 mg/kg	40 mg/kg	80 mg/kg	40 mg/kg	80 mg/kg
ALT	↑ 4.5 fold	↑ 4.7 fold	↑ 2.9 fold	↑ 3.8 fold	-	↑ 1.7 fold	-	↑ 2.5 fold
AST	↑ 2.8 fold	↑ 3.7 fold	↑ 2 fold	↑ 3 fold	-	↑ 1.4 fold	-	↑ 1.7 fold
ALP	-	↑ 58%	-	↑ 53%	-	↑ 25%	-	↑ 38%
Total Cholesterol	↑ 27%	↑ 29%	↑ 32%	↑ 29%	↑ 15%	↑ 31%	↑ 20%	↑ 40%
Triglycerides	↓20%	↓24%	↓14%	↓22%	-	↓10%	-	-
Calcium	↓7%	↓13%	↓14%	↓18%	↓5%	↓10%	↓12%	↓14%

-Indicates that values are not considered meaningfully different from controls
↑: Increase ↓: Decrease

ALT and AST increase in all the treated males and high dose females (G3a & G3b) and ALP increase in high dose males and females (G3a & G3b) was considered test-item related change as microscopically it was associated with hepatocyte single cell necrosis and degeneration.

Urinalysis: No drug related effects were observed.

Organ weights: Liver weights were increased in females at a HD with both products, i.e. with impurities (6.6* vs 5.8 g in controls, *p<0.05) and without impurities (6.4* vs 5.8 g in controls).

Increase in absolute and relative weights of liver (ratio to body weight) in high dose females (G3a &G3b) was considered test-item related change as microscopically hepatocyte single cell necrosis and degeneration were observed.

TABLE 11. Summary of Terminal Fasting Body Weights and Organ Weights – Females

Refer Appendix 9

Sex: Female		Terminal Fasting BW (g) 1 Way ANOVA (Automatic)	Adrenals (g) 1 Way ANOVA (Automatic)	Brain (g) 1 Way ANOVA (Automatic)	Heart (g) 1 Way ANOVA (Automatic)	Kidneys (g) 1 Way ANOVA (Automatic)	Liver (g) 1 Way ANOVA (Automatic)	Lungs (g) 1 Way ANOVA (Automatic)
		Day 15	Day 15	Day 15	Day 15	Day 15	Day 15	Day 15
G1	Mean	176.86	0.090	1.836	0.630	1.392	5.776	1.066
0	SD	8.43	0.015	0.081	0.043	0.090	0.501	0.090
	N	10	10	10	10	10	10	10
G2a	Mean	176.01	0.088	1.806	0.637	1.365	5.676	1.013
40	SD	11.57	0.013	0.090	0.057	0.120	0.415	0.067
	N	10	10	10	10	10	10	10
G3a	Mean	176.06	0.087	1.842	0.659	1.402	6.403 *(+11)	1.080
80	SD	11.71	0.013	0.068	0.051	0.139	0.479	0.095
	N	10	10	10	10	10	10	10

*: Significantly higher than the vehicle control group (at 5% level of significance)

TABLE 13. Summary of Terminal Fasting Body Weights and Organ Weights – Females

Refer Appendix 9

Sex: Female		Terminal Fasting BW (g) 1 Way ANOVA (Automatic)	Adrenals (g) 1 Way ANOVA (Automatic)	Brain (g) 1 Way ANOVA (Automatic)	Heart (g) 1 Way ANOVA (Automatic)	Kidneys (g) 1 Way ANOVA (Automatic)	Liver (g) 1 Way ANOVA (Automatic)	Lungs (g) 1 Way ANOVA (Automatic)
		Day 15	Day 15	Day 15	Day 15	Day 15	Day 15	Day 15
G1	Mean	176.86	0.090	1.836	0.630	1.392	5.776	1.066
0	SD	8.43	0.015	0.081	0.043	0.090	0.501	0.090
	N	10	10	10	10	10	10	10
G2b	Mean	175.06	0.087	1.873	0.634	1.340	5.523	1.056
40	SD	10.31	0.009	0.082	0.066	0.069	0.442	0.108
	N	10	10	10	10	10	10	10
G3b	Mean	176.78	0.087	1.818	0.650	1.484	6.566 *(+14)	1.069
80	SD	12.97	0.011	0.084	0.072	0.151	0.642	0.108
	N	10	10	10	10	10	10	10

*: Significantly higher than the vehicle control group (at 1% level of significance)

Gross pathology: No drug related effects were observed.

Histopathology: The following drug related effects were observed.

Hepatocyte single cell necrosis and hepatocyte degeneration observed in all the treated males and high dose females (G3a & G3b) were considered test-item related changes. These microscopic changes had (increase in ALT, AST and ALP) clinical chemistry correlates.

TABLE 16 contd. Summary of Histopathological Findings

Refer Appendix 11 and 12

Observations: Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL SACRIFICE	G1	G2a	G3a	G2b	G3b	G1	G2a	G3a	G2b	G3b
	0	40	80	40	80	0	40	80	40	80
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
LIVER;										
Examined	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	7	0	0	2	0	9	9	1	9	0
Hepatocellular necrosis; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0	0	0
Hepatocyte degeneration	(0)	(1)	(6)	(1)	(4)	(0)	(0)	(1)	(0)	(1)
minimal	0	1	4	1	2	0	0	1	0	1
mild	0	0	2	0	2	0	0	0	0	0
Hepatocytic single cell necrosis	(0)	(10)	(10)	(8)	(10)	(0)	(0)	(7)	(0)	(10)
minimal	0	9	8	8	7	0	0	7	0	10
mild	0	1	2	0	3	0	0	0	0	0
Increased mitotic acitivity; hepatocyte	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	0	1	0	0	1	0	0
Portal leukocytic infiltration	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(2)	(0)	(0)
minimal	0	0	0	0	1	0	0	2	0	0
Pigmented kupffer cells; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
Chronic inflammatory focus(i)	(2)	(0)	(0)	(1)	(0)	(1)	(1)	(0)	(1)	(0)
minimal	2	0	0	1	0	1	1	0	1	0
LYMPH NODE, MESENTERIC;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
MAMMARY GLANDS;										
Examined	(8)	(0)	(8)	(0)	(9)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	8	0	8	0	9	10	0	10	0	10
Not Examined: Not Present	2	0	2	0	1	0	0	0	0	0

The following microscopic changes in liver were considered test-item related.

	MALES					FEMALES				
Microscopic change	ATORVASTATIN CALCIUM			(b) (4) IMPURITY		ATORVASTATIN CALCIUM			(b) (4) IMPURITY	
	G1	G2a	G3a	G2b	G3b	G1	G2a	G3a	G2b	G3b
mg/kg/day	0	40	80	40	80	0	40	80	40	80
Hepatocyte Single cell necrosis	0/10	10/10	10/10	8/10	10/10	0/10	0/10	7/10	0/10	10/10
Hepatocyte Degeneration	0/10	1/10	6/10	1/10	4/10	0/10	0/10	1/10	0/10	1/10

Sponsor's conclusions are provided below

The results of this study indicated that the 14 day repeated oral administration of the test item-without impurities (Atorvastatin Calcium) and with impurities (b) (4) Impurity) to Wistar rats at the dose levels of 40 (G2a/G2b) and 80 (G3/G3b) mg/kg Bwt/day did not cause any moralities and did not elicit any effect on general health status, growth and food consumption of the animals. No treatment-related changes were observed in the functional observation tests. There were no test item-related alterations in hematology, coagulation and urinalysis parameters in both sexes. Treatment with test items resulted increased plasma ALT and AST levels in all the test items treated group males and in high dose females (80 mg/kg - G3a & G3b).The increases were also seen in plasma ALP level of high dose groups (80 mg/kg - G3a & G3b) and total cholesterol at all the test item treated groups in both sexes whereas decreases were seen in triglycerides level of all the test item treated males and high dose group females (80 mg/kg - G3a) and also decreases were seen in plasma calcium level in all the test items treated groups in both sexes. Increased absolute and relative weights of liver (ratio to body weight) were seen in high dose females (80 mg/kg - G3a &G3b) and these changes were associated with histological changes observed in the liver (hepatocyte single cell necrosis/degeneration). Microscopically, hepatocyte single cell necrosis/ degeneration observed in all the treatment group males and high dose females (80 mg/kg - G3a & G3b) and these changes were associated with increased in plasma ALT, AST and ALP level.

CONCLUSION

In view of the results discussed above, it is apparent that the observed findings in rats treated with Atorvostatin Calcium-without impurity were similar and no novel toxicity was seen when compared to Atorvastatin Calcium ((b) (4) Impurity) with impurities. Further no changes of toxicological significance were noted among female Wistar rats that received a dose of 40 mg/kg body weight/day for test items Atorvostatin Calcium-without impurity or Atorvastatin Calcium ((b) (4) Impurity) with impurities, hence this dose level is considered as No Observed Effect Level (NOEL) for the females and NOEL/NOAEL could not be established for males treated with test item alone or with the impurity under the test conditions and doses employed.

In summary: In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurity to rats. The impurity was (b) (4) (b) (4) (b) (4) present at (b) (4)% of API. The TK parameters (such as Cmax and AUC values) of the drug were not measured in this study. The drug (with and without impurity) produced some neuromuscular changes in the functional observation battery (such as grip strength and motor activity), but since RLD was not used, it is unclear if these were unique to the current drug product. Both products had no effects on clinical signs. BW gains in male rats were higher with impurity at a HD (19.4* vs 15.3 g in controls), *p<0.05) than without the impurity (17.6 vs 15.3 g in controls). In hematological/coagulation parameters, prothrombin time was decreased at all doses of the drug with impurity (16.6, 15.1*, 15.4* sec at 0, 40, 80 mg/kg/day respectively, *p<0.05), vs only at a HD without impurity. Similarly, ALP levels were increased at all doses of the drug with impurity (71, 98, 98 IU/L at 0, 40, 80 mg/kg/day respectively), these were not increased in the drug product without impurity. The histopathological changes were in general similar in the liver (i.e. with or without impurities in the drug). No NOAEL could be established in this study since even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one.

Genetic toxicology studies

Following gene-toxicity studies have been conducted with the (b) (4) (at concentration of (b) (4)%) to qualify this impurity.

1) AMES test was conducted with atorvastatin calcium, without and with (b) (4)% of (b) (4) impurity. As seen below, atorvastatin calcium was negative in the AMES test at doses up to 5000 ug/plate in the presence and absence of impurities (report # G7009). The study was conducted by (b) (4) (completed on 3/9/10).

Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted] (b) (4) impurity was tested for its mutagenic potential in the bacterial reverse mutation assay. The study was conducted using TA 98, TA 100, TA 1535 and TA 1537 strains of *Salmonella typhimurium* and WP2 uvrA (pKM 101) strain of *Escherichia coli*. The study consisted of a preliminary toxicity test and two mutation assays (trials) comprising four independent experiments. The bacterial tester strains were exposed to the test item in the presence and absence of metabolic activation system (S-9 fraction prepared from Aroclor 1254 induced rat liver).

The test items were found to be soluble at the required concentration of 50000 µg/mL in [redacted] (b) (4) The test item was also found to be stable for at least 6 hours in [redacted] (b) (4)

In a preliminary toxicity test, the mean number of revertant colonies and the intensity of the bacterial background lawn was comparable to the solvent control up to 5000 µg/plate, both in the presence and absence of metabolic activation. Hence, it was decided to test a maximum of 5000 µg/plate in the mutation assay.

In the first mutagenicity assay, the test items were exposed in triplicate to 50, 158, 500, 1581 and 5000 µg/plate test concentrations in the presence and absence of metabolic activation using direct plate incorporation procedure. In the confirmatory (second) assay, the test items were exposed in triplicate to concentrations of 100, 266, 707, 1880 and 5000 µg/plate in the presence and absence of metabolic activation using direct plate incorporation procedure. The solvent control [redacted] (b) (4) and the appropriate positive controls were tested simultaneously. The mean and standard deviation of numbers of revertant colonies were calculated for each test concentration and the controls for all the tester strains.

All formulations of the test doses from the mutation assay were analysed and the API concentrations were well within the acceptable range.

The results of the study, from the first as well as from the confirmatory assays showed that the mean numbers of revertant colonies neither doubled for strains TA 98, TA 100 and WP2 uvrA (pKM 101) nor tripled for strains TA 1535 and TA 1537 when compared to the respective solvent control plates, either in the presence or in the absence of the metabolic activation at any of the tested concentrations.

Under identical test conditions, there was a statistically significant increase in the mean numbers of revertant colonies in the positive controls, demonstrating the sensitivity of the assay procedure used.

The study indicated that the test items, Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted] (b) (4) - [redacted] (b) (4) impurity, were not mutagenic in this Bacterial Reverse Mutation Assay up to the highest tested concentration of 5000 µg/plate.

Purity as per Certificate of Analysis	:	Atorvastatin Calcium: [redacted] (b) (4) % on [redacted] (b) (4) basis [redacted] (b) (4) impurity ATC ARL(A-489) 13-D: [redacted] (b) (4) % ATC ARL(A-489) 51B: [redacted] (b) (4) %
Batch No.	:	Atorvastatin Calcium: AC0160708 [redacted] (b) (4) impurity: ATC ARL(A-489) 51B

TABLE 3. Summary Results of Bacterial Reverse Mutation Test (Trial 1)

Refer Appendix 2

Group	Treatment [µg/plate]	No. of revertants/plate*/ Presence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - [redacted] (b) (4) (100 µL)	24	4	97	5	12	3	14	1	135	3
G2	50	23	3	105	5	12	2	13	2	136	4
G3	158	22	0	104	6	+ 17	2	13	2	147	15
G4	500	23	1	111	2	9	1	13	1	130	6
G5	1581	22	2	+ 115	6	9	1	12	2	128	6
G6	5000	23	4	111	11	9	1	13	4	131	4
G7	50	22	3	104	10	11	2	14	2	132	5
G8	158	22	2	97	8	9	1	11	2	130	3
G9	500	26	2	99	8	14	1	11	3	137	6
G10	1581	23	2	110	8	13	2	14	1	141	7
G11	5000	23	1	+ 116	2	15	3	13	2	143	7
G12	Positive control	+ 538	11	+ 769	4	+ 137	4	+ 116	6	+ 575	13

*: Values are means of three replicates and are rounded off to the nearest whole number.
+ : Significantly higher than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with [redacted] % o [redacted] (b) (4) Impurity.
Group No. G12 had respective positive controls.

TABLE 3. contd. Summary Results of Bacterial Reverse Mutation Test (Trial 1)

Refer Appendix 3

Group	Treatment [µg/plate]	No. of revertants/plate*/ Absence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - [redacted] (b) (4) (100 µL)	20	2	114	7	11	3	13	3	128	9
G2	50	25	3	- 80	9	9	2	9	2	121	1
G3	158	21	2	95	13	9	3	11	2	129	8
G4	500	22	2	103	9	13	1	11	3	135	10
G5	1581	25	5	102	9	12	2	13	2	117	18
G6	5000	20	4	97	11	14	2	13	3	117	4
G7	50	20	4	102	13	11	3	12	1	118	11
G8	158	21	4	103	4	12	5	13	1	122	3
G9	500	21	6	128	15	11	1	12	2	124	10
G10	1581	22	4	112	1	13	3	14	1	137	7
G11	5000	19	4	110	6	11	4	11	1	129	11
G12	Positive control	+ 232	10	+ 552	8	+ 127	9	+ 120	5	+ 575	8

*: Values are means of three replicates and are rounded off to the nearest whole number.
+/- : Significantly higher/lower than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with [redacted] % o [redacted] (b) (4) mpurity.
Group No. G12 had respective positive controls.

TABLE 4. Summary Results of Bacterial Reverse Mutation Test (Trial 2)

Refer Appendix 4

Group	Treatment [µg/plate]	No. of revertants/plate*/ Presence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - (b) (4) (100 µL)	18	3	123	16	11	2	15	4	117	4
G2	100	20	2	- 106	3	10	1	15	3	115	4
G3	266	24	5	- 104	2	14	3	11	1	116	3
G4	707	23	3	114	2	12	3	15	2	116	4
G5	1880	24	3	108	7	9	2	14	1	122	4
G6	5000	23	4	111	7	11	4	13	1	120	8
G7	100	22	5	- 106	6	10	3	11	1	122	3
G8	266	19	1	108	5	12	3	11	2	127	7
G9	707	19	2	112	5	11	3	13	2	121	5
G10	1880	18	3	- 100	3	14	2	13	2	121	9
G11	5000	19	2	- 105	4	11	3	14	2	130	8
G12	Positive control	+ 537	8	+ 721	17	+ 148	3	+ 125	4	+ 579	4

*: Values are means of three replicates and are rounded off to the nearest whole number.
+/- : Significantly higher/lower than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with (b) % of (b) (4) Impurity.
Group No. G12 had respective positive controls.

TABLE 4. contd. Summary Results of Bacterial Reverse Mutation Test (Trial 2)

Refer Appendix 5

Group	Treatment [µg/plate]	No. of revertants/plate*/ Absence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - (b) (4) (100 µL)	22	7	112	8	10	2	12	2	116	4
G2	100	23	2	108	2	13	2	13	1	115	3
G3	266	18	2	112	7	14	3	14	2	122	6
G4	707	19	2	107	4	13	4	13	3	123	5
G5	1880	23	6	108	6	13	4	11	2	115	3
G6	5000	22	3	111	4	15	3	12	2	115	2
G7	100	21	5	102	3	11	2	12	2	122	3
G8	266	24	4	109	6	13	2	13	1	121	5
G9	707	21	4	113	3	10	1	13	1	122	4
G10	1880	19	2	107	4	13	2	13	1	115	3
G11	5000	19	1	113	4	14	1	13	2	118	3
G12	Positive control	+ 237	19	+ 553	7	+ 130	9	+ 125	5	+ 577	8

*: Values are means of three replicates and are rounded off to the nearest whole number.
+ : Significantly higher than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with (b) % of (b) (4) Impurity.
Group No. G12 had respective positive controls.

Conclusion: Thus as noted above, atorvastatin calcium drug product was negative in the AMES test at doses up to 5000 ug/plate in the absence and presence of (b)% of (b) (4) impurity (report # G7009)

2. In vitro chromosomal aberration test in Peripheral blood lymphocytes:. Atorvastatin calcium spiked with (b)% (b) (4) impurity was tested in an 'in vitro cultured Chinese Hamster ovary (CHO) cell in the mammalian chromosome aberration test. The drug was negative in the above assay with and without impurities (study # G7010). This assay was conducted at (b) (4) (b) (4).

The details on the drug product and the study are provided below:

Purity as per Certificate of Analysis	:	Atorvastatin Calcium: (b) (4)% on (b) (4) basis (b) (4) impurity ATC ARL(A-489) 13-D: (b) (4)% ATC ARL(A-489) 51B: (b) (4)%
Batch No.	:	Atorvastatin Calcium: AC0160708 (b) (4) impurity: ATC ARL(A-489) 13-D and ATC ARL(A-489) 51B
Manufactured date	:	Atorvastatin Calcium: Nov 2007 (b) (4) impurity: Nov 2009

The clastogenic potential of the test items, Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4) (b) (4) impurity, to induce chromosome aberrations in mammalian cells was evaluated using cultured Chinese Hamster Ovary (CHO) cells.

The study consisted of a preliminary toxicity test and a chromosome aberration assay comprising three independent experiments, one each in the presence and absence of metabolic activation and a confirmatory experiment in the absence of metabolic activation. CHO cells were exposed to the test items in the presence and absence of metabolic activation system (S-9 fraction prepared from Aroclor 1254 induced rat liver).

Both the test items formed a solution in (b) (4) at the tested concentration of 50 mg/mL. The dose formulations of the test items at 450 µg/mL and 50000 µg/mL were found to be homogeneous and stable in (b) (4) for at least 6 hours at room temperature. The test items did not cause any appreciable change in the pH of the test medium at the end of 3-hour exposure to treatment either in the presence or in the absence of metabolic activation.

In a preliminary cytotoxicity test for the selection of test doses, a significant reduction in the growth of CHO cells was observed at and above 150 µg/mL both in the presence and absence of metabolic activation in 3-hour exposure and at 150 µg/mL in 21-hour exposure in the absence of metabolic activation compared to the (b) (4) control with Atorvastatin Calcium and spiked Atorvastatin Calcium.

In the definitive chromosome aberration assay, CHO cells were exposed for 3 hours to Atorvastatin Calcium and spiked Atorvastatin Calcium in duplicate at the concentrations of 12, 36 and 108 µg/mL of the medium in the presence of metabolic activation and at 14, 44 and 140 µg/mL of the medium the absence of metabolic activation. Similarly, CHO cells were

exposed in duplicate at concentrations of 9, 28 and 90 μg/mL for 21 hours in the absence of metabolic activation.

In a similar way, concurrent solvent control and the positive controls, cyclophosphamide monohydrate in the presence of metabolic activation and ethylmethanesulphonate in the absence of metabolic activation were also tested in triplicate.

In each case, the cells in C-metaphase were harvested at 21 hours after the start of the treatment from the solvent control, test concentrations and the positive controls.

At the highest tested concentration of Atorvastatin Calcium, the reduction in the cell growth was 53% in the presence of metabolic activation, 57 and 58% in the absence of metabolic activation with 3 and 21-hour exposure, respectively, compared to the solvent control.

Similarly, at the highest tested concentration of spiked Atorvastatin Calcium, the reduction in the cell growth was 55% in the presence of metabolic activation, 56 and 56% in the absence of metabolic activation with 3 and 21-hour exposure, respectively, compared to the solvent control.

A total of 200 metaphases per dose level from triplicate cultures from the solvent control, treatment and the positive control were evaluated for chromosome aberrations. The data from the treatment groups and the positive control were statistically compared with the solvent control.

There was no evidence of induction of chromosome aberrations, either in the presence or in the absence of metabolic activation in any of the tested concentrations either including or excluding gaps.

Reference ID: 2926976

In each of these experiments, the respective positive control substances produced a large and statistically significant increase in aberrant metaphases, under identical conditions.

The study indicated that Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) (b) (4) Impurity do not have the potential to cause chromosome aberrations at the concentrations tested and under the conditions of testing.

TABLE 5. Summary Results of *In vitro* Mammalian Chromosome Aberration Test in the Presence of Metabolic Activation (Experiment 1)

Refer Appendices 2 and 3

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
(b) (4) (300 µL)	200	0	2 (1.0)	0	1 (0.5)	0	0	0	2 (1.0)	1 (0.5)	-
12	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	5
36	200	0	0	0	0	0	0	0	0	0	26
108	200	0	1 (0.5)	0	0	0	0	0	1 (0.5)	0	53
12	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	17
36	200	1 (0.5)	2 (1.0)	0	0	0	0	0	3 (1.5)	0	22
108	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	55
CPA 55	200	20 (10.0)	33 (16.5)	1 (0.5)	18 (9.0)	61 (30.5)	41 (20.5)	0	+ 122 (61.0)	+ 98 (49.0)	21

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations
Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome CPA: Cyclophosphamide monohydrate
+: Significantly higher than control ($p \leq 0.05$) by Fisher exact test
Groups G2 to G4 represents Atorvastatin Calcium and groups G5 to G7 represents spiked Atorvastatin Calcium

TABLE 6. Summary Results of *In vitro* Mammalian Chromosome Aberration Test in the Absence of Metabolic Activation (Experiment 2)

Refer Appendices 2 and 4

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
(b) (4) (300 µL)	200	0	2 (1.0)	1 (0.5)	1 (0.5)	0	0	0	4 (2.0)	2 (1.0)	-
14	200	0	3 (1.5)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	22
44	200	0	4 (2.0)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	29
140	200	0	2 (1.0)	2 (1.0)	2 (1.0)	0	0	0	5 (2.5)	4 (2.0)	57
14	200	0	4 (2.0)	0	4 (2.0)	0	0	0	5 (2.5)	4 (2.0)	27
44	200	1 (0.5)	3 (1.5)	1 (0.5)	2 (1.0)	0	0	0	5 (2.5)	3 (1.5)	36
140	200	1 (0.5)	2 (1.0)	0	1 (0.5)	0	0	0	3 (1.5)	1 (0.5)	56
EMS 600	200	18 (9.0)	57 (28.5)	51 (25.5)	42 (21.0)	32 (16.0)	25 (12.5)	1 (0.5)	+ 127 (63.5)	+ 99 (49.5)	21

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations
Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome EMS: Ethylmethane sulphonate
+: Significantly higher than control ($p \leq 0.05$) by Fisher exact test
Groups G2 to G4 represents Atorvastatin Calcium and groups G5 to G7 represents spiked Atorvastatin Calcium

TABLE 6. Summary Results of *In vitro* Mammalian Chromosome Aberration Test in the Absence of Metabolic Activation (Experiment 2)

Refer Appendices 2 and 4

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
(b) (4) (300 µL)	200	0	2 (1.0)	1 (0.5)	1 (0.5)	0	0	0	4 (2.0)	2 (1.0)	-
14	200	0	3 (1.5)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	22
44	200	0	4 (2.0)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	29
140	200	0	2 (1.0)	2 (1.0)	2 (1.0)	0	0	0	5 (2.5)	4 (2.0)	57
14	200	0	4 (2.0)	0	4 (2.0)	0	0	0	5 (2.5)	4 (2.0)	27
44	200	1 (0.5)	3 (1.5)	1 (0.5)	2 (1.0)	0	0	0	5 (2.5)	3 (1.5)	36
140	200	1 (0.5)	2 (1.0)	0	1 (0.5)	0	0	0	3 (1.5)	1 (0.5)	56
EMS 600	200	18 (9.0)	57 (28.5)	51 (25.5)	42 (21.0)	32 (16.0)	25 (12.5)	1 (0.5)	+ 127 (63.5)	+ 99 (49.5)	21

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations
Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome EMS: Ethylmethane sulphonate
+: Significantly higher than control ($p \leq 0.05$) by Fisher exact test
Groups G2 to G4 represents Atorvastatin Calcium and groups G5 to G7 represents spiked Atorvastatin Calcium

Conclusion: Atorvastatin calcium spiked with (b) (4)% (b) (4) impurity was tested in an 'in vitro cultured Chinese Hamster ovary (CHO) cell in the mammalian chromosome aberration test. The drug was negative in the above assay with and without impurities.

L-Arginine safety assessment

In the previous consult review on L-arginine (see DARRTs, signed off on 6/16/09), we had recommended that the sponsor establish the safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), at levels intended (b) (4)) for chronic use.

As indicated previously, L-arginine has been approved by FDA in injectable drug products in antibiotics, as an aid to solubilize the drug (at doses up to of 780 mg per gram of the drug, NDA 50-580, NDA 50-632, NDA 50-679 or Maxipime), these antibacterial drugs are not for a chronic use. Maxipime is dosed up to 2 g every 8 hours (the lowest dose is 500 mg every 12 hours). At these doses, L-arginine exposure with Maxipime will range from 1.5 g to 4.35 g/day, this dose is much higher than the dose that will be used in the atorvastatin calcium drug product (b) (4)). However, L-arginine has not been approved by FDA in any oral drug products.

There is a study conducted at John's Hopkins in post-myocardial infarction patients taking L-arginine 3 g, three times a day (TID), for 6 months. This study reported that these high doses of L-arginine did not have a beneficial effect on cardiac outcomes and in fact had a detrimental effect {JAMA 2006 295(1):58-64}. In this study, L-arginine use was associated with higher post-infarction mortality (3 g TID). This study suggests that L-arginine should not be recommended following acute myocardial infarction.

Therefore, there is published clinical literature suggesting that patients with cardiovascular disease may have adverse outcomes from L-arginine. Patients with frank and underlying disease as well as those with cardiovascular (CV) risk are given atorvastatin to lower cholesterol (and implied CV risk) in combination of various drugs. Safe levels of L-arginine have not been established in this patient population. The literature supports the safety of L-arginine in an otherwise healthy population and more importantly reports significant adverse outcomes with L-arginine in patients with CV risk without establishing a safe level. The information provided by the sponsor does not address this body of literature at all.

Note that nonclinical studies may not address or establish the risk because they are performed in otherwise healthy animals. Animal CV disease models have a tenuous association to human risk and it is unclear which CV models are most relevant to this situation. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population i.e. subjects with CV disease. There may be data available from patients with CV disease that have received a particular level of L-arginine chronically in other approved drugs at levels intended for use here ((b) (4)). While this may be supportive, additive effects of other co-administered medications with L-arginine can not be excluded. There are known drug interactions with L-arginine and common medications in this patient population (e.g. potassium sparing diuretics, ACE inhibitors etc.).

In conclusion, the long term effects of oral L-arginine (the semi-essential amino acid) are unknown. The current generic drug product atorvastatin calcium would be used by patients for many years. Because the patient population in ANDA (b) (4) is very different (i.e. patients with frank and underlying diseases, as well as those with cardiovascular risk), and there's cause for heightened concern in patients with CV disease based on clinical literature, which is the intended patient population for atorvastatin; safe levels of L-arginine in the patient population have not been established. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), as well as the additive effects of other co-administered medications with L-arginine. This data may be available from the literature from

patients with CV disease that have received a particular level of L-arginine chronically in other approved drugs at levels intended for use here ((b) (4)).

We had provided following recommendations on 6/16/2009:
The long term effects of oral L-arginine are unknown. The generic atorvastatin calcium is for chronic use, it is important to know at what doses it produces toxicity, especially in patients with cardiovascular (CV) risk. Therefore, sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease). This data may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use here (b) (4)

In the current submission (4/8/2010), sponsor has provided more justification for use of the inactive ingredient L-Arginine, in their atorvastatin calcium drug product. Sponsor in response to our recommendation has provided a summary of published and unpublished studies from the Medline/toxline search as stated below.

Sponsor has provided following summary of studies on L-Arginine:

> The purpose of this document is to review the available clinical safety information on L-Arginine to provide an assessment of the safe use in the proposed product in cardiovascular disease subjects. This review was based on available published and unpublished information. The published clinical information was identified through searching the internet as well as the National Library of Medicine databases (MEDLINE/TOXLINE) back to 1965. The CAS number and the generic names/synonyms were used in the database searches. The search resulted in the identification of a large number of publications including a number of review articles which include assessments of safety and efficacy in patient populations for a number of cardiovascular diseases as well as associated risk factors. Collectively, these publications demonstrate the strong acceptability of the use of L-Arginine supplementation in subjects with cardiovascular disease and indicate good tolerability at doses far exceeding the proposed limit of (b) (4) in Matrix's atorvastatin calcium drug product formulation.
>
> ***Hypertension:*** NO plays a crucial role in regulating blood pressure; thus, L-Arginine or NO deficiency results in hypertension in animals and humans. Much research has shown that intravenous or oral L-Arginine administration increases NO synthesis and prevents endothelial dysfunction in animal models of pulmonary hypertension or salt-induced hypertension. The same beneficial effect of L-Arginine has been observed in most studies involving hypertensive patients, who exhibit elevated plasma levels of ADMA and reduced NO synthesis.

Summary reviews have been previously published and established the safety and efficacy in these cardiovascular conditions (Cheng, 2001; Bode-Boger, 2006; Shao 2008).

L- Arginine in clinical trials

Based on observations from experimental clinical studies, which showed vasodilation and enhanced NO production after administration of L-Arginine, a series of clinical trials have been performed to investigate the potential of this amino acid to improve the symptoms of cardiovascular disease. The first clinical application of L-Arginine in an attempt to improve vascular function in patients with cardiovascular disease was published almost 20 years ago. Since then, there have been many studies with L-Arginine in healthy human subjects or in patients with various cardiovascular conditions.

L-Arginine has generally been well tolerated by healthy volunteers and patients when administered via the intravenous or oral route in doses <30 g. When high doses of L-Arginine are given intravenously, local irritation and phlebitis may occur because of the high osmolality of the solution.

The following trails are aimed at determining the efficacy and safety of L-Arginine administered in long- term clinical trails as summarized below.

1. Bednarz et al, 2005 examined 792 patients with acute ST-segment elevation myocardial infarction admitted within 24h after the onset of symptoms. This multicenter, randomized, double-blind, placebo-controlled study examined the effects of placebo or 3 grams of L-Arginine orally in capsules three times daily for a period of 30 days. The end point which was the composite of 30 day cardiovascular death, reinfarction, successful resuscitation, shock/pulmonary edema or recurrent myocardial ischemia occurred in 24% patients treated with L-Arginine and 27% with placebo. These results demonstrated a beneficial trend in patients with an acute MI while also demonstrating that 9 grams of L-Arginine orally is safe and well tolerated.
2. Gutman and colleagues (2005) studied the effects of L-Arginine supplementation 45 patients with multiple risk factors or evidence of vascular disease. The study was a randomized, double-blind assessment of 6 grams of L-Arginine or placebo daily for 6 months. The results demonstrated that L-Arginine supplementation is well tolerated and serves to reduce systolic blood pressure and increase large artery elasticity.
3. Lucotti et al, 2009 studied the effect of oral L-Arginine supplementation (6.4 grams per day) in 32 non-diabetic cardiopathic patients following aortocoronary bypass in a six month duration placebo controlled clinical trail. The results of this study conclude that L-Arginine supplementation (6.4 grams per day) in Non-diabetic cardiopathic patients improved glucose tolerance in coronary artery bypass grafted (CABG) patients; this was achieved through significant improvement of Serum Insulin (SI) levels, endothelial function. There was no added risk when L-Arginine was added in the therapy, and on the contrary there was a significant benefit as explained above.
4. Koga Y et al 2006 evaluated the effects of administration of L-Arginine in 15 young patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS) and 20 control subjects in long term study after administration of L-Arginine orally in a dose range of 4-24 g/day for at least a 24 months treatment period. The outcome of the study indicated that the frequency and severity of clinical symptoms of stroke-like episodes decreased without serious adverse effects.
5. Lerman A, et al 1998 evaluated the effects of L-Arginine supplementation in a long-term placebo controlled study after administration of L-Arginine orally 3g TID for 6 months treatment period in 26 patients without coronary artery disease (CAD). The outcome of the study indicated that the L-Arginine supplementation for 6 months in human improves coronary small vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentrations. Update
6. Hambrecht, et al 2000 evaluated the effects of L-Arginine supplementation and exercise in a short term placebo controlled study after administration of L-Arginine orally 8g/day in chronic heart failure patients with endothelial dysfunction. Forty patients were studied in a crossover fashion in 4 groups receiving L-Arginine with or without exercise and a control group without L-Arginine and exercise for 4 weeks in each period with a one week washout with each treatment. The outcome of the study indicated that the L-Arginine

supplementation for 4 weeks leads to a fourfold increase in endothelium dependent vasodilatation in patients with CHF after four weeks of treatment.

7. Martina and colleagues (2008) studied the effects of L-Arginine in 24 male subjects with hypertension and Type 2 Diabetes. The study was a randomized, double-blind, placebo-controlled study which evaluated 1200 mg of L-Arginine once daily and 600 mg n-acetylcysteine twice daily for 6 months. In this study, N-acetylcysteine and L-Arginine were demonstrated to improve endothelial function by improving NO bioavailability via a reduction of oxidative stress and increase in NO production without any adverse effects.
8. Reul et al. 2008 studied the effects of L-Arginine and vascular endothelial growth factor or placebo for 3 months in 19 severe diffuse coronary artery disease patients. Subjects were randomized in 2 X 2 factorial fashion to receive ten 200-mg injections of vascular endothelial growth factor-165 plasmid DNA or placebo in the anterior myocardium along the proximal and mid-left anterior descending arteries, plus oral L-Arginine supplementation at a dose of 6 g per day or placebo for 3 months. Patients who received the combination of vascular endothelial growth factor and L-Arginine had improved anterior wall perfusion on positron emission tomography (P=0.02), a trend toward smaller perfusion defects (P=0.10), and better anterior wall contractility (P=0.02, Kruskal–Wallis) at 3 months vs. baseline. In this study L-Arginine administration was not associated with any major adverse events.
9. The Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) published by Schulman (2006) was a single-center, randomized, double-blind, placebo-controlled trail examining the effects of L-Arginine (3g tid) or matching placebo in 153 myocardial infarction subjects for 6 months. In this study, L-Arginine added to standard postinfarct medications did not reduce noninvasive measures of vascular stiffness, improve ejection fraction, or improve clinical outcomes. Six-month clinical events, including death, myocardial infarction, and hospitalization for heart failure, occurred in 12 (16.7%) patients in the L-Arginine group compared with 7 (10.1%) patients in the placebo group. However, 6 participants (8.6%) in the L-Arginine group died during the 6-month study period vs. none in the placebo group (*P*=.01). Because of the safety concerns, the data and safety monitoring committee closed enrollment.
10. The Nitric Oxide in Peripheral Arterial Insufficiency (known as the NO-PAIN study) published by Wilson (2007) was a single center, randomized, double-blind, placebo-controlled trail examining the effects of L-Arginine (3/day) or matching placebo in 133 patients with Peripheral Artery Disease for 6 months. In this trial oral L-Arginine supplementation significantly increased plasma L-Arginine levels, however, measures of nitric oxide were reduced or not improved compared with placebo. There were 9 adverse events reported in each group that were considered serious including 1 death in both the placebo and L-Arginine, however, no group differences existed in serious or total adverse events.

Note that none of the studies provided above are standard toxicity studies. The studies provided are clinical publications using higher doses in CV patients for 6 months. Pharmacology /toxicology can not make this safety call on the summary of some clinical literature in subjects with CV disease from a literature search, this needs to be determined by the medical officer. As indicated earlier, the patient population from the Johns Hopkins study with 3 g L-arginine was associated with increased mortality in subjects with post acute myocardial infarction (MI, see reference 9 on page 59 by Schulman JAMA 295:58, 2006). Note that although (b) (4) is considerably less, we do not have any data that suggests that the long-term use at this dose is safe in patients with MI, who will likely be given atorvastatin chronically.

We have a concern, because the literature studies provided are not adequate to support the levels of L-arginie in their atorvastatin drug product. Thus, proposed generic atovastatin calcium may not be "the same as Lipitor" based on the L-arginine being present. The 2-week toxicity studies provided by the sponsor (to qualify the impurities) or the 13-week toxicity study (from this reviewer's literature search) are not sufficient to establish safety for a chronic use product with a potential safety risk in the patient population its indicated for.

Safety Evaluation

1. Qualification of (b) (4) and (b) (4) impurities in the atorvastatin calcium drug product.

Sponsor has conducted a 2-week toxicity study and two in vitro geno-toxicity studies to qualify above impurities in their drug product. The summary of these studies are provided below.

In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurities to rats. The impurities were (b) (4) (b) (4) (at concentration of (b) (4)%) and (b) (4) (at concentration of (b) (4)%), both relative to atorvastatin calcium drug product. The TK parameters of the drug (such as Cmax and AUC values) were not measured in this study. The drug had no effects on clinical signs and BWs with and without the impurities. Food consumption was not significantly altered with both. Hematological parameters, such as hemoglobin and hematocrit were increased at all doses of the drug (with or without impurities); since the reference listed drug (RLD) was not used in the study, it is hard to know if these toxicities were unique to the current drug product. In clinical chemistry parameters, similar effects were observed on liver enzymes, etc. with or without impurities. The histopathological changes in the liver were also in general similar in the presence or absence of impurities in the drug. No NOAEL could be established in this study, as even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. However, toxicity of both products (with or without impurities) were in general similar.

Mutagenicity: Atorvastatin calcium without and with impurity (spiked with (b) (4)% of (b) (4) (b) (4) and (b) (4)% of (b) (4) in the atorvastatin calcium drug product) was not mutagenic/cytogenic in the following 2 tests: Ames test at doses up to 5000 ug/plate, and in vitro in chromosomal aberration assay in human peripheral blood lymphocytes at concentration up to 150-300 ug/ml with 50% mitotic index.

2. Qualification of (b) (4) impurity in the atorvastatin calcium drug product.

Sponsor has conducted a 2-week toxicity study and two in vitro geno-toxicity studies to qualify above impurity in their drug product. The summary of these studies are provided below.

In summary: In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurity to rats. The impurity was (b) % (b) (4) in the drug product. The TK parameters (such as Cmax and AUC values) of the drug were not measured in this study. The drug (with and without impurity) produced some neuromuscular changes in the functional observation battery (such as grip strength and motor activity), but since RLD was not used, it is unclear if these were unique to the current drug product. Both products had no effects on clinical signs. BW gains in male rats were higher with impurity at a HD (19.4* vs 15.3 g in controls, *p<0.05); which was not seen without the impurity (17.6 vs 15.3 g in controls). In hematological/coagulation parameters, prothrombin time was decreased at all doses of the drug with impurity (16.6, 15.1*, 15.4* sec at 0, 40, 80 mg/kg/day respectively, *p<0.05), vs only at a HD without impurity. Similarly, ALP levels were increased at all doses of the drug with impurity (71, 98, 98 IU/L at 0, 40, 80 mg/kg/day respectively), these were not increased in the drug product without impurity. The histopathological changes were in general similar in the liver (i.e. with or without impurities in the drug). No NOAEL could be established in this study since even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one, so this study has limited value. Thus, although some subtle differences in toxicity of the drug with impurities vs without impurities were observed as noted above, the toxicity of both products (without or with (b) (4) impurity) were in general similar.

Mutagenicity: Atorvastatin calcium without and with impurity (spiked with (b) % (b) (4) impurity in the atorvastatin calcium drug product) was not mutagenic/cytogenic in the following 2 tests: Ames test at doses up to 5000 ug/plate, and in vitro in chromosomal aberration assay in cultured Chinese Hamster Ovary (CHO) cells at concentration up to 108-140 ug/ml.

In summary, Sponsor by providing 2-week toxicity study in one species (rats) with the atorvastatin with impurities (spiked with (b) (4) and (b) (4) in the atorvastatin calcium drug product, as well as with (b) (4) impurity) and without impurities, as well as by conducting two geno-toxicity studies (Ames and chromosome aberration assay) has qualified the impurities in their atorvastatin calcium, and these are acceptable.

3. Safety of L-arginine: In the current submission, sponsor has provided additional clinical studies to support the (b) (4) of L-arginine in 80 mg of atorvastatin drug product. Pharmacology /toxicology can not evaluate the safety of clinical literature summaries in subjects with CV disease, this needs to be determined by the medical officer.

The 2-week toxicity studies provided by the sponsor (to qualify the impurities) or the 13-week toxicity study (from this reviewer's literature search on L-arginine) are not sufficient to establish safety for a chronic use product with a potential safety risk in the patient population its indicated for. At present the proposed generic atovastatin calcium may not be "the same as Lipitor" based on the L-arginine being present.

Internal Recommendations:

From the pharmacology/toxicologyy point of view, the proposed levels of [redacted] (b) (4) and [redacted] (b) (4) impurities, as well as [redacted] (b) (4) impurity in the atorvastatin calcium drug product are qualified, based on submitted toxicity studies.

As far as the safety of L-arginine is concerned, pharmacology /toxicology can not determine the safety of the summary of clinical studies provided by the sponsor in subjects with CV disease from a literature search, these need to be assessed by the medical officer. The proposed generic atovastatin calcium may not be "the same as Lipitor" based on the L-arginine being present. The 2-week toxicity studies provided by the sponsor (to qualify the impurities) or the 13-week toxicity study (from this reviewer's literature search) are not sufficient to establish safety for a chronic use product with a potential safety risk in the patient population it's indicated for.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/aljuburi/TranTrang/Leigh Ann Bradford/Ripper, L
File name: ANDA 91226-10-OGD consult (atorvastatin- Matrix)

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/s/

INDRA ANTONIPILLAI
09/29/2010
Please see the internal pharmacology/toxicology recommendations.

KAREN L DAVIS BRUNO
09/29/2010

L-Arginine Safety Assessment

Background

L-Arginine (2-amino-5-guanidino-pentanoic acid) is a conditionally essential, proteinogenic α-amino acid that is a natural constituent of dietary proteins. It is not considered essential because humans can synthesize it *de novo* from glutamine, glutamate, aspartate, citrulline and proline. However, dietary intake remains the primary determinant of plasma arginine levels, since the rate of biosynthesis does not increase to compensate for depletion or inadequate supply.

Arginine can be synthesized in mammals from glutamine via pyrroline 5-carboxylate (P5C) synthetase and proline oxidase in a multi-step metabolic conversion or through several steps from the amino acids aspartate and citrulline by arginine synthase. In healthy adults with adequate protein intakes, endogenous synthesis is sufficient to meet physiologic needs.

Decarboxylation of L-Arginine by L-Arginine decarboxylase (ADC) can produce agmatine, a biogenic amine metabolite which can activate _α-1 adrenoreceptors and imidazolguanidine receptors and when infused into the renal interstitium increases glomerular filtration and tubular reabsorption. L-Arginine is also involved in protein degradation through the ubiquitin-proteasome pathway. Another biologically important pathway involves L-Arginine as the substrate of a family of enzymes named nitric oxide synthases (NO synthases, NOS). The reaction mechanism of NO synthases involves a 2-electron transfer from molecular oxygen via a number of cofactors to L-Arginine, resulting in the release of NO and L-citrulline.

L-Arginine is also the substrate for arginases, a group of enzymes that are involved in tissue repair processes and that metabolize L-Arginine to L-ornithine. Arginase I is expressed in the liver while arginase II is expressed in the kidney and macrophages. L-ornithine is the first step in the synthesis of the polyamines putrescine, spermine, and spermidine via the enzyme ornithine decarboxylase. Increased activity of this enzyme has been associated with tissue repair and cell growth and may play an important role in renal disease.

Mostly based on the aforementioned biological pathways, L-Arginine has physiologically been shown to have antiatherogenic, antiischemic, antiplatelet, and antithrombotic properties and has been demonstrated to play essential roles in the healing of wounds, removing ammonia from the body, immune function, and cell division. Moreover, L-Arginine appears to have significant effects on endocrine function mainly through effects on adrenal and pituitary secretion. In this regard, through mechanism yet to be identified, L-Arginine administration to humans and animals has been demonstrated to stimulate the release of catecholamines, insulin, glucagon, prolactin, and growth hormone (GH). Lastly, additional claims have been made for its biological effects such as increasing

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muscle mass and reducing the size of fat depots in the body, but these claims remain unproven.

There is no data available on recommended daily amount (RDA) of L-Arginine needed, but it is believed to be about 2000 mg/day. L-Arginine is present to a great extent in foods (animal protein such as beef, poultry, milk etc., seafood such as lobster, salmon, shrimp, etc. and many vegetable sources such as nuts, seeds, wheat flour, etc.). Some of the foods that contain the highest amount of L-Arginine (values per 200 calorie serving or approximately 100 g[1,2]) are:
-Sesame flour---4465 mg
-Soy protein isolate, K type ---4156 mg
-Gelatins, dry powder, unsweetened---3951 mg
-Crustaceans, Alaska King raw---3805 mg
- " Dungeness cooked---3538 mg
- " Shrimp raw---3349 mg
-Poultry, Turkey raw---2866 mg
-Pork Chops---2348 mg

In general, the relative amounts of L-Arginine in various proteins range from 3% to15%. As noted above, soy protein, peanuts, walnuts, and fish are relatively rich in L-Arginine, with ~7% of the amino acids being L-Arginine in fish and ~15% in walnuts. In contrast, cereals are protein sources that are comparatively devoid of L-Arginine, with only 3–4% of their low protein content being L-Arginine. Therefore, differing dietary habits between populations may account for differences in L-Arginine plasma levels in various parts of the world. The mean dietary intake of L-Arginine in industrialized countries is estimated to be 3-6 g/day (Visek, 1986), whereas about 5 g of L-Arginine is estimated to be ingested each day in a normal Western diet (Böger, 2007). Following oral consumption, L-Arginine is absorbed in the bowel by an active transport system, but is partly metabolized by enterocytes. It is transported to the liver through portal circulation, where additional amounts are metabolized. Peak concentration after oral administration is reached after 1-2 hours (Szczepkowski, 2006). The usual range of L-Arginine plasma levels has been determined as 81.6 ± 7.3 mmol/L in young men and 113.7 ± 19.8 µmol/L in elderly men, as compared with 72.4 ± 6.7 µmol/L in young women and 88.0 ± 7.8 µmol/L in elderly women (Böger, 2007**).**

Statement of Intent

The level of L-Arginine in Matrix Laboratory Ltd.'s 80 mg atorvastatin calcium tablets is identified as (b) (4) per tablet. The maximum recommended daily dose for atorvastatin calcium is 80 mg. Therefore, the maximum potential exposure to L-Arginine through consumption of Matrix's drug product is considered to be (b) (4) per day. This daily exposure would amount to (b) (4) of L-Arginine for a 60 kg subject. The purpose of the current document is to provide a written qualification to support the

[1] http://www.nutritiondata.com/foods-000089000000000000000.html
[2] http://www.supplementnews.org/wiki/arginine

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prescense of L-Arginine in Matrix Laboratory Ltd.'s atorvastatin product in response to the Minor Deficiency Comment Letter received from FDA dated 8/28/2009, requesting Matrix to establish and justify the safety of L-Arginine in the atorvastatin calcium drug product with particular focus on patients with cardiovascular risk.

Regulatory Approvals

Currently, there are multiple entries for Arginine within the FDAs Inactive Ingredients Database for injectable dose formulation products which allow for its presence up to 88% potency. As such, L-Arginine is known to be a component of several human injectable antibiotic products as an aid to solubilize the antibiotic. Some of these products are listed below and can be expected to be used in subjects with cardiovascular risk factors or disease.

- Azactam (aztreonam) at a level of 780 mg per gram of aztreonam
- Maxipime (cefepime) at a level of 725 mg per gram of cefepime
- Velosef (cephradine) quantity not listed.

A summary of the search results from the IIG is presented in the table below:

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IIG Database Listings[3]

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
ARGININE	IM - IV; INJECTION	74793	94ZLA3W45F	
ARGININE	IM - IV; POWDER, FOR INJECTION SOLUTION	74793	94ZLA3W45F	
ARGININE	INTRAVENOUS; INJECTABLE	74793	94ZLA3W45F	5.00%
ARGININE	INTRAVENOUS; INJECTION	74793	94ZLA3W45F	62.40%
ARGININE	INTRAVENOUS; POWDER, FOR INJECTION SOLUTION	74793	94ZLA3W45F	78.00%
ARGININE	INTRAVENOUS; SOLUTION, INJECTION	74793	94ZLA3W45F	
ARGININE	IV(INFUSION); INJECTION	74793	94ZLA3W45F	88.00%
ARGININE	IV(INFUSION); SOLUTION, INJECTION	74793	94ZLA3W45F	29.00%

L-Arginine is generally recognized as safe as per 21 CFR **§** 582.5145 for use as a nutrient and/or dietary supplement. In addition, L-Arginine is listed as an approved food additive permitted for direct addition to food for human consumption (21 CFR § 172.320) at levels up to 6.6% (percent by weight of the total protein of the finished food). Importantly, L-Arginine is also approved as an active ingredient in over-the-counter (OTC) drug products (21 CFR § 310.545) and is generally recognized as safe when used in accordance with good manufacturing or feeding practice (21 CFR §582.5145).

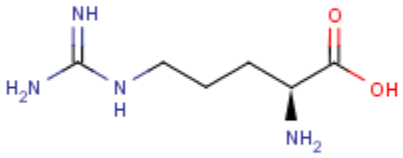
L-Arginine has been the subject of regulatory safety and toxicity assessments by the World Health Organization and is considered to be a macronutrient and a normal component of protein with no safety concern at current levels of intake when used as a flavouring agent by the Joint FAO/WHO Expert Committee on Food Additives (2004 Report TRS 928-JECFA 63/98 and Tox Monograph FAS 54-JECFA 63/435).

[3] Data Through: October 2, 2009; Database Last Updated: October 14, 2009

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Introduction

L-Arginine occurs as white crystals or as a white crystalline powder. It is soluble in water, insoluble in ether, and sparingly soluble in alcohol. It is strongly alkaline, and its water solutions absorb carbon dioxide from the air. L-Arginine's molecular formula is (C_6-H_{14}-N_4-O_2) with the following structural formula:



L-Arginine (CAS No. 74-79-3) has the following alternate names:

• (L)-Arginine • (S)-2-Amino-5-((aminoiminomethyl)amino)pentanoic acid • 1-Amino-4-guanidovaleric acid • 4-04-00-02648 (Beilstein Handbook Reference) • AI3-24165 • Arginina • Arginina [INN-Spanish] • Arginine • Arginine (VAN) • Argininum • Argininum [INN-Latin] • BRN 1725413	• CCRIS 3609 • EINECS 200-811-1 • HSDB 1429 • L-(+)-Arginine • L-Norvaline, 5-((aminoiminomethyl)amino)- • L-Ornithine, N5-(aminoiminomethyl)- • L-alpha-Amino-delta-guanidinovaleric acid • NSC 206269 • Pentanoic acid, 2-amino-5-((aminoiminomethyl)amino)-, (S)- • UNII-94ZLA3W45F

The purpose of this document is to review the available clinical safety information on L-Arginine to provide an assessment of the safe use in the proposed product in cardiovascular disease subjects. This review was based on available published and unpublished information. The published clinical information was identified through searching the internet as well as the National Library of Medicine databases (MEDLINE/TOXLINE) back to 1965. The CAS number and the generic names/synonyms were used in the database searches. The search resulted in the identification of a large number of publications including a number of review articles which include assessments of safety and efficacy in patient populations for a number of cardiovascular diseases as well as associated risk factors. Collectively, these publications demonstrate the strong acceptability of the use of L-Arginine supplementation in subjects with cardiovascular disease and indicate good tolerability at doses far exceeding the proposed limit of (b) (4) in Matrix's atorvastatin calcium drug product formulation.

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Pharmacological Role of L-Arginine and its Safety in Cardiovascular Disease:

As a precursor for syntheses of nitric oxide (NO), ornithine, proline, polyamines, creatine, agmatine and protein, and as an allosteric activator of N-acetylglutamate synthase, L-Arginine plays vital roles in nutrition and metabolism. On the basis of growth or nitrogen balance, L-Arginine is classified as an essential amino acid for birds, carnivores and young mammals, and as a conditionally essential amino acid for adults particularly at times of trauma or disease. Because NO is the endothelium-derived relaxing factor essential for regulating vascular tone and hemodynamics , there has been growing interest in the last 10 years in using L-Arginineinine to prevent and treat cardiovascular disorders, the leading cause of death in developed nations (Guoyao, 2000). In this regard, it can be utilized in therapeutic regimens for angina pectoris, congestive heart failure, hypertension, coronary heart disease, hypercholesterolemia, peripheral artery disease, systemic sclerosis, preeclampsia, intermittent claudication, myocardial infarction, vascular headaches, as well as erectile dysfunction.

In addition, L-Arginine has been studied in the treatment of HIV/AIDS, athletic performance, burns and trauma, cancer, diabetes and syndrome X, sickle cell disease, Raynaud's Phenomenon, MELAS, hereditary spherocytosis, gastrointestinal diseases, male and female infertility, interstitial cystitis, immunomodulation, senile dementia, bodybuilding, and prevention of wasting in people with critical illnesses

L-Arginine is available from various foods and naturally occurring compound with no toxic effects after taking many years. As seen from the data from different food sources **(**Fetuga, 1974**),** L-Arginine is available at a quantity greater than 50mg from each of these food servings, which is much higher than the (b) (4) present in Matrix's 80 mg atorvastatin calcium drug product formulation.

L-Arginine Reversal of Endothelial Dysfunction in Patients with Cardiovascular Risk Factors.

Epidemiologic and clinical studies over the last 50 years have established hypercholesterolemia, smoking, hypertension, diabetes, obesity/insulin resistance and advanced age as major cardiovascular risk factors, all of which are associated with impaired endothelium-dependent relaxation. Although extensive cardiovascular research has focused historically on dietary fat and cholesterol due to the recognition of their roles in atherosclerosis, studies over the last 10 years have shown the promise of using L-Arginine to reverse endothelial dysfunction associated with these major cardiovascular risk factors as mentioned below Guoyao, 2000).:.

> ***Hypercholesterolemia:*** Using the rabbit model of hypercholesterolemia, many studies have consistently shown that oral L-Arginine administration (22.5 g/L in drinking water for 10–12 wk) alleviates or completely reverses endothelial dysfunction in cerebral and coronary arteries, hind-limb microvasculature and

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thoracic aorta, and inhibits the progression of atherosclerosis. Human studies have also consistently demonstrated the beneficial effect of L-Arginine on improving endothelium-dependent relaxation in hypercholesterolemic patients

Smoking: Cigarette smoke contains a large number of oxygen-derived radicals and prooxidants, and causes endothelial dysfunction in coronary and peripheral conductance and resistance vessels, as well as in veins. The discovery that cigarette smoke extract decreases endothelial NO synthesis has provided a metabolic basis for using L-Arginine to reverse smoking-induced endothelial dysfunction in humans and animal models. Oral L-Arginine (22.5 g/L in drinking water) prevents endothelial dysfunction associated with environmental tobacco smoke in normocholesterolemic and hypercholesterolemic rabbit models. Remarkably, intravenous L-Arginine infusion (30 g over 45 min) normalizes coronary vasomotion in long-term smokers.

Hypertension: NO plays a crucial role in regulating blood pressure; thus, L-Arginine or NO deficiency results in hypertension in animals and humans. Much research has shown that intravenous or oral L-Arginine administration increases NO synthesis and prevents endothelial dysfunction in animal models of pulmonary hypertension or salt-induced hypertension. The same beneficial effect of L-Arginine has been observed in most studies involving hypertensive patients, who exhibit elevated plasma levels of ADMA and reduced NO synthesis.

Summary reviews have been previously published and established the safety and efficacy in these cardiovascular conditions (Cheng, 2001; Bode-Boger, 2006; Shao 2008).

L- Arginine in clinical trials

Based on observations from experimental clinical studies, which showed vasodilation and enhanced NO production after administration of L-Arginine, a series of clinical trials have been performed to investigate the potential of this amino acid to improve the symptoms of cardiovascular disease. The first clinical application of L-Arginine in an attempt to improve vascular function in patients with cardiovascular disease was published almost 20 years ago. Since then, there have been many studies with L-Arginine in healthy human subjects or in patients with various cardiovascular conditions.

L-Arginine has generally been well tolerated by healthy volunteers and patients when administered via the intravenous or oral route in doses <30 g. When high doses of L-Arginine are given intravenously, local irritation and phlebitis may occur because of the high osmolality of the solution.

The following trails are aimed at determining the efficacy and safety of L-Arginine administered in long- term clinical trails as summarized below.

1. Bednarz et al, 2005 examined 792 patients with acute ST-segment elevation myocardial infarction admitted within 24h after the onset of symptoms. This multicenter, randomized, double-blind, placebo-controlled study examined

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the effects of placebo or 3 grams of L-Arginine orally in capsules three times daily for a period of 30 days. The end point which was the composite of 30 day cardiovascular death, reinfarction, successful resuscitation, shock/pulmonary edema or recurrent myocardial ischemia occurred in 24% patients treated with L-Arginine and 27% with placebo. These results demonstrated a beneficial trend in patients with an acute MI while also demonstrating that 9 grams of L-Arginine orally is safe and well tolerated.

2. Gutman and colleagues (2005) studied the effects of L-Arginine supplementation 45 patients with multiple risk factors or evidence of vascular disease. The study was a randomized, double-blind assessment of 6 grams of L-Arginine or placebo daily for 6 months. The results demonstrated that L-Arginine supplementation is well tolerated and serves to reduce systolic blood pressure and increase large artery elasticity.
3. Lucotti et al, 2009 studied the effect of oral L-Arginine supplementation (6.4 grams per day) in 32 non-diabetic cardiopathic patients following aortocoronary bypass in a six month duration placebo controlled clinical trail. The results of this study conclude that L-Arginine supplementation (6.4 grams per day) in Non-diabetic cardiopathic patients improved glucose tolerance in coronary artery bypass grafted (CABG) patients; this was achieved through significant improvement of Serum Insulin (SI) levels, endothelial function. There was no added risk when L-Arginine was added in the therapy, and on the contrary there was a significant benefit as explained above.
4. Koga Y et al 2006 evaluated the effects of administration of L-Arginine in 15 young patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS) and 20 control subjects in long term study after administration of L-Arginine orally in a dose range of 4-24 g/day for at least a 24 months treatment period. The outcome of the study indicated that the frequency and severity of clinical symptoms of stroke-like episodes decreased without serious adverse effects.
5. Lerman A, et al 1998 evaluated the effects of L-Arginine supplementation in a long-term placebo controlled study after administration of L-Arginine orally 3g TID for 6 months treatment period in 26 patients without coronary artery disease (CAD). The outcome of the study indicated that the L-Arginine supplementation for 6 months in human improves coronary small vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentrations. Update
6. Hambrecht, et al 2000 evaluated the effects of L-Arginine supplementation and exercise in a short term placebo controlled study after administration of L-Arginine orally 8g/day in chronic heart failure patients with endothelial dysfunction. Forty patients were studied in a crossover fashion in 4 groups receiving L-Arginine with or without exercise and a control group without L-Arginine and exercise for 4 weeks in each period with a one week washout with each treatment. The outcome of the study indicated that the L-Arginine supplementation for 4 weeks leads to a fourfold increase in endothelium dependent vasodilatation in patients with CHF after four weeks of treatment.

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7. Martina and colleagues (2008) studied the effects of L-Arginine in 24 male subjects with hypertension and Type 2 Diabetes. The study was a randomized, double-blind, placebo-controlled study which evaluated 1200 mg of L-Arginine once daily and 600 mg n-acetylcysteine twice daily for 6 months. In this study, N-acetylcysteine and L-Arginine were demonstrated to improve endothelial function by improving NO bioavailability via a reduction of oxidative stress and increase in NO production without any adverse effects.
8. Reul et al. 2008 studied the effects of L-Arginine and vascular endothelial growth factor or placebo for 3 months in 19 severe diffuse coronary artery disease patients. Subjects were randomized in 2 X 2 factorial fashion to receive ten 200-mg injections of vascular endothelial growth factor-165 plasmid DNA or placebo in the anterior myocardium along the proximal and mid-left anterior descending arteries, plus oral L-Arginine supplementation at a dose of 6 g per day or placebo for 3 months. Patients who received the combination of vascular endothelial growth factor and L-Arginine had improved anterior wall perfusion on positron emission tomography (P=0.02), a trend toward smaller perfusion defects (P=0.10), and better anterior wall contractility (P=0.02, Kruskal–Wallis) at 3 months vs. baseline. In this study L-Arginine administration was not associated with any major adverse events.
9. The Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) published by Schulman (2006) was a single-center, randomized, double-blind, placebo-controlled trail examining the effects of L-Arginine (3g tid) or matching placebo in 153 myocardial infarction subjects for 6 months. In this study, L-Arginine added to standard postinfarct medications did not reduce noninvasive measures of vascular stiffness, improve ejection fraction, or improve clinical outcomes. Six-month clinical events, including death, myocardial infarction, and hospitalization for heart failure, occurred in 12 (16.7%) patients in the L-Arginine group compared with 7 (10.1%) patients in the placebo group. However, 6 participants (8.6%) in the L-Arginine group died during the 6-month study period vs. none in the placebo group (*P*=.01). Because of the safety concerns, the data and safety monitoring committee closed enrollment.
10. The Nitric Oxide in Peripheral Arterial Insufficiency (known as the NO-PAIN study) published by Wilson (2007) was a single center, randomized, double-blind, placebo-controlled trail examining the effects of L-Arginine (3/day) or matching placebo in 133 patients with Peripheral Artery Disease for 6 months. In this trial oral L-Arginine supplementation significantly increased plasma L-Arginine levels, however, measures of nitric oxide were reduced or not improved compared with placebo. There were 9 adverse events reported in each group that were considered serious including 1 death in both the placebo and L-Arginine, however, no group differences existed in serious or total adverse events.

In addition to studies summarized above, a large number of studies were identified in the literature examining the effects of L-Arginine in cardiovascular disease subjects. All together, 89 independent investigations were identified summarizing L-Arginine therapy in over 3000 subjects. L-Arginine was most commonly given as an oral dose formulation (solution, capsule or bar), however, several investigations administered L-Arginine via

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intracoronary, intravenous, intrabrachial artery infusion. L-Arginine exposure durations ranged from single administration to as long as 24 months. With the exception of Egashira (1996), in which patients received an intravenous infusion of 50 mg/min L-Arginine for 10 min (500 mg), all other studies had a daily L-Arginine exposure of at least 3 grams. Most commonly, doses fell into the 7-15 grams per day range, depending on the condition being treated and the maximum exposure daily exposure noted was 30 grams, although higher dosages up to 42 g/d for 6 weeks were identified in non-cardiovascular trials (i.e. cystic fibrosis and cancer). Across all studies, L-Arginine was exceptionally well tolerated.

With regard to oral administration, sample size, dosage and duration, presence of multiple active ingredients and outcome measures varied widely among studies. The most common adverse effects noted were gastrointestinal disturbance (diarrhea, upset stomach and nausea) and hypotension. However, consistent with the safety assessment and review published by Shao (2008), none of the randomized, controlled studies reviewed in the present assessment reported gastrointestinal side effects, or any other consistent adverse effects in response to oral L-Arginine supplementation considered significantly different from placebo responses.

For ease of review, the identified publications have been summarized in the table below.

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Clinical L-Arginine Trials Conducted in Cardiovascular Diseases Subjects[4]

Table-1A: L- Arginine in Subchronic Clinical Trials (Less than 12 weeks) conducted in Cardiovascular Disease.

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Adult Subjects with Hypercholesterolemia (*n*=47)	Randomized double-blind, placebo-controlled	HeartBar containing 3.3 g L-Arginine each, or a placebo bar, consumed twice daily for 2 weeks.	Showed no favorable effects on endothelial or platelet function. Baseline and follow-up levels of L-Arginine were 78.5 ± 28.2 µmol/L and 80.7 ± 26.7 µmol/L, respectively (P=0.54).	No adverse effects reported during the trial and during 2-week follow-up period.	Abdelhamed, 2003
Male Coronary Artery Disease Subjects (*n*=10)	Prospective, double-blind, randomized, placebo-controlled, crossover	Oral 7g t.i.d. for 3 days with 10 day washout period.	After oral L-Arg, compared to placebo, endothelium-dependent dilatation of the brachial artery was improved and monocyte/endothelial cell adhesion was reduced. Serum L-Arg levels were 318±18 vs. placebo levels of 124 ± 9 µmol/L, p< 0.01.	Well tolerated with no significant side-effects	Adams, 1997

[4] L-Arginine was administered orally unless otherwise specified.

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Coronary Artery Disease Subjects (*n*=25)	Randomized double-blind, placebo-controlled, crossover	6 g/24 h for 3 days with 3 day washout	Significantly increased exercise duration from 604±146 to 647±159 (s) ($p<0.03$). However, it had no effect on the sum of exercise-induced ST segment depressions (1.9±2.3 and 2.4±3.3 on and off arginine, respectively, NS	No adverse effects noted to occur with treatment.	Bednarz, 2000
Mild to Moderate CHF (NYHA II-III) Subjects (*n*=21)	Randomized double-blind, placebo-controlled, crossover	9 g /day for 7 days	Higher prolongation of exercise duration time after L-Arginine than after placebo (99 ± 106 vs. 70 ± 99 (s), $p<0.05$). There were no significant differences in markers of free radical activity.	All patients were compliant to the treatment and completed the study without side effects.	Bednarz, 2004
Patients with acute ST-segment elevation MI admitted within 24h after the onset of symptoms (*n*=792)	Multicenter, randomized double-blind, placebo-controlled	3.0 g t.i.d for 30 days (n=394)	The end point which was the composite of 30 day cardiovascular death, reinfarction, successful resuscitation, shock/pulmonary edema or recurrent myocardial ischemia occurred in 24% patients treated with L-Arginine and 27% with placebo.	The study medications were withdrawn because of adverse effects, considered to be related to the study treatment, in 9 pts in the L-Arginine group (2 hypotension and 7 GI disorders) and 10 pts in the placebo group. No serious adverse effects were observed during L-Arginine supplementation.	Bednarz, 2005
Microvascular Angina (MVA) (*n*=10)	Randomized, double-blind, placebo-controlled, cross-over	7 g bd for4 weeks. No washout phase.	Increase in exercise tolerance.	No adverse side effects.	Bellamy, 1996

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Normotensive children with chronic renal failure and endothelial dysfunction (*n*=21)	Randomized, double-blind, placebo-controlled, crossover trial	2.5 g/m^2 or 5 g/m^2 3/day for 4 weeks with a 4 week washout period.	Plasma levels rose from 82 ±20 to 179±110 µmol/L ($p < 0.001$). No improvement in endothelial function.	No adverse effects reported.	Bennett-Richards, 2002
Chronic Stable Coronary Artery Disease Subjects (*n*=18)	Randomized, double-blind, placebo-controlled, crossover trial.	9 g daily for 1 month. 1 month washout period.	L-Arginine therapy increased L-Arginine levels (mean ± SD: 70.6 ± 15.2 vs. 121.7 ± 49.4 pmol/L, $p < 0.001$) without improvement on NO-dependent vascular function.	No adverse effects reported.	Blum, 1999a
Coronary Artery Disease Patients (*n*=35)	Randomized, double-blind, placebo-controlled, crossover trial.	9 g daily for 1 month. 1 month washout period	L-Arginine significantly increased arginine levels in plasma (130±53 versus 70±17 µmol/L, $p<0.001$) compared with placebo. Did not improve NO bioavailability.	2 patients dropped out of the study during the L-Arginine treatment phase because of nausea and stomach cramps.	Blum, 2000
Congestive Heart Failure (*n*=7)	Open Label	500 mg/kg iv infusion	L-Arginine exerted no effect on contractility; however, by acting on systemic vascular resistance it improved cardiac performance. L-Arginine showed a negative chronotropic effect.	In four patients, L-Arginine infusion was not associated with side effects. In two patients, systemic hypotension continued for 2 and 3 h, respectively, after infusion. One patient with previous right bundle-branch block and Chagas' heart disease developed a transitory complete AV block.	Bocchi, 2000

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Peripheral Arterial Occlusive Disease Patients (*n*=10)	Randomized, controlled study (Prostaglandin $E_{1)}$	30 g iv over 60 minutes	L-Arginine induces NO-dependent peripheral vasodilation in patients with critical limb ischemia. Plasma arginine levels increased from 84.6±14.1 to 3780.3±380.5 µmol/L (*P*<.05)	No adverse effects reported.	Bode-Böger, 1996
Peripheral Arterial Occlusive Disease (*n*=39)	Randomized, double-blind, placebo-controlled	8 g bid by iv infusion for 3 weeks	L-Arginine improved the pain-free walking distance by 230 ± 63% and the absolute walking distance by 155 ± 48% and improved endothelium-dependent vasodilation in the femoral artery.	One subject experienced a mild allergic skin reaction of arms and legs, which was relieved using an oral antihistaminic without interrupting L-Arginine treatment.	Böger , 1998
Coronary Artery Disease (n=7) Atherosclerosis (*n*=8)	Open label	100 mg/kg oral single dose	Post occlusion hyperemic calf blood flow is restored to near normal levels following single dose administration of oral L-Arginine. There were no changes in mean blood pressure or heart rate.	No side effects were reported.	Bokelman, 1995
Obese -hypertensives (*n* =10).	Open-label	IV infusion over 30 min, 500 mg/kg total dose)	Significantly reductions in systolic and diastolic BP.	No adverse effects reported.	Castejon, 2002
Coronary Artery Disease with Stable Angina Pectoris (*n*=22)	Randomized, double-blind, placebo-controlled	2 g tid for 3 days	Increased time to maximal ST depression by 169 sec vs. 54 sec for placebo ($p < 0.04$) during exercise.	L-Arginine was well tolerated and no adverse effects of the drug were observed.	Ceremuzynski, 1997

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Severe Heart Failure (*n*=20)	Randomized, double-blind, placebo-controlled	20 g/day for 28 days	Ineffective in influencing endothelial function.	One subject developed unstable angina 3 to 4 days after commencement of the active supplement and discontinued therapy, one complained of diarrhea, nausea and malaise; one of diarrhea and stomach cramps; and another of diarrhea. Placebo reported AEs included muscle pain in the back and abdominal areas, nausea, diarrhea, and gastrointestinal upset leading to flatus.	Chin-Dusting, 1996
Hypercholesterolemic Young Adults (*n*=27)	Randomized, double-blind, placebo-controlled, crossover	7 g tid x 4 weeks with 4 week washout period.	Improved endothelial dilation.	L-arg and placebo were well tolerated with minor complaints of ↑ stool frequency and abdominal bloating in 5 subjects on L-arg and 2 subjects on placebo. 3 subjects suffered diarrhea, requiring dose reduction to 7g bid w/o unblinding and symptoms quickly resolved.	Clarkson,1996
Hypercholesterolemic (*n*=14)	Open label	IV infusion of 14 g over 20 min	Intravenous administration of L-Arginine augmented the forearm blood flow response to methacholine in the hypercholesterolemic individual.	No adverse effects reported.	Creager , 1992

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Type 2 Diabetes with Coexisting Arterial Hypertension (*n*=23)	Open label	IV infusion 100 mg/kg over 30 min	L-Arginine infusion similarly influenced renal hemodynamics in patients and reference subjects:	No adverse effects reported.	Delles, 2003
Hypercholesterolemic Patients (*n*=8)	Open label	Intra-coronary 160 µmol/min	L-Arginine restored the acetylcholine-induced increase in blood flow in patients with hypercholesterolemia.	No adverse effects reported.	Drexler, 1991
Stent Implantation Subjects (*n*=60)	Randomized, double-blind, placebo-controlled	200 mg/kg IV over 4 hours, 12 and 3 hrs before PCI, and 500 mg over 10 minutes prior to stent implantation, followed by oral 6 g/day for 14 days after PCI.	No effect on quantitative coronary angiography (QCA) and intracoronary ultrasonography (ICUS). Did not ↓ the in-stent neointimal proliferation	No adverse effects reported.	Dudek, 2002; Dudek, 2004
Angina Pectoris (*n*=8)	Open label	IV infusion of 50 mg/min for 10 min	L-Arginine significantly augmented the coronary blood flow responses to acetylcholine in patients.	No adverse effects reported.	Egashira, 1996
Hypertension (*n*=13)	Prospective trial	2g tid for 4 weeks	↓in resting SBP (from 154.8 ±26.7 mmHg to 145.8 ±12.2 mmHg, p=0.005).	No adverse effects reported.	Fragasso, 2001

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Angina Pectoris Patients (*n*=12)	Randomized, controlled, crossover	2.5 mmol/kg for 30 minutes	L-Arginine improved myocardial perfusion during exercise in a subset of patients with angina pectoris and normal coronary arteries. Exercise time was prolonged in the L-Arginine study compared with the control	SBP, DBP and HR fell gradually by 13.6 mmHg, 14.4 mmHg, and 4.8 beats/min on average, respectively. 10/12 subjects were slightly thirsty but did not have side effects serious enough to suspend administration of L-Arginine.	Fujita, 2000
Peripheral Arterial Occlusive Disease (*n*=22)	Prospective trial	IV infusion of 60 mmol/day for 7 days	Increased pain-free walking distance.	No adverse effects reported.	Gryglewski, 1995
Chronic Heart Failure (*n*=40)	Randomized, prospective controlled in-patient trial	8 g/day for 4 weeks	Improved endothelium-dependent vascular dilation	No adverse effects on heart function and physical performance indices; no other adverse effects reported.	Hambrecht, 2000
Mild to Moderate Essential Hypertension (*n*=39)	Open label	500 mg/kg intravenously over 30 min	L-Arginine infusion reduced the mean blood pressure and decreased renal vascular resistance. No effect on GFR.	The side effects associated with L-Arginine infusion were minimal. Two subjects reported slight pain on the site where the catheter was inserted.	Higashi, 1999
Essential and Secondary Hypertension (*n*=8)	Open label	IV infusion 500 mg/kg over 30 minutes	Arginine administration caused hypotension with tachycardia by reducing the total peripheral resistance in patients with essential hypertension and secondary hypertension.	No adverse effects reported.	Hishikawa, 1992

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Essential and Secondary Hypertension (*n*=16)	Open label	IV infusion 500 mg/kg over 30 minutes	Caused hypotension with tachycardia by ↓ total peripheral resistance. No changes in plasma renin activity or plasma aldostesone, noradrenaline or adrenaline.	No adverse effects reported.	Hishikawa, 1993
Mild Hypertension and Type 2 Diabetes (*n*=6)	Prospective , Crossover	Oral 3 g/h for 10 h	Arginine reduced systolic BP from 135 ± 7 to 123 ± 8 mmHg; $p < 0.05$. Diastolic BP fell from 86.9 ± 1.7 to 80.7 ± 2.4 mmHg; $p < 0.05$.	No adverse effects reported.	Huynh, 2002
Coronary Artery Disease (*n*=119)	Randomized, placebo-controlled, double-blind	L-Arginine (9 g/ day), creatinine (21 g/day), L-Arginine (9 g/day) plus creatinine (21 g/day), or placebo for 4 days	There was a 2- to 2.5-fold increase in plasma L-Arginine levels with L-Arginine supplementation. Study showed no benefit of short-term L-Arginine supplementation on vascular function in patients with stable coronary artery disease.	No adverse effects reported.	Jahangir, 2009
Hypertensive Female with Unstable Angina (*n*=1)	Open Label	62.5 mg of nitroglycerin and 30 grams L-arg HCL in a total of 312.5 ml	Chest pain and blood pressure both responded with blood pressure decreasing to 115/70 mmHg within 30 min.	No adverse effects reported.	Kaesemeyer, 1997
Female with Accelerated Hypertension (*n*=1)		40 µg/min for 4 hours	Blood pressure decreased to approximately 160/80 mmHg. She became totally asymptomatic		

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Raynaud's Phenomenon (*n*=10) Control Subjects (*n*=10)	Randomized, placebo-controlled, double-blind, crossover	8 g/day for 28 days with 28 day washout	L-Arginine had no significant effect on cutaneous vascular responses to acetylcholine or sodium nitroprusside in control subjects or patients with primary RP.	L-arg was well tolerated. L-arg was missed for 2 days in 1 control and for 3 days in 1 pt. Heartburn was experienced by 1pt during placebo treatment. During L-Arginine tx, 1 pt had nausea for 3 days, and another had mild headaches.	Khan, 1997 Veale, 1996
Systemic Sclerosis (*n*=8)	Randomized, placebo-controlled, double-blind, crossover	*8* g of L-Arginine or matching placebo for *28* days with 28 day washout	L-Arginine supplementation had no significant effect on vascular responses to acetylcholine and sodium nitroprusside.	L-Arginine was well tolerated with no adverse events except mild diarrhea for 2 days in one patient.	Khan, 1999
Heart Failure Secondary to Coronary Heart Disease (*n*=9)	Prospective, Open label	losartan 50 mg orally for 2 days. On second day, 1 hr after losartan, L-Arginine 20 g was given IV	The combination of L-Arginine and losartan seems to have superior effects on hemodynamic variables and endothelium-dependent vasodilatation compared with losartan alone.	No adverse effects reported.	Koifman, 2006
Heart Failure (*n*=5)	Randomized, double-blind, placebo-controlled, crossover	4.6 gm/day or matching placebo for 6 weeks	The mean FBF response to methacholine increased from 6.5 on placebo to 10.1 on L-Arginine (p=0.19) while the mean response nitroprusside was 8.4 on placebo and 9.4 on L-Arginine (p=0.51).	No adverse effects reported.	Kubo, 1994 (abstract only)
Essential Hypertension (*n*=35) Control subjects (*n*=17)	Randomized, double-blind, placebo-controlled	6 g m or placebo	L-Arginine improved endothelium dependent vasodilatation.	No adverse effects were noted during administration of L-Arginine or placebo.	Lekakis, 2001 Lekakis, 2002

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Young Orthotopic Heart Transplant Patients (*n*=8) Control subjects (*n*=15)	Randomized, double-blind, placebo controlled, crossover	6 g/day for 2 weeks with a 2 week washout	In OHT patients, L-Arginine significantly decreased MAP to 83±5mmHg (p=0.001, compared to baseline) and increased FMD to 11.5±1 3% (p=0.007, compared to baseline). The effect of L-Arginine on MAP was greater in OHT patients (14±2% decrease) than in control subjects (1±3%, p=0.02. No effect on left ventricular function.	One patient was unable to swallow the L-Arginine tablets, 2 were dropped because of noncompliance, and 1 patient had sudden death on placebo before initiating L-Arginine. No adverse effects reported on treatment.	Lim, 2001 Lim, 2004
Hyperlipidemia (*n*=41)	Single-blind	6–9 g/day for 2 weeks	Acetylcholine and nitro- glycerin-mediated vasodilatation significant improvement ($p < 0.05$).	None noted.	Maxwell, 1999 (Cited in Cheng, 2001)
Coronary Artery Disease and Class II or III Angina (*n*=36)	Randomized, double-blind, single crossover trial	3.3 g bid or placebo for 2 weeks with 1 month washout period.	Better brachial artery endothelial function (flow-mediated dilation), greater exercise duration on treadmill testing and higher scores on quality of life. There were no differences between the placebo and active periods in parameters of safety. There were no significant changes in values with respect to serum chemistry, hematologic or lipid levels except for a significant reduction in uric acid.	No serious adverse events were reported. 11 of 36 subjects reported minor adverse events during the active period, while 10 reported events during the placebo period. Minor adverse events included: flatulence (two active and two placebo), bowel habit change (one active, two placebo), increased chest pain or leg pain (two active), headache (one active, one placebo),	Maxwell, 2002

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
				outbreak of cold sores (one active), bloating (one active), increase in blood glucose (one active), hematochezia (one placebo), colitis (one placebo), increased fatigue (one placebo) and rash (one placebo).	
Pulmonary Hypertension (*n*=10) Heart Failure without Pulmonary Hypertension (*n*=5) Control subjects (*n*=10)	Prospective, placebo-controlled	500 mg/kg of L-Arginine by IV infusion over 30 min.	Infusion of I.-arginine reduced mean PAP and pulmonary vascular resistance (PVR).	I.-arginine produced no side effects in any of the subjects with pulmonary hypertension or the control subjects.	Mehta, 1995
Sickle Cell Disease with Pulmonary Hypertension (*n*=4)	Open label	0.1 g/kg TID for 5 days	Decrease in pulmonary artery pressure and platelet aggregation.	No adverse effects reported.	Morris, 2000 (abstract only)
Sickle Cell Disease with Pulmonary Hypertension (*n*=10)	Open label	0.1 g/kg three times a day for 5 days	Oral arginine produced a 15.2% mean reduction in estimated pulmonary artery systolic pressure (63.9± 13 to 54.2±12 mmHg, p = 0.002).	Arginine supplementation was well tolerated, and no adverse effects were reported.	Morris, 2003
Familial Hypercholesterolemia (*n*=9) Control subjects (*n*=21)	Open label	IV infusion of 25 g of L-Arginine for 30 min	No significant correlations were found between the HGH, IRI, and GLI behavior after arginine.	No adverse effects reported.	Muggeo, 1975

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Pulmonary Hypertension Patients (*n*=17)	Randomized, double-blind, placebo-controlled	1.5 g/10kg/day or placebo for 1 week	↑ serum L-citrulline, 11% ↓ in mean PAP, ↓ In total pulmonary resistance.	No adverse effects reported.	Nagaya, 2000 (abstract only)
Precapillary Pulmonary Hypertension Patients (*n*=19)	Randomized, double-blind, placebo-controlled	1.5 g/10 kg body weight/day for 1 week or placebo	Improved hemodynamics and exercise capacity; no adverse effects on cardiopulmonary capacity indices.	No other adverse effects reported.	Nagaya, 2001
Various Stage Atherosclerosis (*n*=21)	Open label	16.7 mg/kg, was administered IV over a 30-minute period.	L-Arginine reverses ACh-induced vasoconstriction in human coronary arteries in the early stages of atherosclerosis, whereas L-Arginine does not reverse the response in the advanced stage of atherosclerosis.	No adverse effects reported.	Otsuji, 1995
Essential Hypertension (*n*=12)	Randomized, double-blind, placebo-controlled, cross-over	2 g tds	Arginine significantly decreases BP levels.	No adverse effects reported.	Pagnotta, 1997 (abstract only)
Grade 2-3 Hypertensive Patients (*n*=13)	Randomized, double-blind, placebo-controlled, cross-over	2g tid for 4 weeks	L-Arginine significantly improved angina class, systolic blood pressure at rest, and quality of life.	Oral L-Arginine was well tolerated by all subjects, and no side effects related to the drug were reported.	Palloshi, 2001 Palloshi, 2004

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Hypertension (*n*=14) Control subjects (*n*=12)	Prospective, single-blind, controlled study	Brachial artery infusion of 10, 20, 40, 80,and 160 µmol/min for 5 min or 40 µmol/min for 20 min	L-Arginine did not significantly change basal blood flow or vascular resistance in either group.	No adverse effects reported.	Panza, 1993
Stable Angina Pectoris (*n*=14)	Randomized, placebo-controlled, crossover study	700 mg 4x/day or placebo were administered four times daily during a period of transdermal nitroglycerin therapy for 5 to 10 days	During continuous TD-GTN, the administration of L-Arginine increased Treadmill walking time at 4 h and 24 h after patch application.	No adverse effects reported.	Parker, 2002
Essential Hypertension (*n*=20)	Randomized, placebo-controlled	2g tid for 6 weeks or placebo	Reduced systolic BP by 14 mm Hg wk and diastolic BP by 8 mm Hg; $p < 0.05$	No adverse effects were reported.	Pezza, 1998
Cardiac Syndrome X (*n*=9) Control subjects (*n*=14)	Randomized, placebo-controlled	IV 0.125 g/min for 120 minutes or saline	L-Arginine infusion increased basal forearm blood flow, nitrite and nitrate (NOx), and forearm cGMP release and decreased endothelin-1.	No adverse effects were reported.	Piatti, 2003

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Heart Failure (*n*=18)	Randomized, double-blind, placebo-controlled, crossover	20g or placebo 14 day washout	I.-arginine produced marked sustained elevation of plasma levels of I.-arginine (fourfold at 60, 120, and 180 min) inpatients with heart failure,vasodilation responses to acetylcholine were only transiently improved.	No adverse effects were reported.	Prior, 2000
Obese Hypertensive Patients (*n*=20)	Prospective, placebo-controlled	3g/day or placebo for 4 weeks	We observed tendency to decline of TNF-α levels in patients treated with L-Arginine but there was no significant difference.	No adverse effects reported.	Pupek-Musialik, 2002 (abstract only)
Stable Coronary Artery Disease Patients with Exercise-induced ST-segment Depression (*N*=22)	Prospective, double-blind, cross- over	5 mg/kg/min x 20 min	Forearm blood flow increased with both L- and D-arginine (33% ± 6% and 38% ± 7%, respectively, $p < 0.001$). Acetylcholine-mediated forearm vasodilation also improved with both L- and D-arginine ($p < 0.0001$).	No adverse effects reported.	Quyyumi, 1998
Heart Failure (*n*=17)	Randomized, double-blind, placebo-controlled, crossover	5.6–12.6 g/day for 6 weeks	L-Arginine significantly increased forearm blood flow during forearm exercise and overall functional status	One patient experienced diarrhea during the placebo period. Two patients, one in each treatment period, had acute episodes of gout during the trial.	Rector, 1996
Hypertriglyceridemic Patients (*n*=33)	2-arm, randomized, double-blind	6-week run-in phase, 6 weeks of treatment with L-Arginine 1.5 g bid or placebo and a 6-	L-Arginine alone had no effects on serum lipids compared to placebo. The combination of L-Arginine with simvastatin led to a significantly stronger reduction in	No adverse effects were noted on L-Arginine treatment. L-Arginine helps reduce adverse effects to simvastatin.	Schulze, 2009

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
		week extension period where simvastatin (20 mg qd) was added.	triglycerides compared to placebo plus simvastatin.		
Male Peripheral Arterial Occlusive Disease Patients (*n*=14)	Prospective, placebo controlled	IV infusion of 12.6g over 3hrs for 7 days	In both limbs a statistically significant increase in the ankle-arm pressure ratio and improvement of impaired blood flow was achieved after the infusions L-ARG, but not after the placebo infusions.	No adverse effects were reported.	Slawinski, 1996
47 year old Male Patient with Hereditary Spherocytosis with complaints of recurrent chest pains and gradually progressive dyspnea. (*n*=1)	Case Report	warfarin (international normalized ratio 2–4), aspirin 100 mg daily and L -arginine orally at a dose of 100 mg/kg 3 times daily for 4 weeks	Reassessment after 4 weeks of treatment with L -arginine showed normalization of ECG right ventricular repolarization abnormalities, a decrease in right-sided pressures and pulmonary vascular resistance.	No adverse effects.	Smedema, 2007
Sickle Cell Disease (*n*=6) Acute Chest Syndrome (*n*=5)	Phase II	0.025 g/kg/dose Q8hr for 3 days	Increased NO levels.	No side effects.	Styles, 2002

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Peripheral Arterial Occlusive Disease Patients with hyperhomocysteinemia (*n*=27)	Double-blind, placebo-controlled	oral treatment with combined B vitamins (folate, 10 mg; vitamin B-12, 200 mg; vitamin B-6, 20 mg/day), L-Arginine (24 g/day) or placebo, for 8 weeks	L-Arginine treatment did not affect homocyst(e)ine levels, but significantly improved endothelial function in these patients.	No adverse effects.	Sydow, 2003
Mildy Hypertensive Type 2 Diabetic Volunteers (*n*=6)	Randomized, placebo-controlled	3 g/hr starting at 4 AM until 2 PM on day 2 or day 3	Oral arginine reduced BP in all subjects (13 point reduction).	Arginine was well tolerated with no adverse effects reported	Tayek, 1999 (abstract only)
Hypercholesterolemic Subjects (*n*=5)	Open-label	three capsules four times daily (for a total daily dose of 8.4 g arginine hydrochloride, equivalent to 7.0 g L-Arginine), for 2 weeks	Arginine treatment resulted in a 38% decrease in monocyte adhesiveness.	No adverse effects reported.	Theilmeier, 1997
Hypercholesterolemic Subjects (*n*=10) Control Subjects (*n*=6)	Double-blind, placebo-controlled, randomized		An absolute reduction of 53% in MNC binding.		

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Hypercholesterolemic Subjects (*n*=9) Smokers (*n*=9) Insulin-dependent Diabetes Mellitus (*n*=9) Control Subjects (*n*=9)	Randomized, double-blind, placebo-controlled	0.1 g/kg intravenously over 20 min.	Acetylcholine-induced vasodilation smokers: ↑ from 2% to 3.1% ($p = 0.02$); hypercholesterolemic pts ↑ from 1.9% to 4.1%.($p = 0.03$); control pts: 6.9% to 6.7% (p =NS); diabetic pts: 1.8% to 2.2% (p = NS).	No subject had side effects after the L-Arginine or placebo infusions.	Thorne, 1998
Coronary Artery Disease and Stable Angina (*n*=24)	Open label	Intracoronary infusions of normal saline, L- and D-arginine (50 and 150 µmol/min for 8 minutes)	During L-Arginine infusion a larger proportion of complex stenoses than smooth stenoses dilated by > 10% ($p < 0.01$), and the magnitude of dilatation was greater at the site of complex stenoses ($p < 0.05$).	No adverse effects reported.	Tousoulis, 2001
Infants with Persistent Pulmonary Hypertension (*n*=10) Control Infants (*n*=8)	Prospective	IV infusion 2.5 g/kg/24 h	Increased plasma arginine concentrations.	No adverse effects reported.	Vosatka, 1994
Stable Angina (*n*=40)	Randomized, double-blind parallel-group, placebo-controlled	15 g/day or placebo for 2 weeks	No benefits for endotheliumdependent vasodilation, oxidative stress or exercise performance.	One subject in the L-Arginine group developed unstable angina and was admitted for percutaneous angioplasty; a second subject in the placebo	Walker, 2001

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
				group was unable to complete the study, because of a viral illness. No other adverse effects were observed.	
Hypercholesterolemia Patients (*n*=9)	Randomized, double-blind, placebo-controlled	IV infusion of 16 g. in 50 ml saline over 20 min	Plasma levels of Arginine were raised significantly. Maximal working capacity, indices of myocardial ischemia, and basal and post-occlusive blood flow in the skin or forearm did not differ between the treatments.	No adverse effects noted.	Wennmalm, 1995
Hypercholesterolemic (*n*=16)	Randomized, placebo-controlled, crossover	12g/d for 3 week with 1 week washout period	L-Arginine changed cardiac output (-0.4 L/m), diastolic BP (-1.9 mm Hg), pre-ejection period (-3.4 ms), and plasma homocysteine (-2.0 umol/L) ($P \leq 0.03$).	No adverse effects were noted during administration of L-Arginine or placebo.	West, 2005 Likos, 2003
Hyperlipidemia (*n*=23) Control Subjects (*n*=14)	Randomized, double-blind, placebo-controlled	8.4 g/d or placebo for 2 weeks	Platelet reactivity is increased in hypercholesterolemic patients compared control subjects. L-Arginine supplementation modestly attenuates platelet aggregation, although the magnitude of this effect varies significantly among individual patients. The inhibitory effect of L-Arginine on platelet aggregation persists for at least 2 weeks after discontinuing arginine supplementation.	L-Arginine was well tolerated without objective evidence of side effects by patient reports or physical examination. However, one patient complained of slight nausea while taking L-Arginine.	Wolf, 1997

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Stable Coronary Artery Disease (*n*=31)	Single center, randomized, active controlled (vitamin C), crossover, open-label	10 g L-Arg/day or 500 mg vitamin C for 4 weeks (28 d) with 2 week washout period	Oral L-Arginine supplement improved endothelial function and reduced LDL oxidation in stable CAD patient.	The adverse events diagnosed as possibly, probably or related were considered as treatment-related adverse events. No deaths were reported and there were no treatment discontinuations or interruptions due to adverse ----- events. One SAE (muscle sprain) was reported in pt approx. 2 weeks after vitamin C tx. The treatment-related adverse events after Larginine treatment were frequent bowel movements (5 patients, 15.2%), epigastralgia (1 patient, 3%), atypical chest pain (1 patient, 3%) and increased glucose levels (1 patient, 3%).	Yin, 2005
Male Congestive Heart Failure Patients (*n*=50)	Prospective, randomized, double-blind, Parallel-group, placebo-controlled	6 g/day of L-Arginine or placebo for 1 week.	Increased exercise duration, forearm blood flow and flow mediated dilation and decreased exercise-induced constriction of brachial artery.	No adverse effects reported.	Yousufuddin, 2001

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Table-1B: L- Arginine in Long- term Clinical Trials conducted in Cardiovascular Disease.

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Coronary Artery Disease with Intractable Angina Pectoris (*n*=10)	Prospective, case-controlled, pilot study	9 g daily for 3 months.	Seven patients improved clinically (from angina pectoris functional class IV to functional class II); One patient improved to functional class III, and 2 patients remained in functional class IV.	No one reported side effects from the L-Arginine.	Blum, 1999
Hypertension (*n*=10)	Open label	14-21g/day for 3 months	Chronic oral administration of L-Arginine restored plasma L-Arginine/ADMA ratios to those seen in NC subjects and was associated with the normalization of mononuclear cell adhesiveness.	No adverse effects reported.	Chan, 2000
Severe Diffuse Coronary Artery Disease (*n*=19)	Randomized, placebo-controlled	6 g/day for 3 months in combination with 200µg VEGF	Improved post surgical anterior wall perfusion and contractility on PET (p=0.02)	No adverse effects reported.	Chan, 2007
Multiple Risk Factors or Evidence of Vascular Disease (*n*=45)	Randomized, double-blind, placebo-controlled	6 grams/day for 6 months	SBP decreased from 144.62 ± 19.98 to 133.21 ± 16.12 mmHg ($p< 0.007$). Large artery elasticity (LAEI) increased from 10.03 to 12.76 ± 3.48 ml/mmHgx10 ($p< 0.0001$).	No adverse effects reported.	Gutman, 2005; Shargorodsky, 2006 (abstract only)

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
MELAS (*n*=24) Control subjects (*n*=72)	Prospective, placebo-controlled	4- 24 g of L-Arginine for 18 months	L-Arginine infusions significantly improved all strokelike symptoms, suggesting that oral administration within 30 minutes of a stroke significantly decreased frequency and severity of strokelike episodes.	No adverse effects occurred except for headache when L-Arginine was infused too rapidly in two patients.	Koga, 2005 Koga, 2007
MELAS (*n*=15) Control subjects (*n*=20)	Prospective, controlled	4- 24 g of L-Arginine for at least 24 months	The frequency and severity of symptoms caused by the stroke were decreased dramatically.	No adverse effects reported.	Koga, 2006
Coronary Angiography as Result of Recurrent Chest Pain (*n*=26)	Randomized, double-blind, placebo-controlled	3 g TID for 6 months	Coronary blood flow in response to acetylcholine in the subjects who were taking L-Arginine increased compared with the placebo group (149±20% versus 6±9%, P<0.05).	One patient from each group discontinued the study secondary to minor gastrointestinal side effects.	Lerman, 1998
Cardiopathic Nondiabetic Patients after an Aortocoronary Bypass (*n*=32)	Randomized, double-blind, placebo-controlled	6.4 g/day or placebo for 6 months	L-Arginine decreased asymmetric dimethylarginine levels (P<0.01), indices of endothelial dysfunction, and increased cyclic guanosine monophosphate (P<0.01), L-Arginine to asymmetric dimethylarginine ratio (P< 0.0001), and reactive hyperemia (P< 0.05).	No adverse effects were noted during administration of L-Arginine or placebo.	Lucotti, 2009

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Male Hypertension and Type 2 Diabetes (*n*=24)	Randomized, double-blind, placebo-controlled	L-Arginine (ARG) 1,200 mg once daily and *N*-acetylcysteine (NAC) 600 mg bid for 6 months	NAC and ARG improve endothelial function in hypertensive patients with type 2 diabetes by improving NO bioavailability via reduction of oxidative stress and increase of NO production.	No adverse effects were noted during the treatment. There was one dropout in each group, both not for medical reasons.	Martina, 2008
Peripheral Arterial Disease (*n*=41)	Randomized, double-blind, placebo-controlled study with open label extension	3 g/day, 6 g/day, or placebo for 2 weeks Open label 6 g./day for 10 weeks	Pain-free walking distance increased 66% while the total walking distance increased 23% in the group taking 6 g/day. The general and emotional/social functioning components of the SF-36 also improved. These effects were not observed in the 3g/day and placebo groups. There were no differences between the placebo and Tx groups in parameters of safety. There were no significant changes in values with respect to serum chemistry, and hematologic or lipid levels	No serious adverse events were reported during the 10-week intervention. Minor adverse events included dry mouth, which was reported by two subjects in the 6g/day group. One subject in the Placebo Group reported a change in bowel habits.	Maxwell, 2000

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Severe Diffuse Coronary Artery Disease (*n*=19)	Randomized, placebo controlled	6 g per day or placebo for 3 months	Patients who received the combination of vascular endothelial growth factor and L-Arginine had improved anterior wall perfusion on positron emission tomography (P=0.02), a trend toward smaller perfusion defects (P=0.10), and better anterior wall contractility (P=0.02, Kruskal–Wallis) at 3 months vs. baseline.	L-Arginine was not associated with major adverse events.	Ruel, 2008
Myocardial Infarction (*n*=153)	Single-center, randomized, double-blind, placebo-controlled	3 g tid or matching placebo for 6 months.	The VINTAGE MI study demonstrated that 6 months of L-Arginine added to standard postinfarct medications did not reduce noninvasive measures of vascular stiffness, improve ejection fraction, or improve clinical outcomes.	Six-month clinical events, including death, myocardial infarction, and hospitalization for heart failure, occurred in 12 (16.7%) patients in the L-Arginine group compared with 7 (10.1%) patients in the placebo group. 6 participants (8.6%) in the L-Arginine group died during the 6-month study period vs. none in the placebo group (*P*=.01). Because of the safety concerns, the data and safety monitoring committee closed enrollment.	Schulman, 2006 (VINTAGE MI)

Study Population	Design	L-Arginine Dosage/Duration	Notes	Noted Treatment Emergent Adverse Events	Reference
Hypertriglyceridemic Patients (*n*=33)	2-arm, randomized, double-blind	6-week run-in phase, 6 weeks of treatment with L-Arginine 1.5 g bid or placebo and a 6-week extension period where simvastatin (20 mg qd) was added.	L-Arginine alone had no effects on serum lipids compared to placebo. The combination of L-Arginine with simvastatin led to a significantly stronger reduction in triglycerides compared to placebo plus simvastatin.	No adverse effects were noted on L-Arginine treatment. L-Arginine helps reduce adverse effects to simvastatin.	Schulze, 2009
Hypercholesterolemic Subjects (*n*=10)	Prospective, open label	IV 10 or 30 g oral 5 or 7 g 12-week period of oral L-Arginine administration 14-21 g/day	There were no significant changes in peak plasma L-Arginine concentrations or in the AUC0-8 after oral and intravenous doses during subsequent visits.	No adverse effects were reported during intravenous infusion of L-Arginine.	Tangphao, 1999
Pregnant Hypertensive Subjects (*n*=7)	Prospective, open-label	1.5 -2.5g/day from 13th week of pregnancy	Bp was reduced >15 mmHg in 3 subjects. All subjects born healthy children.	No adverse effects reported.	Zdebski, 1995 Zdebski, 1996

Assessment of Risk

The level of L-Arginine in Matrix Laboratory Ltd.'s 80 mg atorvastatin calcium tablets is identified as (b) (4). The maximum recommended daily dose for atorvastatin calcium is 80 mg. Therefore, the maximum potential exposure to L-Arginine through consumption of Matrix's drug product is considered to be (b) (4) This daily exposure would amount to (b) (4) of L-Arginine for a 60 kg subject.

In a recent risk assessment published in Regulatory Toxicology and Pharmacology by Shao and Hathcock (2008), an observable safe level (OSL) was derived on the basis of all available published controlled trials in both healthy subjects as well as subjects with a wide variety of disease states. The authors concluded based on the available data at the time of review, that the evidence for the absence of adverse effects is strong for L-Arginine at intakes up to 20 grams per day. The authors noted that much higher levels of L-Arginine had been tested without adverse effects and may be also be safe but using appropriate uncertainty factors based on a variety of factors including sample size, trial design, completeness of study reporting, variation within the human population in healthy as well as patients with common disease states for which the amino acid is likely to be used, that a value of 20 grams per day was a conservative and balanced value. This publication and risk assessment has subsequently been utilized as the sole basis for a recent GRAS Notification for Arginine submitted to FDA in May of 2008 for its use as a food additive (Hibbert, 2008). This OSL of 20 grams per day is (b) (4) times greater than the potential daily ingestion amount from the prescribed use of the Matrix 80 mg atorvastatin calcium product.

The current risk assessment is consistent with that described by Shao and Hathcock (2008) in their assessment. Based on the facts available on use of L-Arginine as a food supplement in variety of disease conditions and especially in cardiovascular diseases, L arginine has been shown to be safe in humans. The beneficial effects of L- arginine up to the dose of 6.4 g/day in many long term clinical trials in cardiovascular diseases as mentioned above and its safety was never in question in any of these trials. In fact, even if one was to extend the level of uncertainty factors and come to an even more conservative conclusion of an OSL of 6 grams per day the potential daily exposure from consumption of the Matrix product formulation would still be on the order of (b) (4) times less. Moreover, the amount of L-Arginine contained within the Matrix product is far less then the level found in common foods and the amounts given parenterally in FDA approved drug products to sick patients with bacterial infections and orally to patients with acute MI

It is concluded, based on the results of the studies and reviews presented herein, that the proposed level of L-Arginine in the Matrix Laboratories Ltd's 80 mg atorvastatin calcium generic equivalent is safe for use independent of cardiovascular disease status.

Reference ID: 2926976

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/s/

LINDA M FORSYTH
04/01/2011

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MATRIX

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To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
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Gratuitous CMC Amendment

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. This amendment provides for increase in the intended commercial batch size for Atorvastatin Calcium Tablets, 10 mg and 20 mg strengths (to be same as that proposed for 40 mg and 80 mg strengths). The proposed increase in batch size is (b) (4) of the (b) (4) employed for exhibit batch. As such, all strengths i.e. 10 mg, 20 mg, 40 mg and 80 mg now will have same (b) (4) batch size. As discussed earlier with the Agency and approved in several submissions for IR products, this has been considered as an acceptable scale-up approach. This proposal is being submitted to have flexibility in meeting the expected commercial requirements. Please note, there is no change in the manufacturing process or operating principle of the equipments. As a result of change in batch size, the equipment capacities and consequential process parameters have been proposed, which shall be finalized during manufacturing process validation studies. Please refer to the comparison tables below.

Comparison of exhibit and proposed commercial batch size

Strength	Exhibit batch size		Intended Commercial batch size (Originally proposed)		Intended Commercial batch size (New proposal)	
	Kg	Units	Kg	Units	Kg	Units
(b) (4)						(b) (4)
10 mg						
20 mg						
40 mg						
80 mg						

Comparison of equipments

Operation	Exhibit batch	Intended commercial batch		Comment
		Originally proposed	New proposal	
[redacted]				(b) (4)

Through this amendment Matrix is also submitting revised intended batch manufacturing records for Atorvastatin calcium tablets 40 mg and 80mg. Although there is no change in batch scale for these strengths, in-process weight variation limits (for all strengths) have been tightened to allow weight variation based on theoretical target tablet weight instead of observed batch-specific average weight, as given below.

Strength	Individual weight variation limit
10 mg	[redacted] (b) (4)
20 mg	
40 mg	
80 mg	

The revised batch manufacturing records with proposed changes is provided in **section 3.2.P.3.3.**

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

for

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Tel : 91-40-27700363, 66327722, Fax : 27700343
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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

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On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
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Date: March 7, 2011

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
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Metro Park North VII
7620 Standish Place,
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QUALITY MINOR AMENDMENT

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to quality review comments dated February 25, 2011, during review of the subject ANDA of Matrix Laboratories Limited, India (Matrix). In this amendment we respond fully to all of the comments. For each item, we first restate the question **(in bold)** and then present our response. It may please be noted that some of the comments presented in subject communication (dated Feb 25, 2011) had been provided to Matrix through an email and have been responded as a telephone amendment on March 01, 2011. For ease of Agency's review, the same comments, responses and data have been presented in this amendment also.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

S. Wayne Tall for KG

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

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RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: March 1, 2011

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Telephone CMC Amendment

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to CMC review comments (received through e-mail) dated February 23, 2011, during review of the subject ANDA of Matrix Laboratories Limited, India (Matrix). In this amendment we respond fully to all of the questions. For each item, we first restate the question **(in bold)** and then present our response.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

for

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

For KG

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
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Intellectual Property

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Consult No: 2011-0499

TO: *(Division/Office)*	FROM:
OGD/Medical Officer	Mark Gonitzke/Leigh Ann Sears/Susan Zuk

DATE:	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/28/2011		091226	Amendment	9/29/2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Atorvastatin Calcium	30 days	Lipid Lowering	3/30//2011

NAME OF FIRM Matrix Labs LTD

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE 11 MEETING
- ☐ RESUBMISSION SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(Specify Below)* Impurity Medical Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL BIOPHARMACEUTICS
- ☐ IN VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS

The Division of Chemistry is requesting a consult for Atorvastatin (generic version of Lipitor). The product contains (b) (4) of L-aginine per tablet as a (b) (4) Since this ingredient exceeds the IIG level and is not found in the RLD, we sent a Pharm/Tox consult to OND toxicologists to receive an opinion on the safety of the ingredient at the level proposed. Pharm/tox was not able to evaluate the safety of the clinical literature summaries in subjects with Cardiovascular disease and advised to seek medical consult. The Tox review is in DARRTs (9/29/2010 submit date) and the firm's response is also in DARRTS (Quality Response 4/8/2010, see TOC link 3.2, P.1.2). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when checked into DARRTs.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY (Check one)
Mark Gonitzke	☒ MAIL e-mail ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

Reference ID: 2911454

CC: ANDA

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
02/28/2011

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
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Intellectual Property

QUALITY DEFICIENCY - MINOR

ANDA 091226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Matrix Laboratories Limited

TEL: (304) 554-5899

ATTN: Keith Giunta

FAX: (304) 285-6407

FROM: Mark Gonitzke

FDA CONTACT PHONE: (240) 276-8422

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendments dated November 18 and December 14, 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 ____ 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*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

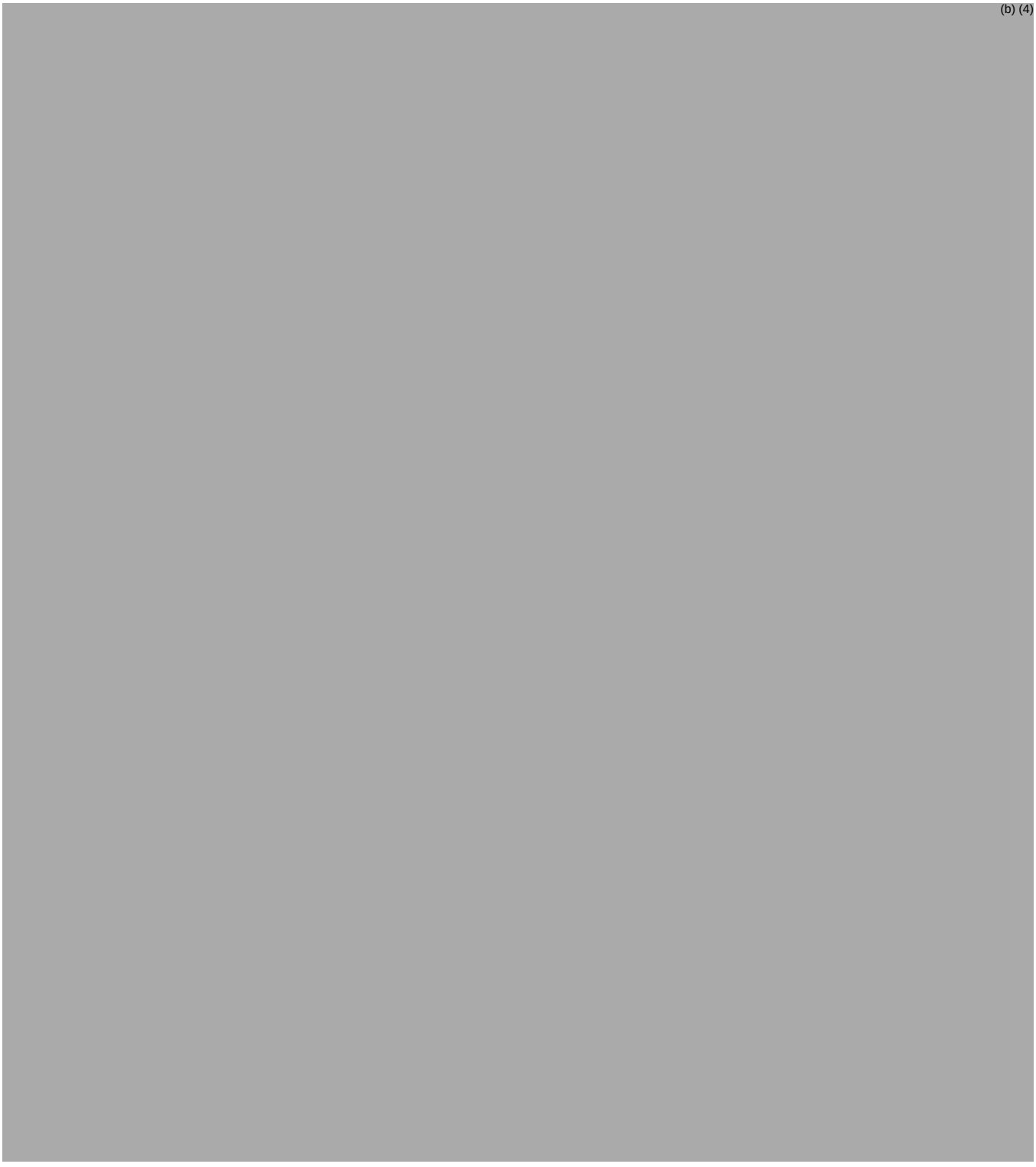
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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

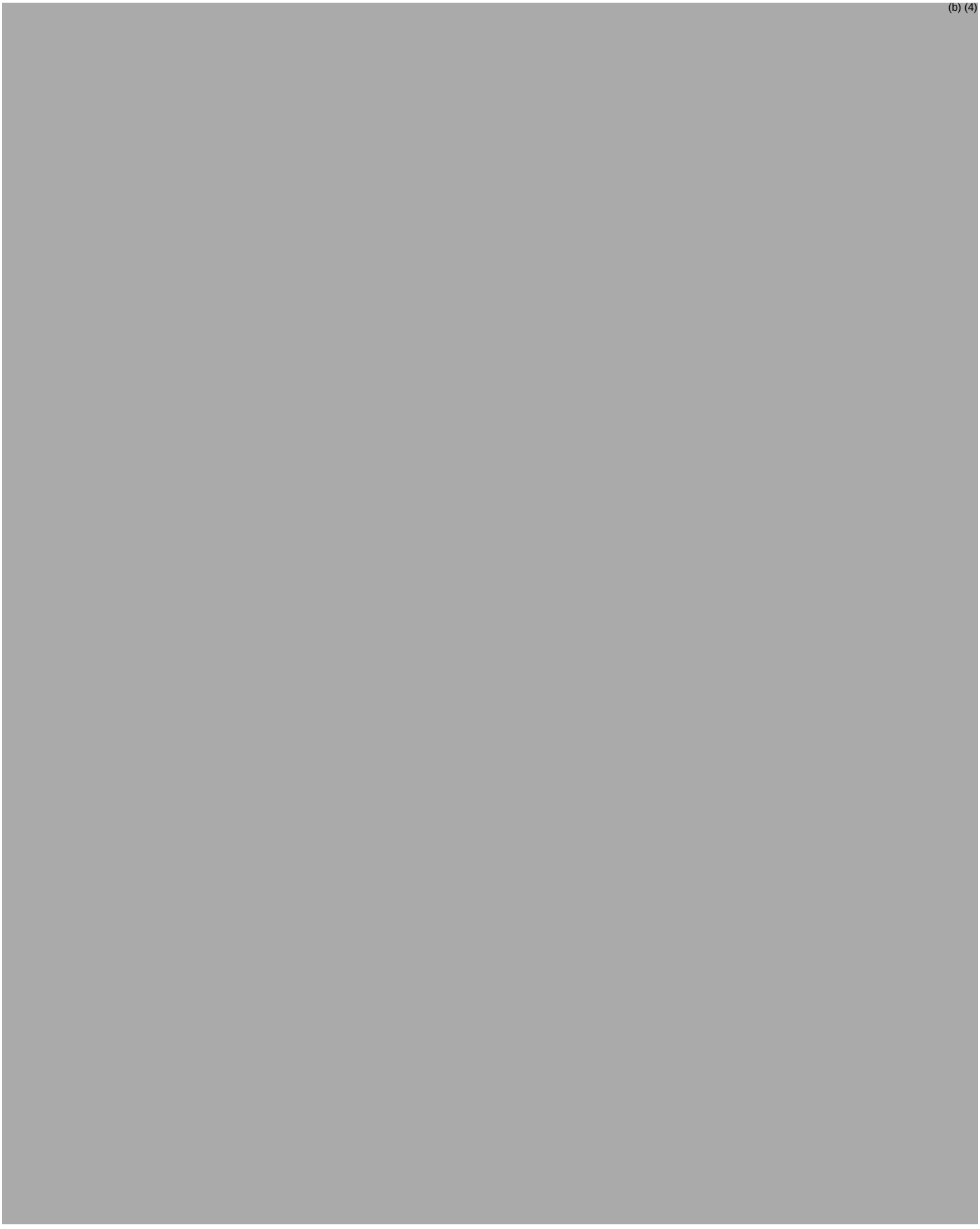
ANDA: 091226 **APPLICANT:** Matrix Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)




(b) (4)



B. Please acknowledge and respond to the following comments:

1. Please provide up to date long-term stability data for drug product.

2. The Pharm/Tox consult for L-arginine in this product was not definitive. Based on comments from the Pharm/Tox reviewer, we have submitted your data package to our Clinical Staff for an opinion. We await the outcome of this consult.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

SUSAN ZUK
02/25/2011

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

February 23, 2011

GENERAL CORRESPONDENCE

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG
ANDA 091226
(Submission of General Correspondence dated February 22, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. On February 22, 2011, correspondence was submitted to your attention by Hyman, Phelps and McNamara, P.C. on behalf of Mylan regarding the 180-day exclusivity status for this product. The purpose of this submission is to provide a copy of the February 22, 2011 correspondence directly to our ANDA.

This correspondence is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President, Regulatory Affairs
Mylan Pharmaceuticals Inc.
US Agent, Matrix Laboratories Limited India

SWT/dn

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
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Keith Webber, Ph.D., Acting Director
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RE: ATORVASTATIN CALCIUM TABLETS,
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ANDA # 091226

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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 (b) (4), (b) (5) (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

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
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February 1, 2011

GENERAL CORRESPONDENCE

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RE: ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG
ANDA 091226
(Submission of General Correspondence dated January 31, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. On January 31, 2011, correspondence was submitted to your attention by Hyman, Phelps and McNamara, P.C. on behalf of Mylan regarding the 180-day exclusivity status for this product. The purpose of this submission is to provide a copy of the January 31, 2011 correspondence directly to our ANDA.

This correspondence is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President, Regulatory Affairs
Mylan Pharmaceuticals Inc.
US Agent, Matrix Laboratories Limited India

SWT/dn

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

Dear Dr. Webber:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were and remain correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. 7,790,197) by the holder of the referenced drug (Lipitor®), which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 7,790,197 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. This patent expires October 14, 2025.

In addition, pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95, Matrix certifies it has, at the time of the filing of this amendment, given notice to each owner of the patent which is the subject of the certification, or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patent. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice. Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend its application to provide documentation that the notifications sent to the patent owner(s) and application holder have been received.

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

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January 26, 2011

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
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ANDA # 091226

PATENT AMENDMENT

Dear Dr. Webber:

Reference is made to the above referenced ANDA as well as Matrix Laboratories Limited's ("Matrix") August 12, 2009 patent amendment in which Matrix notified FDA that suit had been filed against Matrix within the statutory 45 day period in connection with Matrix's previously filed Paragraph IV certifications contained in Matrix's ANDA. Reference is also made to Matrix's January 5, 2011 ANDA correspondence, in which Matrix requested that FDA determine that Ranbaxy is not eligible for 180-day exclusivity with respect to Ranbaxy's ANDA for Atorvastatin Calcium Tablets if Ranbaxy's ANDA is covered by the Application Integrity Policy that FDA has imposed against Ranbaxy.

The purpose of this amendment is to advise FDA that, as provided in the attached press release, Matrix has entered into a settlement agreement with Pfizer, and as a result, the above referenced suit will be dismissed on or around June 28, 2011, making Matrix's ANDA 091226 immediately eligible for final approval upon expiration of the pediatric exclusivity of U.S. Patent Nos. 5,273,995 and RE40667 on June 28, 2011.

Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg immediately upon completion of the regulatory review process and immediately upon the June 28, 2011 expiration of the pediatric exclusivity associated with U.S. Patent Nos. 5,273,995 and RE40667.

Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod MMC

Sandeep K. Rathod
Intellectual Property



« Previous Release

January 25, 2011

Mylan Announces Lipitor® Settlement Agreement

PITTSBURGH, Jan. 25, 2011 /PRNewswire/ -- Mylan Inc. (Nasdaq: MYL) today announced that it has entered into a settlement agreement with Pfizer Inc. which will resolve litigation related to Lipitor® Tablets, 10 mg, 20 mg, 40 mg and 80 mg, known generically as Atorvastatin Calcium Tablets. The terms of the agreement are confidential, and the agreement itself is subject to review by the U.S. Department of Justice and the Federal Trade Commission.

Lipitor had U.S. sales of $7.27 billion for the twelve months ending Sept. 30, 2010, according to IMS Health.

Mylan Inc. ranks among the leading generic and specialty pharmaceutical companies in the world and provides products to customers in more than 140 countries and territories. The company maintains one of the industry's broadest and highest quality product portfolios supported by a robust product pipeline; operates one of the world's largest active pharmaceutical ingredient manufacturers; and runs a specialty business focused on respiratory, allergy and psychiatric therapies. For more information, please visit www.mylan.com.

This press release includes statements that constitute "forward-looking statements," including with regard to the settlements and the marketing of the products. These statements are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Because such statements inherently involve risks and uncertainties, actual future results may differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to: any legal or regulatory challenges to one or both settlements; strategies by competitors or other third parties to delay or prevent product introductions; risks inherent in legal and regulatory processes; and the other risks detailed in the company's periodic filings with the Securities and Exchange Commission. The company undertakes no obligation to update these statements for revisions or changes after the date of this release.

SOURCE Mylan Inc.

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MATRIX

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Sandeep K. Rathod

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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January 6, 2011

GENERAL CORRESPONDENCE

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG
ANDA 091226
(Submission of General Correspondence dated January 5, 2011)

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. On January 5, 2011, correspondence was submitted to your attention by Hyman, Phelps and McNamara, P.C. on behalf of Mylan regarding the 180-day exclusivity status for this product. The purpose of this correspondence is to submit a copy of the January 5, 2011 correspondence directly to our ANDA.

This correspondence is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President, Regulatory Affairs
Mylan Pharmaceuticals Inc.
US Agent, Matrix Laboratories Limited India

SWT/dn

cc: Elizabeth H. Dickinson, Esq, Office of Chief Counsel, FDA
David T. Read, Esq., Office of Generic Drugs, FDA

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Sincerely,

On behalf of Matrix Laboratories Limited

Sandeep K. Rathod

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 091226

U.S. PATENT NO. 7,790,197
PARAGRAPH IV CERTIFICATION

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Keith Webber, Ph.D., Acting Director
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7620 Standish Place
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ANDA # 091226

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Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D., Acting Director
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7620 Standish Place
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ANDA # 091226

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Keith Webber, Ph.D., Acting Director
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Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: December 14, 2010

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Minor CMC Amendment

Subject: ANDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to CMC review comments dated August 03, 2010, during review of the subject ANDA of Matrix Laboratories Limited, India (Matrix). In this amendment we respond fully to all of the questions. For each item, we first restate the question **(in bold)** and then present our response.

Kindly note, Matrix had recently submitted a gratuitous CMC amendment dated November 17th, 2010 wherein information on revised drug substance controls complying with recently published USP monograph and also in line with the DMF holders' amended controls were submitted. Also, information on a newly characterized impurity (b) (4) impurity) with supporting characterization/qualification data, analytical validation data, revised finished product controls and available (b) (4) months long-term stability data was submitted for Agency's review. Few of the Agency's comments dated August 03, 2010 were already addressed in this gratuitous amendment. The same is referenced in the response wherever applicable.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

MATRIX

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1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Sincerely,
For Matrix Laboratories Limited, India

for ----------

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
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Date: December 6, 2010

To:
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620, Standish Place,
Rockville Maryland 20855-2810

Telephone Labeling Amendment

Subject: ANDA # 091226, Atorvastatin Calcium Tablets,
10 mg, 20 mg, 40 mg and 80 mg

Dear Dr. Webber:

Reference is made to the Abbreviated New Drug Application (ANDA) of Matrix Laboratories Limited, India and to the Agency's correspondence dated September 20th, 2010.

Reference is also made to telephone discussion dated October 4th, 2010 between Ms. Ann Vu of FDA and Mr. Keith Giunta of Mylan Pharmaceuticals Inc. (U.S. Agent for Matrix Laboratories Ltd.) regarding a gratuitous labeling that was submitted on August 12th, 2010 and to Agency's comments dated September 20th, 2010. Kindly note that Matrix had also submitted a gratuitous labeling amendment dated September 14th, 2010 for revising the drug substance description to be consistent with the Chemistry, Manufacturing and Controls section of the application.

Per the Agency's correspondence dated September 20th, 2010 the container and patient information sheet submitted by Matrix on August 12th, 2010 were acceptable and the comments were only for the insert with respect to the Section headings under 'Full Prescribing Information: Contents". However based on the October 4th, 2010 discussion it was concluded that Matrix's labeling was acceptable as submitted and that Matrix need not respond with any revised labeling.

MATRIX

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For Matrix Laboratories Limited, India

for

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Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

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Date: November 17, 2010

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Gratuitous CMC Amendment

Subject:A NDA # 091226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80mg

Dear Dr. Webber:

Reference is made to subject ANDA of Matrix Laboratories India (Matrix) which is currently under review. Reference is also made to a DMF amendment dated 16th August, 2010 wherein the DMF holder amended DMF in accordance with Agency's comments.

This gratuitous CMC amendment provides for following:

1. Revised drug substance controls complying with recently published USP monograph and also in line with the DMF holders' amended controls ;
2. Information on a newly characterized impurity ((b) (4) impurity) with supporting characterization/qualification data, analytical validation data, revised finish product controls and available (b) (4)-months long-term stability data ;

Revised Drug Substance Controls:

In this amendment, we are providing revised drug substance controls complying with the USP monograph of Atorvastatin Calcium and also inline with the DMF holders' amended controls as provided in DMF amendment (See below).

1. Inclusion of "Identification test for Calcium (By AAS)" in line with the USP monograph ;
2. Tightening of the residual solvents limits ;

A comparison (between USP & Matrix) of specifications of Atorvastatin Calcium is presented in table below for the ease of Agency's review.

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Kindly note, Matrix shall continue to follow its in-house developed and validated methods for analysis of Assay and Related substances. The existing related substance method which is part of the original submission is able to quantify all the impurities (USP listed & non-USP). A copy of the addendum validation report demonstrating specificity for Assay method and addendum validation report for related substance method to cover additional USP Related compound C is enclosed in **Section 3.2.S.4.3.** A copy of the USP method equivalence report for assay and related substances method is enclosed in **Section 3.2.S.4.3.** Said report summarizes the results of assay and related substances data for three batches of Atorvastatin Calcium using both USP and in-house methods. The results demonstrate that both the methods are equivalent.

Specifications:
(Only those tests where Matrix differs from USP monograph have been presented with explanation. All other tests are in line with USP)

Tests	Specifications		Comment
	Matrix	USP	
Heavy metals	NMT (b) (4) ppm	NMT 20ppm	(b) (4)
Impurities (USP listed)			
Atorvastatin related compound A	NMT (b) (4) %	NMT 0.3%	
Atorvastatin related compound B	NMT %	NMT 0.3%	
Atorvastatin related compound C	NMT %	NMT 0.3%	
Atorvastatin related compound D	NMT %	NMT 0.1%	
Impurities (Non-USP)			
(b) (4)	NMT (b) (4) %	NMT (b) (4) %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	(b) (4) % - (b) (4) %	

* The limits for non-USP impurities are based on the available trend and in line with the ICH guidelines. According to the USP, General Notices, interpretation of significant figures reporting, a limit of 0.1 % would actually translate into an operational limit of up to 0.14%.

@ Note that USP monograph provides for both trihydrate form and (b) (4) form. Matrix manufactures (b) (4) form of Atorvastatin calcium (b) (4) . Matrix controls polymorphism through (b) (4) in specifications.

In CMC response dated April 08, 2010, Matrix had adopted for enantiomeric purity method as provided in the proposed USP monograph. However, Matrix discovered during suitability study validation that USP method lacks adequate resolution between the peaks of interest. A concern regarding this has been communicated to the Scientific Liaison of USP (Elena Gonikberg). In view of the problem encountered with USP method, Matrix (b) (4) method and has fully validated the same. A copy of the validation report is enclosed in **Section 3.2.S.4.3.** A

MATRIX

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copy of the revised drug substance specifications and test method is enclosed in **Section 3.2.S.4.1** and **3.2.S.4.2** respectively. Owing to addition of few tests in the drug substance specifications and based on current site practice, the outside testing plan has been updated. A copy of the revised outside testing plan is enclosed in **Section 3.2.P.3.1.** The revised plan proposes use of Matrix Unit-8, Matrix Unit-11 and (b) (4) in addition to those proposed in the original submission. cGMP information and related certifications for these newly proposed labs are enclosed in **Section 3.2.P.3.1.** All these sites have had satisfactory USFDA inspections in past.

Newly Characterized impurity in DP specifications ((b) (4) impurity)

Matrix is updating the ANDA with information regarding an impurity at RRT (b) (4) which crossed the qualification threshold during the stability studies of the product[1] and was characterized and qualified accordingly. The finished product specifications have been revised to include this impurity (at RRT (b) (4)) identified as (b) (4) impurity.

A report explaining the characterization of (b) (4) impurity, its degradation pathway and also addressing safety of (b) (4) impurity at proposed level is provided in **Section 3.2.P.5.6.** Based on well reported literature, (b) (4) impurity is an (b) (4) in the (b) (4) of atorvastatin to (b) (4) and (b) (4) impurities. Complete qualification for (b) (4) and (b) (4) impurities has been performed by Matrix and is part of this ANDA (Data provided in amendment dated 8th April, 2010 in response to Agency's comments dated 28th August 2009).

The drug product assay and related substances method have been validated for (b) (4) (b) (4) impurity and a copy of the supplemental analytical validation report is enclosed in **3.2.P.5.3.** Matrix has included this impurity in the specification with a limit of NMT (b) (4)% in release (based on observed release result of (b) (4)%) and (b) (4)% in shelf life respectively (based on observed release result of above (b) (4)%). A copy of the revised finished product specification and test procedure is enclosed respectively in **Sections 3.2.P.5.1** and **Section 3.2.P.5.2.** (b) (4) s a (b) (4) that has been used in analytical validation studies is also provided in **section 3.2.P.6**

An updated (b) (4)-months long-term stability data for exhibit batches is enclosed in **Section 3.2.P.8.3.** Kindly note, In view of inclusion of a new impurity (b) (4), the interpretation of stability data has been done again. As a consequence, there are changes in the earlier reported values of highest unknown and total impurities. The data fully complies with the proposed shelf-life specifications.

[1] The batch that triggered characterization is an exhibit batch used for submission to TPD, Canada, different from USANDA batch. Atorvastatin tablets developed by Matrix for US and Canada have same composition and the USANDA batch is also part of ANDS submitted to TPD as TPD requires two exhibit batches.

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This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

MATRIX

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Date: November 8, 2010

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North VII
7620, Standish Place,
Rockville MD 20855-2810

Bioequivalence SOPs

Bioequivalence Response to Information Request

Subject: ANDA 091226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Dr Webber:

Reference is made to bioequivalence comments dated September 07, 2010 received upon review of subject ANDA of Matrix Laboratories Limited, India. In this amendment, we fully respond to all of the questions. We first restate the question **(in bold)** and then provide our response.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

for

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited, India

Signed off in DARRTS on 9/29/10

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 91-226

Date of submission: 4/8/10. OGD is requesting the pharmacology /toxicology consult on the impurities in the atorvastatin calcium drug product under ANDA 91-226.

Review Number: 2 (Previous consult on this ANDA wa signed off in DARRTS on 6/16/2009

Drug Names: Atorvastatin Calcium, 10, 20, 40, 80 mg tablets.

Consult #: 20009-0443 for atorvastatin calcium tablets.

Consult from: Leigh Ann Bradford, and Trang Tran.
Request date: 8/10/2010

Generic drug name: Atorvastatin calcium tablets.
Drug class: Statins (generic atorvastatin). **Indication**: Lipid lowering.

Type of document: Electronic submission dated 4/8/10.

Subject of Consult: OGD is requesting a pharmacology/toxicology consult because the impurities listed are higher than the RLD (see submission 8/4/10 in EDR, module 3). Sponsor has provided number of toxicity studies to qualify the impurities in the drug product. Additionally, they have provided justification for use of the inactive ingredient L-Arginine, in the current drug product. L-Arginine is present at doses of (b) (4) in the sponsor's 80 mg dosage form atorvastatin calcium tablets. Note that in the previous consult review (see DARRTs), we recommended that the sponsor establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), which may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use here ((b) (4)).

The consult comments are stated below:

OGD is requesting a Pharm/Tox Review. "Impurities listed are higher than the RLD." Please evaluate the amendment ANDA in EDR Module 3 (see attached documents for reference). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Bradford, HFD-617 (Leigh.bradford@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.

Division: Division of Metabolic and Endocrinology products.

Review completion date: 9/17/10.

Introduction

OGD wants us to review the proposed levels of impurities in the drug product which are higher than RLD in the abbreviated NDA (ANDA) 91-226 (Matrix laboratories, Inc). OGD wants us to review the completed studies submitted in the support of higher impurities in the drug product and to provide information if they are acceptable.

Following information is provided on the impurities in the drug substance and the drug product
Impurities information:

(b) (4)

Impurities control in Drug Substance ATORVASTATIN CALCIUM

TEST	RESULTS		SPECIFICATION
	AC0090408 (DS Manufacturer)	1004608 (DP Manufacturer)	
Related Substances (by HPLC)			

(b) (4)

Impurities control in Drug Product
Impurities limit in Finished Product Specification- Atorvastatin Calcium Tablets, 10 mg, 20, 40 and 80 mg.

Test	Specification	
	Release	Shelf life
Related Substances (by HPLC)		

(b) (4)

Chemical names of the impurities:

(b) (4)

The firm submits 3 reports for (b) (4) impurity for DP specification (b) (4)% for release and (b) (4)% for stability).

1. Bacterial Reverse Mutation Test Report (b) (4) impurity (93 page)
2. In Vitro Mammalian Chromosome Aberration Test Report (b) (4) impurity (93 page)
3. 14-Day repeated dose oral toxicity study by Gavage in wistar rats- (b) (4) impurity (373 page)

The firm submits 2 reports for (b) (4) and (b) (4) Impurities for DS and DP specification (see attached for specification).

1. Baterial Reverse Mutation Assay for Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) (b) (4) and (b) (4)% (b) (4) Impurities of Atrovastatin (89 page)
2. In Vitro Mammalian Chromosome Aberration Test Report for Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atrovastatin (129 page)

The firm submits 1 report for L-Arginie Safety Assessment.

1. L-Arginine Safety Assessment (47 page).

Additionally, sponsor has submitted a 2-week toxicity study of atorvastatin calcium drug product containing (b) (4) and (b) (4) impurities.

Following toxicity studies have been conducted to support the impurity (b) (4) and (b) (4) (b) (4) impurities in the atorvastatin calcium drug product.

1. A 2-Week Oral Toxicity Study of atorvastatin calcium containing atorvastatin (b) (4) (b) (4) impurity in Rats (Study No. Tox 037-003)

The purpose of this study was to qualify atorvastatin (b) (4) and atorvastatin (b) (4) (b) (4) impurities in the atorvastatin drug product at the (b) (4) and (b) (4)% level, respectively. The study

Study no: Tox 037-003
Volume #, and page #: eCTD submission dated 8/4/10

Conducting laboratory and location: (b) (4)

Date of study initiation: 8/28/09
GLP compliance: Yes
QA report: yes (X) no ( )

Drug lot #, and % purity:

Drug without impurity

6.1.1. Test Articles

Identification	Atorvastatin Calcium
Lot Number	AC0160708
Assigned Testing Facility ID	09001E
Purity	(b) (4)%
Receipt Date	21-Jul-2009
Expiration Date	31-Oct-2009

Drug with impurity: The impurities present were atorvastatin (b) (4) and (b) (4) impurities; the lot numbers were similar for both products, but receipt dates were different. It is not clear how these two were different; analytical description is provided below. Note that the sponsor states that the atorvastatin (b) (4) impurity is present at concentration of (b) (4)% and atorvastatin (b) (4) impurity is present at concentration of (b) (4)% (relative to atorvastatin calcium drug product), see the foot note below in the Experimental design Table.

Identification	(b) (4) impurity
Lot Number	ADL/941(149)/1008
Assigned Testing Facility ID	09001F
Purity	(b) (4)%
Receipt Date	21-Jul-2009
Expiration Date	None provided

Identification	(b) (4) impurity
Lot Number	ADL/941(149)/1008
Assigned Testing Facility ID	090037
Purity	(b) (4)%
Receipt Date	28-Aug-2009
Expiration Date	None provided

ANALYTICAL DESCRIPTION

PRODUCT: (b) (4) Impurity	CONTROL NUMBER: ADL/941(149)/1008

(b) (4)

PRODUCT: (b) (4) Impurity	CONTROL NUMBER: ATC/IMP/918/118

(b) (4)

Methods (unique aspects):

Doses in administered units: 0, 40, 80 mg/kg/day with and without impurities were administered to rats (male and female Sprague Dawley Crl:CD{SD}, 9 weeks of age, BWs of males were 325-379 g; females were 207-256 g).

Groups 3 and 5: The Atorvastatin Calcium and (b) (4) impurity were combined at ratios of (b) (4) ((b) (4) impurity to Atorvastatin Calcium). Since this ratio already provided an approximate (b) (4) impurity concentration of (b) (4)% relative to Atorvastatin Calcium, additional (b) (4) impurity was not required to be added to the preparation.

The dose levels were selected based on information found in the summary basis of approval for atorvastatin calcium (Lipitor®; NDA 20-702) in an attempt to produce graded responses to the test article while preserving large multiples of the human daily exposure potential. The high-dose level was expected to produce some toxic effects, but not excessive lethality that would prevent meaningful evaluation and represents approximately (b) (4) the maximum human dosage on a body surface area basis (mg/m^2). The low-dose level was expected to produce no observable indications of toxicity.

Experimental design Table below

Experimental Design

Group No.	No. of Toxicity Animals		Test Material	Atorvastatin Dose Level (mg/kg/day)	Atorvastatin Dose Concentration (mg/mL)	Atorvastatin Dose Volume (mL/kg)	Atorvastatin Adjusted Dose Concentration[a] (mg/g^b)
	Male	Female					
1	10	10	(b) (4)% CMC	0	0	10	0
2	10	10	Atorvastatin Calcium	40	4	10	4.136
3	10	10	Atorvastatin Calcium + impurities[c,d]	40	4	10	4.136
4	10	10	Atorvastatin Calcium	80	8	10	8.272
5	10	10	Atorvastatin Calcium + impurities[c,d]	80	8	10	8.272

[a]Expressed as (b) (4) concentration. Correction factor o (b) (4) applied (based on (b) (4)
[b]The dose concentrations were based on an approximate density of 1 g/mL.
[c]The (b) (4) impurity was adjusted by (b) (4) for purity.
[d]The Atorvastatin Calcium and (b) (4) impurity was combined at a ratio o (b) (4) (b) (4)% concentration of (b) (4) impurity relative to Atorvastatin Calcium). This provided an approximate (b) (4) impurity concentration of (b) (4)% relative to Atorvastatin Calcium.

Formulation/vehicle: 1% carboxymethylcellulose in reverse osmosis deionized water. Dosing volume was 10 ml/kg.

Methods and results are described below.

The following variables and end points were evaluated in this study: clinical signs, body weights, body weight changes, food consumption, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), gross necropsy findings, organ weights, and histopathologic examinations.

Gross pathology: At sacrifice.
Organs weighed: Following organs were weighed as shown in the Table below.

Adrenal gland[a]	Prostate gland
Brain	Salivary gland[a]
Epididymis[a]	Seminal vesicle[a]
Heart	Spleen
Kidney[a]	Testis[a]
Liver	Thymus
Lung	Thyroid gland with parathyroid gland[a]
Ovary[a]	Uterus
Pituitary gland	
[a]Paired organ weight.	

Histopathology: This was performed at sacrifice in control and high dosed animals in organs listed in histopathology Table below.

Tissue Collection and Preservation

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic[b]
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland[c]
Bone marrow smear[a]	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired)[b]	Skin (inguinal)
Harderian gland (paired)	Spinal cord (cervical, thoracic, lumbar)
Heart	Spleen
Intestine, cecum	Stomach (nonglandular and glandular)
Intestine, colon	Testis (paired)[d]
Intestine, duodenum	Thymus
Intestine, ileum with Peyer's patch[c]	Thyroid gland (paired)
Intestine, jejunum	Tongue
Intestine, rectum	Trachea
Kidney (paired)	Urinary bladder
Liver	Uterus
Lung	Vagina
Lymph node, mandibular	Gross lesions/masses
Lymph node, mesenteric	

[a]Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).
[b]Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.
[c]Examined only if present in the routine section.
[d]Preserved in modified Davidson's fixative and then transferred to 10% neutral buffered formalin.

Results:

Mortality: No treatment related mortality was observed.

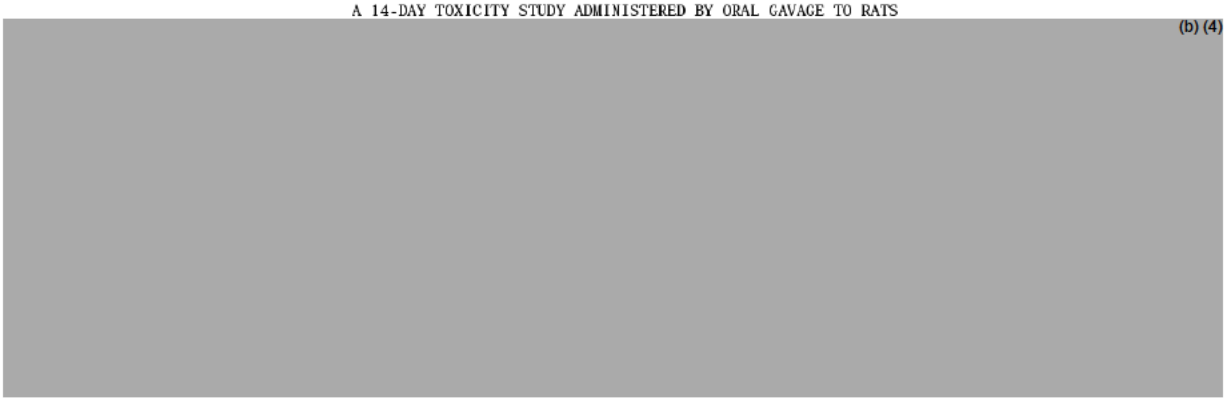
Clinical signs: No drug related effects were observed.

Body weights: Body weight gains were higher in females with both products on days 8-14 with impurities (4,10, 9 g at 0, 40, 80 mg/kg/day respectively) and without impurities (4, 10, 8 g respectively). Since the sponsor did not include the RLD in this study, it is not clear if this is unique to the current drug product. Sponsor states the following on BW changes:

A single statistically significant decrease in mean body weight changes was noted in the 40 mg/kg/day atorvastatin calcium (with impurities)-treated males during the Day 8 to 14 body weight interval; however, in the absence of a dose response, this change was not considered toxicologically meaningful.

A 14-DAY TOXICITY STUDY ADMINISTERED BY ORAL GAVAGE TO RATS

(b) (4)



A 14-DAY TOXICITY STUDY ADMINISTERED BY ORAL GAVAGE TO RATS

(b) (4)



Food consumption: Food consumption (FC) was not affected

Hematology: Hematological parameters such as hemoglobin was increased at a high dose in males with the drug without impurities (14.7, 15.3, 15.9* g/dl at 0, 40, 80 mg/kg/day respectively, *p<0.05) and at all doses with impurities (14.7, 15.4*,15.6* g/dl respectively, *p<0.05). Similar observation were noted for hematocrit values. Since the sponsor did not include the RLD in this study, it is not clear if this is unique to the current drug product.

Sponsor below states that basically similar hematological findings were noted with both products, (the drug with or without impurities).

Atorvastatin calcium and atorvastatin calcium (with impurities)-related changes were observed in mean red cell mass, platelets, and white blood cell counts in males when compared to the controls. There were no test article-related changes noted in females.

Slight, dose-dependent increases in erythrocytes, hemoglobin, and hematocrit were noted across all test article-treated males. The atorvastatin calcium (with impurities)-treated groups were less affected than the atorvastatin calcium only groups; increases in red cell mass up to 7% and 9% were observed in atorvastatin calcium (with impurities)-treated males and atorvastatin calcium only males, respectively. In addition, slight increases in platelets were evident at 80 mg/kg/day in both atorvastatin calcium-treated groups (with and without impurities); increases up to 16% and 17% were noted, respectively.

Increases in mean leukocytes (49%), lymphocytes (49%), monocytes (78%), and basophils (4-fold) were evident in 80 mg/kg/day males treated with atorvastatin calcium only. The increases observed were approximately 2-fold greater than the 80 mg/kg/day atorvastatin calcium with impurities group.

Statistically Significant Differences in Hematology and Coagulation Parameters

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	Erythrocytes	Group 2 ↑	8.24	7.84	7.040-9.660
			Group 4 ↑	8.54		
			Group 5 ↑	8.42		
		Hemoglobin	Group 3 ↑	15.4	14.7	13.40-17.70
			Group 4 ↑	15.9		
			Group 5 ↑	15.6		
		Hematocrit	Group 2 ↑	45.1	42.9	37.80-48.10
			Group 3 ↑	44.9		
			Group 4 ↑	46.3		
			Group 5 ↑	45.0		
		Platelets	Group 4 ↑	1273	1085	737.0-1403.0
			Group 5 ↑	1262		
		Leukocytes	Group 4 ↑	13.79	9.27	4.80-17.72
		Lymphocytes	Group 4 ↑	11.05	7.40	3.53-13.99
		Monocytes	Group 4 ↑	0.66	0.37	0.10-0.89
		Basophils	Group 4 ↑	0.04	0.01	0.00-0.10
Females	15	Hemoglobin	Group 3 ↑	14.8	14.1	12.90-16.90
Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4) Group 4 (80 mg/kg/day) Group 5 (80 mg/kg/day, (b) (4)						

(b) (4)

SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

(b) (4)

(b) (4)

(b) (4)

SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

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SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

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SUMMARY OF HEMATOLOGY AND COAGULATION DATA (b) (4)

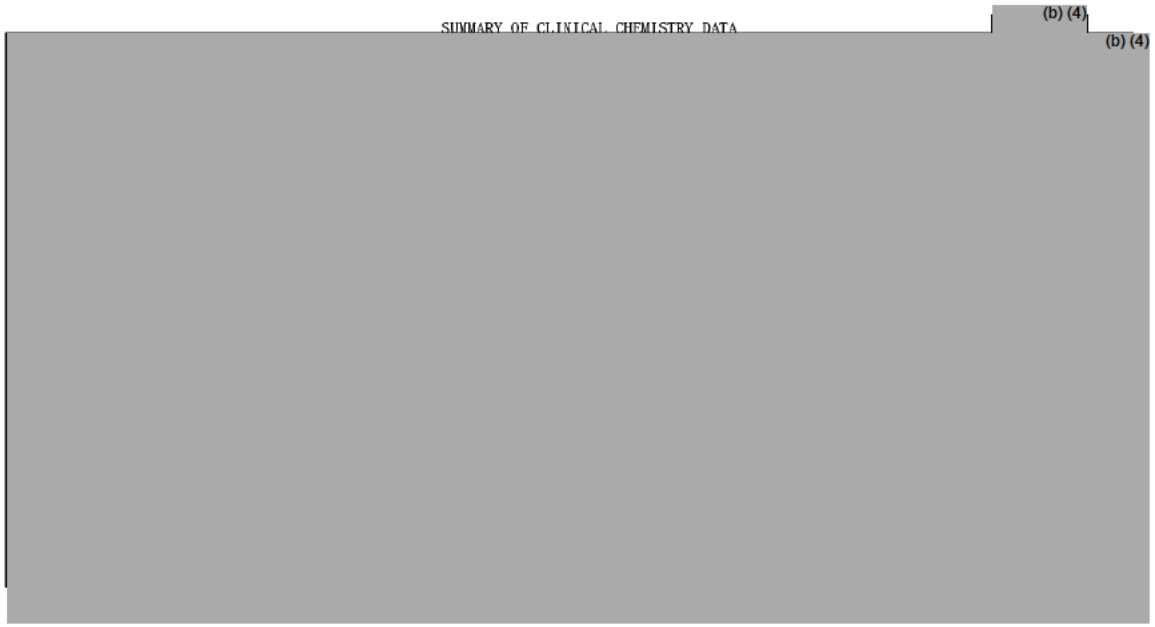
(b) (4)

Clinical chemistry: In general similar drug related effects were observed on clinical chemistry parameters. For example ALT was increased in males at all doses with both drugs (without impurities, the values were 27, 53*,177* IU/L at 0, 40, 80 mg/kg/day respectively, *p<0.05); with impurities the values were 27, 62*, 89* IU/L at 0, 40, 80 mg/kg/day respectively, as seen below

Atorvastatin calcium and atorvastatin calcium (with impurities)-related changes were observed in mean AST, ALT, alkaline phosphatase, serum GGT (males only), total bilirubin, total protein, and globulin. Males appear to be affected more than females.

Dose-dependent increases in ALT were observed in the 40 and 80 mg/kg/day groups. Increases up to 3-fold and 6-fold were noted in the atorvastatin calcium only and atorvastatin calcium with impurities groups, respectively. Increases in mean AST, alkaline phosphatase, and total bilirubin were noted in both groups treated at 80 mg/kg/day; greater differences from control were evident in the atorvastatin calcium only group (up to 4-fold) compared to the atorvastatin calcium with impurities group (up to 2-fold) and were more pronounced in males. ALT, AST, alkaline phosphatase, and total protein are consistent with previous studies conducted in rats with atorvastatin. Increases (up to 10-fold) were noted in mean serum GGT in 40 and 80 mg/kg/day males treated with atorvastatin calcium only and were noted to be within the Testing Facility's historical control range.

Decreases in mean total protein and globulin were evident in males in both groups treated at 80 mg/kg/day (atorvastatin calcium alone or in combination with two impurities) and in 80 mg/kg/day females treated with atorvastatin only. For males, the differences from control were comparable between the groups (up to 7 % and 9% in atorvastatin calcium only and atorvastatin calcium with impurities-treated groups, respectively). Correlating increases (up to 9%) in A/G ratio were noted.



SUMMARY OF CLINICAL CHEMISTRY DATA (b) (4)

(b) (4)

[redacted]

Statistically Significant Differences in Clinical Chemistry Parameters

Sex	Day	Parameter	Group	Statistically Significant Value	Concurrent Control Value	Historical Control Normalized Range
Males	15	AST	Group 4 ↑	368	87	50.0-126.0
			Group 5 ↑	198		
		ALT	Group 2 ↑	53	27	18.0-41.0
			Group 3 ↑	62		
			Group 4 ↑	177		
			Group 5 ↑	89		
		ALK Phosphatase	Group 4 ↑	197	138	49.0-196.0
			Group 5 ↑	226		
		GGT, Serum	Group 4 ↑	0.29	0.03	0.000-0.470
		Total Bilirubin	Group 4 ↑	0.18	0.11	0.090-0.190
			Group 5 ↑	0.15		
		Cholesterol	Group 4 ↑	54	38	33.0-95.0
		Triglyceride	Group 3 ↓	39	42	30.0-119.0
			Group 5 ↓	30		
		Total Protein	Group 5 ↓	5.21	5.49	5.190-6.460
		Globulin	Group 5 ↓	2.40	2.64	2.340-3.360
Females	15	ALT	Group 4 ↑	81	24	15.0-97.0
			Group 5 ↑	72		
		Globulin	Group 4 ↓	2.58	2.86	2.280-3.350
		A/G Ratio	Group 4 ↑	1.17	1.09	0.980-1.440
		Phosphorus	Group 3 ↓	7.14	7.76	3.950-7.870

Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4) Group 4 (80 mg/kg/day)
Group 5 (80 mg/kg/day, (b) (4))

Urinalysis: No drug related effects were observed.

Organ weights: In female rats, liver weights were increased at 80 mg/kg/day with impurities (8.3* vs 7.6 g g in control, *p<0.5, by 8%), not seen with the drug without impurities (7.9 vs 7.6 g in controls)

Statistically Significant Differences in Organ Weights

Sex	Day	Organ	Absolute Weight	Relative to Body Weight	Relative to Brain Weight
Males	Day 15	Liver	--	Group 2 ↓	--
		Kidneys	--	Group 3 ↑	--
		Epididymides	--	Group 4 ↑	--
Females	Day 15	Liver	--	Group 5 ↑	--
Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4) Group 4 (80 mg/kg/day) Group 5 (80 mg/kg/day, (b) (4))					

Gross pathology: The findings in general were similar with both products as shown below in the Table.

Gross (Internal) Necropsy Findings for Main Study Animals

Sex	Day	Finding	Group 1	Group 2	Group 3	Group 4	Group 5
Males	15	Kidney – dilated pelvis	--	--	--	--	1/10
		Kidney – discoloration pale	--	--	1/10	--	--
		Kidney cortex, roughened surface	--	--	1/10	--	--
		Mandibular lymph node, enlarged	--	--	1/10	--	1/10
		Nonglandular stomach, thickened	--	--	1/10	--	--
		Thymus – discoloration dark	1/10	--	--	1/10	--
		Thymus – foci dark	1/10	--	--	--	--
Females	15	Kidney – discoloration pale	--	--	1/10	--	--
		Mandibular lymph node, discoloration dark	--	--	--	1/10	--
		Ovary – periovarian cyst(s)	--	--	--	--	1/10
		Thymus – foci dark	--	--	--	1/10	--
		Thyroid – small	--	1/10	--	--	--
Group 1 (0 mg/kg/day) Group 2 (40 mg/kg/day) Group 3 (40 mg/kg/day, (b) (4) Group 4 (80 mg/kg/day) Group 5 (80 mg/kg/day, (b) (4))							

Histopathology: Histopathology findings in the liver were generally comparable with the drug without and with impurities, as seen below.

	Placebo	Without Impurity		With Impurity	
Doses (mg/kg/day)	Zero	40 m/k/d	80 m/k/d	40 m/k/d	80 m/k/d
Liver, single cell necrosis: **Males**	M=0/10	3/10	10/10	3/10	10/10
Liver, single cell necrosis: **Females**	F=0/10	1/10	5/10	0/10	2/10

Minimal to mild necrosis of individual hepatocytes (single cell necrosis) was noted in the livers of all 80 mg/kg/day atorvastatin calcium and atorvastatin calcium (with impurities)-treated males, five 80 mg/kg/day atorvastatin calcium-treated females, and two 80 mg/kg/day atorvastatin calcium (with impurities)-treated females. This liver change was also present in three males each in 40 mg/kg/day atorvastatin calcium and atorvastatin calcium (with impurities)-treated groups and in one 40 mg/kg/day atorvastatin calcium female, but was not present in 40 mg/kg/day atorvastatin calcium (with impurities) females. These liver changes are consistent with previous studies conduct in rats with atorvastatin[8].

A 14-DAY TOXICITY STUDY OF ATORVASTATIN CALCIUM ADMINISTERED BY ORAL GAVAGE TO RATS
Incidence of Histopathologic Findings for All Study Animals (continued)
Table: 1

PROJECT NUMBER: FMA46A SPECIES: RAT

Tissue/ Diagnosis/ Modifier(s)	Group 1		Group 2		Group 3		Group 4		Group 5	
	M	F	M	F	M	F	M	F	M	F
KIDNEY (continued)										
DEGENERATION/REGENERATION, TUBULAR	5	3	0	0	0	0	1	1	2	3
UNILATERAL, MINIMAL	4	3	0	0	0	0	1	1	2	2
BILATERAL, MINIMAL	1	0	0	0	0	0	0	0	0	1
DILATATION, PELVIS	0	0	0	0	0	0	0	0	1	0
UNILATERAL, MINIMAL	0	0	0	0	0	0	0	0	1	0
NEPHROPATHY, CHRONIC PROGRESSIVE	0	0	0	0	1	0	0	0	0	0
BILATERAL, SEVERE	0	0	0	0	1	0	0	0	0	0
WITHIN NORMAL LIMITS	5	7	0	0	0	1	9	9	7	7
LIVER	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
NECROSIS, SINGLE CELL	0	0	3	1	3	0	10	5	10	2
HEPATOCELLULAR, MINIMAL	0	0	3	1	3	0	7	4	8	2
HEPATOCELLULAR, MILD	0	0	0	0	0	0	3	1	2	0
TENSION LIPIDOSIS	0	0	0	0	1	1	0	0	0	0
MINIMAL	0	0	0	0	1	1	0	0	0	0
WITHIN NORMAL LIMITS	10	10	7	9	6	9	0	5	0	8
LUNG	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
INFLAMMATION, CHRONIC	0	0	0	0	0	0	0	0	1	0
FOCAL, MINIMAL	0	0	0	0	0	0	0	0	1	0
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	9	10
LYMPH NODE, MANDIBULAR	(9)	(10)	(0)	(0)	(1)	(0)	(10)	(10)	(10)	(10)
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS	0	0	0	0	0	0	0	1	0	0
SINUSAL, MILD	0	0	0	0	0	0	0	1	0	0
HYPERPLASIA, LYMPHOID	0	0	0	0	0	0	0	0	1	0
MILD	0	0	0	0	0	0	0	0	1	0
WITHIN NORMAL LIMITS	9	10	0	0	1	0	10	9	9	10
LYMPH NODE, MESENTERIC	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
MAMMARY GLAND	(10)	(10)	(0)	(0)	(0)	(0)	(9)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	9	10	10	10
NERVE, SCIATIC	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
OVARY	(0)	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(10)
WITHIN NORMAL LIMITS	0	10	0	0	0	0	0	10	0	10
PANCREAS	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
PARATHYROID	(7)	(7)	(0)	(0)	(0)	(0)	(7)	(10)	(4)	(8)
WITHIN NORMAL LIMITS	7	7	0	0	0	0	7	10	4	8
PITUITARY	(10)	(10)	(0)	(0)	(0)	(0)	(10)	(10)	(10)	(10)
WITHIN NORMAL LIMITS	10	10	0	0	0	0	10	10	10	10
PROSTATE	(10)	(0)	(0)	(0)	(0)	(0)	(10)	(0)	(10)	(0)
INFLAMMATION, CHRONIC	3	0	0	0	0	0	2	0	2	0
MINIMAL	3	0	0	0	0	0	0	0	1	0

Titles:
Group 1 0 MG/KG/DAY
Group 2 40 MG/KG/DAY
Group 3 40 MG/KG/DAY (b) (4)
Group 4 80 MG/KG/DAY
Group 5 80 MG/KG/DAY (b) (4)

() = Number Of Animals Examined For This Tissue

Toxicokinetics: No TK studies were conducted.

Following is sponsor's conclusions of the above study

> Administration of atorvastatin calcium (alone and in combination with two impurities) by once daily oral gavage for a minimum of 14 days did not result in mortality, but was associated with minimal to mild necrosis of individual hepatocytes (single cell necrosis) in the liver. The liver changes were observed across all groups treated with atorvastatin calcium and atorvastatin calcium with impurities, except for females administered 40 mg/kg/day atorvastatin calcium with impurities. Based on these results, the no-observed-adverse-effect level (NOAEL) for atorvastatin calcium alone could not be identified under the conditions of this study. The no-observed-adverse-effect level (NOAEL) for atorvastatin calcium (with two impurities) was considered to be 40 mg/kg/day for females and could not be identified for males. Taken together, the findings demonstrated that following repeated oral administration to rats, the presence of the two impurities had no differential or novel toxicity when compared to the toxicity profile of atorvastatin alone.

In summary: In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurities to rats. The impurities were (b) (4) (b) (4) (at concentration of (b) (4) %) and (b) (4) (b) (4) (at concentration of (b) (4) %, both relative to atorvastatin calcium drug product). The TK parameters of the drug (such as Cmax and AUC values) were not measured in this study. The drug had no effects on clinical signs, BWs and food consumption with and without the impurities. Hematological parameters, such as hemoglobin and hematocrit were increased at all doses of the drug (with impurities) and at a HD without the impurities. In clinical chemistry parameters, similar effects were observed on liver enzymes, etc. with or without impurities (see the Table in the results section), since the RLD was not used, it is hard to know if these toxicities were unique to the current drug product. The histopathological changes in the liver were also in general similar in the presence or absence of impurities in the drug product. No NOAEL could be established in this study as even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one. They also did not determine the exposures of the drug with and without impurities.

Genetic toxicology studies

Following gene-toxicity studies have been conducted with the (b) (4) (b) (4) (at concentration of (b) (4) %) and (b) (4) (b) (4) (at concentration of (b) (4) %, both relative to atorvastatin calcium drug product) to qualify these impurities.

1) AMES test was conducted with atorvastatin calcium with and without impurities. As seen below, atorvastatin calcium was negative in the AMES test at doses up to 5000 ug/plate in the presence and absence of impurities (report # TOXICITY 037-001).

The study was conducted at (b) (4) at (b) (4) on 8/18/2009.

Methods: these are described below:

[redacted] Code Number	Test Article / Impurity ID	Batch No.	Purity (per protocol)	Test Article Description	Storage Conditions
AC27KV	Atorvastatin Calcium	AC0160708	[redacted]%	White powder	-15 to -40°C, stored in the dark with desiccant
AC27KW	[redacted] Impurity of Atorvastatin	ADL/941(149)/1008	[redacted]%	[redacted]	
AC27KX	[redacted] Impurity of Atorvastatin	ATC/Imp/918/118	[redacted]%		

The test articles, Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted]% [redacted] and [redacted]% [redacted] Impurities of Atorvastatin (referred to as Atorvastatin Calcium with impurities), were tested in the Bacterial Reverse Mutation Assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A in the presence and absence of Aroclor-induced rat liver S9. The assay was performed in two phases, using the plate incorporation method. The first phase, the initial toxicity-mutation assay, was used to establish the dose-range for the confirmatory mutagenicity assay and to provide a preliminary mutagenicity evaluation. The second phase, the confirmatory mutagenicity assay, was used to evaluate and confirm the mutagenic potential of the test article.

[redacted] was selected as the solvent of choice based on the request of the Sponsor, solubility of Atorvastatin Calcium and [redacted] After sonication at 32°C for 20 minutes in the solubility test, Atorvastatin Calcium formed a soluble and clear solution at approximately 500 mg/mL, the maximum concentration tested.

Results

Initial Toxicity-Mutation Assay

The results of the initial toxicity-mutation assay with Atorvastatin Calcium with impurities are presented in Tables 5 and 6. These data were generated in Experiment B1. In the initial toxicity-mutation assay, the maximum dose tested was 5000 µg per plate; this dose was achieved using a concentration of 50 mg/mL and a 100 µL plating aliquot. The dose levels tested were 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg per plate. [redacted] was observed at 5000 µg per plate. Toxicity was observed at 5000 µg per plate with tester strain TA100 only. Based on the findings of the initial toxicity-mutation assay, the maximum dose plated in the confirmatory mutagenicity assay was 5000 µg per plate.

In Experiment B1 (Initial Toxicity-Mutation Assay), no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.

Confirmatory Mutagenicity Assay

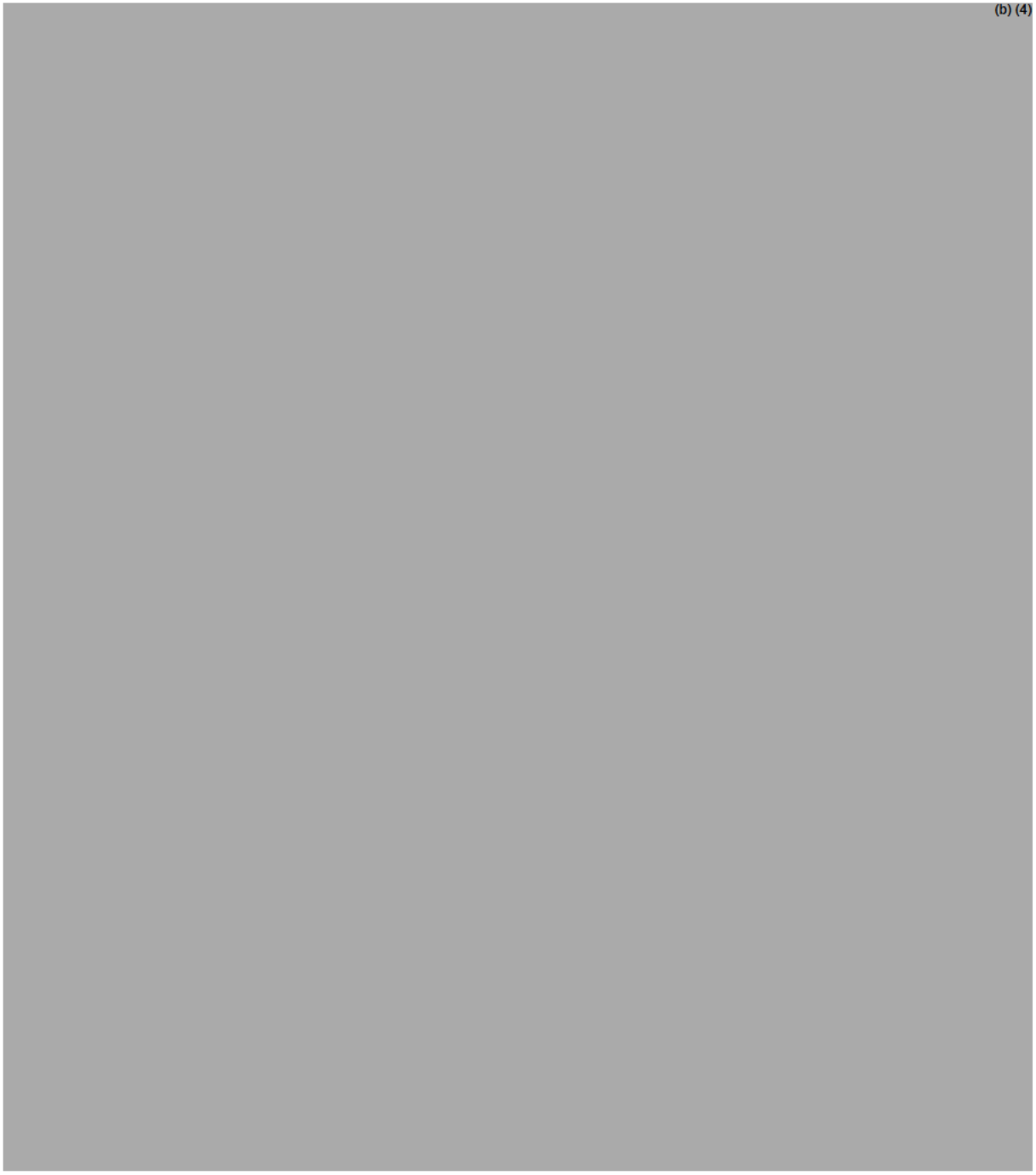
The results of the confirmatory mutagenicity assay with Atorvastatin Calcium with impurities are presented in Tables 7 and 8. These data were generated in Experiment B2. The dose levels

tested were 50, 150, 500, 1500 and 5000 µg per plate. (b) (4) was observed at 5000 µg per plate with several test conditions. Toxicity was observed at 5000 µg per plate with tester strains TA98 and TA100 only.

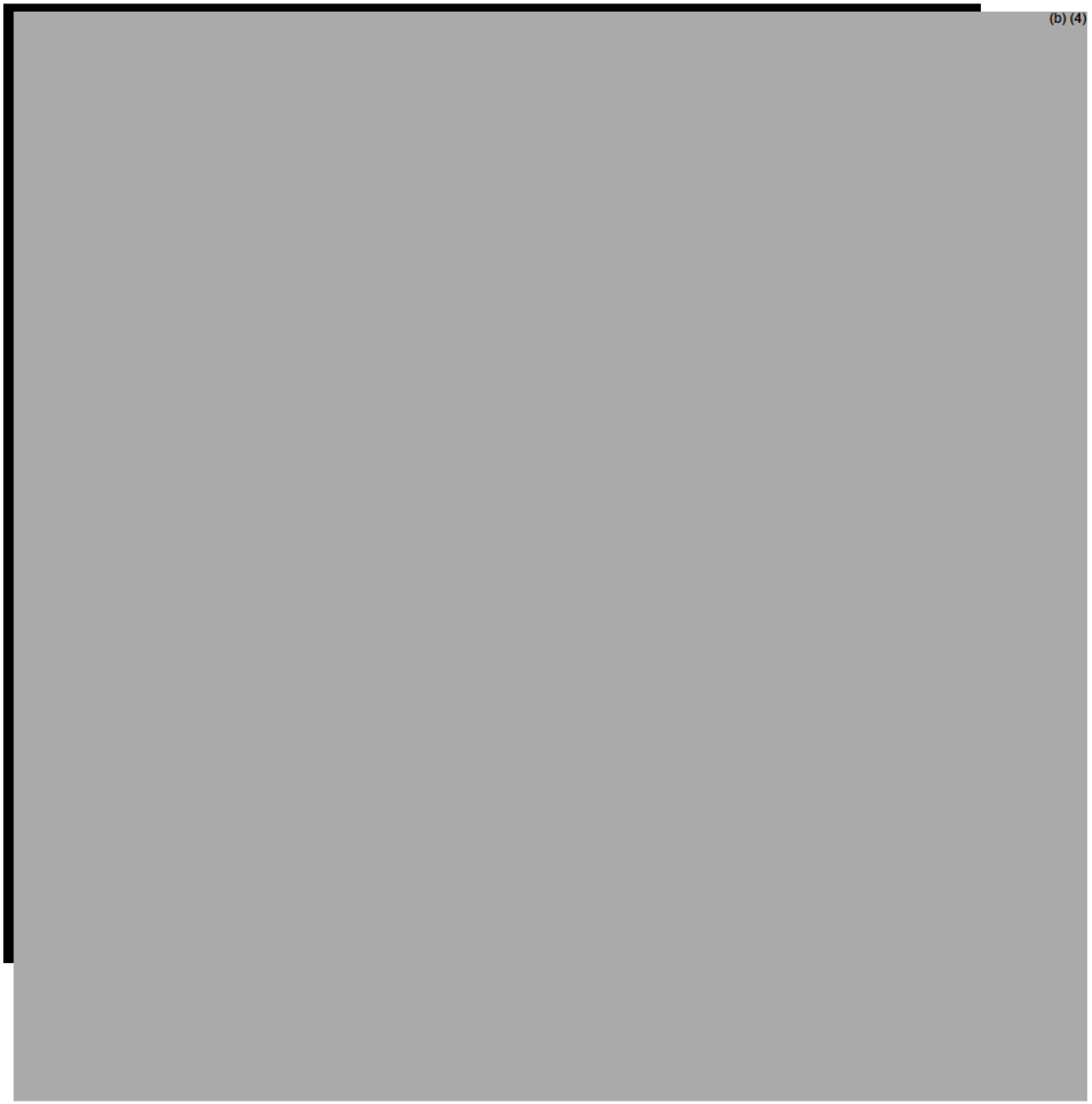
In Experiment B2 (Confirmatory Mutagenicity Assay), no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.

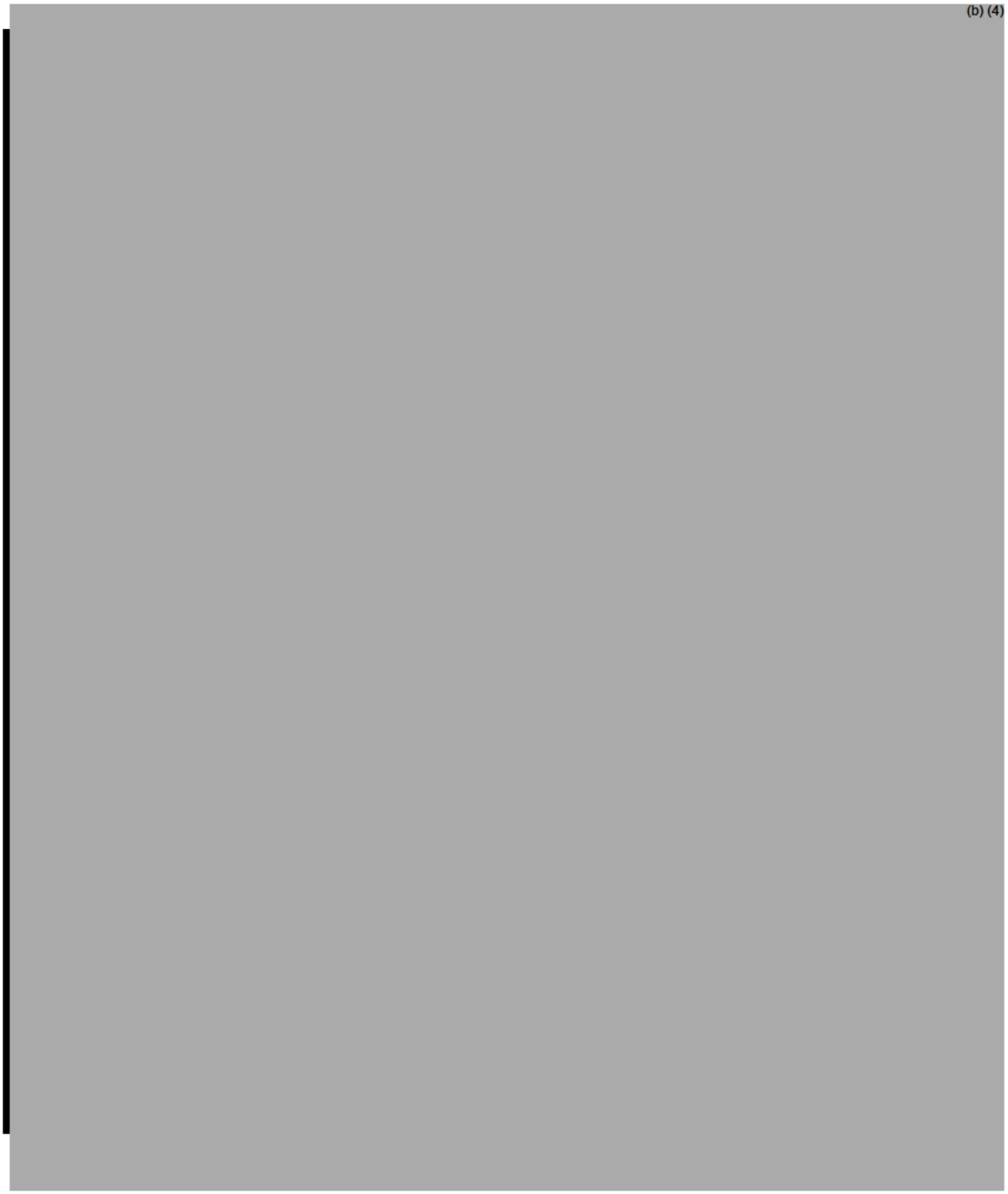
Drug with impurities: Without S-9 activation

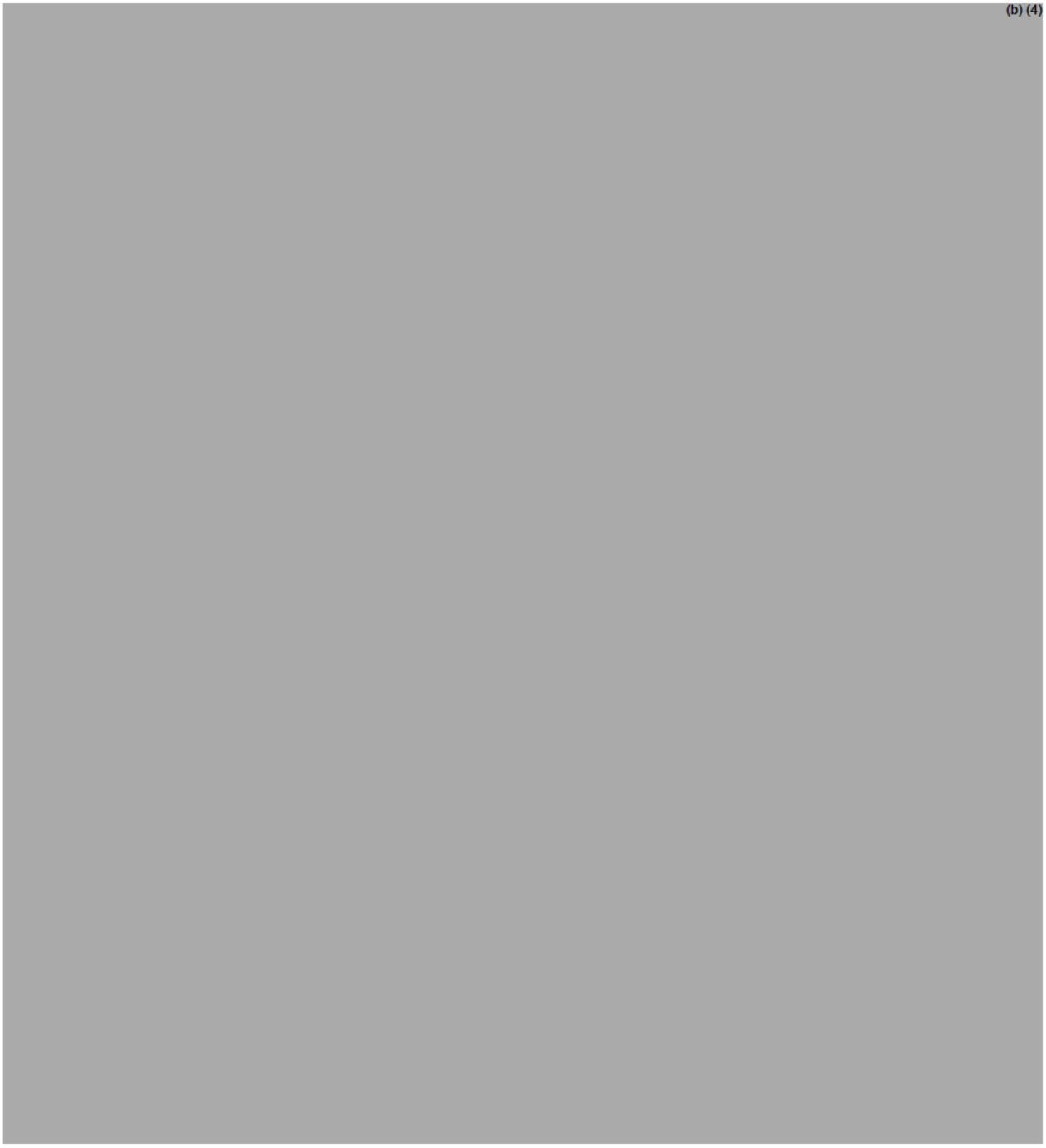
(b) (4)


(b) (4)

Drug with impurities: With S-9 activation




(b) (4)


(b) (4)



Similar observations were made in the confirmatory assay.

Sponsor's conclusions are provided below:

All criteria for a valid study were met as described in the protocol. The results of the Bacterial Reverse Mutation Assay indicate that, under the conditions of this study, neither **Atorvastatin Calcium** nor **Atorvastatin Calcium spiked with** [redacted] **and** [redacted] **Impurities of Atorvastatin** did not cause a positive mutagenic response with any of the tester strains in either the presence or absence of Aroclor-induced rat liver S9.

2. In vitro chromosomal aberration test in Peripheral blood lymphocytes:. Atorvastatin calcium spiked with impurities (with [redacted] and [redacted]) was tested in an 'in vitro mammalian chromosome aberration' test. The drug was negative in the above assay with and without impurities (study # TOX 037-002). This assay was conducted at [redacted] in [redacted]

Methods: These are described below

The test articles, Atorvastatin Calcium (AC27KV) and Atorvastatin Calcium spiked with [redacted] Impurities of Atorvastatin [redacted] were tested in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes (HPBL) in both the absence and presence of an Aroclor-induced S9 activation system. A preliminary toxicity test was performed to establish the dose range for testing in the cytogenetic test. The chromosome aberration assays were used to evaluate the clastogenic potential of the test articles.

***In Vitro* Mammalian Chromosome Aberration Test with Atorvastatin Calcium (AC27KV)**

In the preliminary toxicity assay using Atorvastatin Calcium, the maximum dose tested was 5000 µg/mL. Human peripheral blood lymphocytes were treated in the absence and presence of an Aroclor-induced S9 activation system for 4 hours, and continuously for 20 hours in the absence of S9 activation. The dosing solutions were adjusted for the purity of Atorvastatin Calcium using a correction factor of [redacted] Atorvastatin Calcium was soluble in [redacted] at all concentrations tested. Visible [redacted] was observed in treatment medium at dose levels ≥ 1500 µg/mL and dose levels ≤ 500 µg/mL were soluble in treatment medium at the beginning and conclusion of the treatment period. At the conclusion of the treatment period, hemolysis was observed at dose levels ≥ 1500 µg/mL in the non-activated and S9-activated 4-hour exposure groups and at dose levels ≥ 500 µg/mL in the non-activated 20-hour exposure group.

Selection of dose levels for the chromosome aberration assay was based on a reduction in the mitotic index relative to the solvent control. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was observed at dose levels ≥ 500 µg/mL in all three treatment groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 10 to 450 µg/mL for all three treatment groups.

In the chromosome aberration assay using Atorvastatin Calcium, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. Atorvastatin Calcium was soluble in [redacted] and in the treatment medium at all concentrations tested at the beginning and conclusion of the treatment period.

Selection of doses for microscopic analysis was based on mitotic inhibition (the lowest dose with at least 50% reduction in mitotic index, relative to the solvent control) in all harvests. The dose levels selected for analysis were 300 µg/mL in the non-activated 4-hour exposure group, 250 µg/mL in the S9-activated 4-hour exposure group and 150 µg/mL in the non-activated 20-hour exposure group.

The percentage of cells with structural or numerical aberrations in the Atorvastatin Calcium-treated groups was not increased relative to solvent control at any dose level ($p>0.05$, Fisher's Exact test).

The results of the assay using Atorvastatin Calcium are summarized in the following table:

Treatment Time (hours)	Recovery Time (hours)	Harvest Time (hours)	S9	Mitotic Index Reduction[1] at dose scored (µg/mL)	LED[2] for Structural Aberrations (µg/mL)	LED[2] for Numerical Aberrations (µg/mL)
4	16	20	-	(b) (4)		
20	0	20	-			
4	16	20	+			

[1] relative to the solvent control at high dose evaluated for chromosome aberrations
[2] LED = lowest effective dose level

***In Vitro* Mammalian Chromosome Aberration Test with Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin (b) (4)**

One of the impurities provided by the Sponsor for use in this study was originally named (b) (4) impurity of Atorvastatin with a potency of (b) (4)%, as indicated in the protocol and Technical Data Sheet provided with the original sample. The original potency of the impurity sample ((b) (4)%) was used to determine the correction factor for adjustment of the dosing formulation samples. Subsequently, the Sponsor provided a second Technical Data Sheet with an updated impurity name and potency ((b) (4)%). The updated name for the impurity is (b) (4) impurity of Atorvastatin and will be used throughout the report. The discrepancy between the potencies listed on the Technical Data Sheets is due to the instability of the compound. Since the potency of the impurity decreased by (b) (4)% and the results of the formulation analysis from the confirmatory assay were 100% of target for this impurity, the actual concentration of the (b) (4) impurity was still within (b) (4)% of target, even taking into account the change in potency. Therefore, the Study Director has concluded that the discrepancy between the potency values did not adversely impact the integrity of the data or the validity of the study conclusion.

In the preliminary toxicity assay using Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin, the maximum dose tested was 5000 µg/mL. Human peripheral blood lymphocytes were treated in the absence and presence of an Aroclor-induced S9 activation system for 4 hours, and continuously for 20 hours in the absence of S9 activation. The dosing solutions were adjusted for the purity of Atorvastatin Calcium using a correction factor of (b) (4) for the purity of (b) (4) using a correction factor of (b) (4) and for the purity of (b) (4) using a correction factor of (b) (4) The amount of each spiking agent weighed was also adjusted to compensate for the presence of the (b) (4) impurity in the (b) (4) impurity, as determined during the analytical validation. Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin was soluble in (b) (4) at all concentrations tested. Visible (b) (4) was observed in treatment medium at dose levels ≥ 500 µg/mL and dose levels ≤ 150 µg/mL were soluble in treatment medium at the beginning and conclusion of the

treatment period. At the conclusion of the treatment period, hemolysis was observed at dose levels ≥ 500 µg/mL in all three treatment groups.

Selection of dose levels for the chromosome aberration assay was based on a reduction in the mitotic index relative to the solvent control. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was observed at dose levels ≥ 150 µg/mL in all three treatment groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 5 to 125 µg/mL for the non-activated 4 and 20-hour treatment groups, and from 5 to 150 µg/mL for the S9-activated 4-hour exposure group.

Results

In the chromosome aberration assay using Atorvastatin Calcium spiked with (b) (4)% (b) (4) (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin was soluble in (b) (4) and in the treatment medium at all concentrations tested at the beginning and conclusion of the treatment period.

Selection of doses for microscopic analysis was based on mitotic inhibition (the lowest dose with at least 50% reduction in mitotic index, relative to the solvent control) in all harvests. The dose levels selected for analysis were 25, 75 and 125 µg/mL in the non-activated 4-hour exposure group, 10, 50 and 150 µg/mL in the S9-activated 4-hour exposure group and 25, 50 and 100 µg/mL in the non-activated 20-hour exposure group.

The percentage of cells with structural or numerical aberrations in the Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin-treated groups was not increased relative to solvent control at any dose level ($p>0.05$, Fisher's Exact test).

The results of the assay using Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin are summarized in the following table:

Treatment Time (hours)	Recovery Time (hours)	Harvest Time (hours)	S9	Mitotic Index Reduction[1] at dose scored (µg/mL)	LED[2] for Structural Aberrations (µg/mL)	LED[2] for Numerical Aberrations (µg/mL)
4	16	20	-	(b) (4)		
20	0	20	-			
4	16	20	+			

[1] relative to the solvent control at high dose evaluated for chromosome aberrations
[2] LED = lowest effective dose level

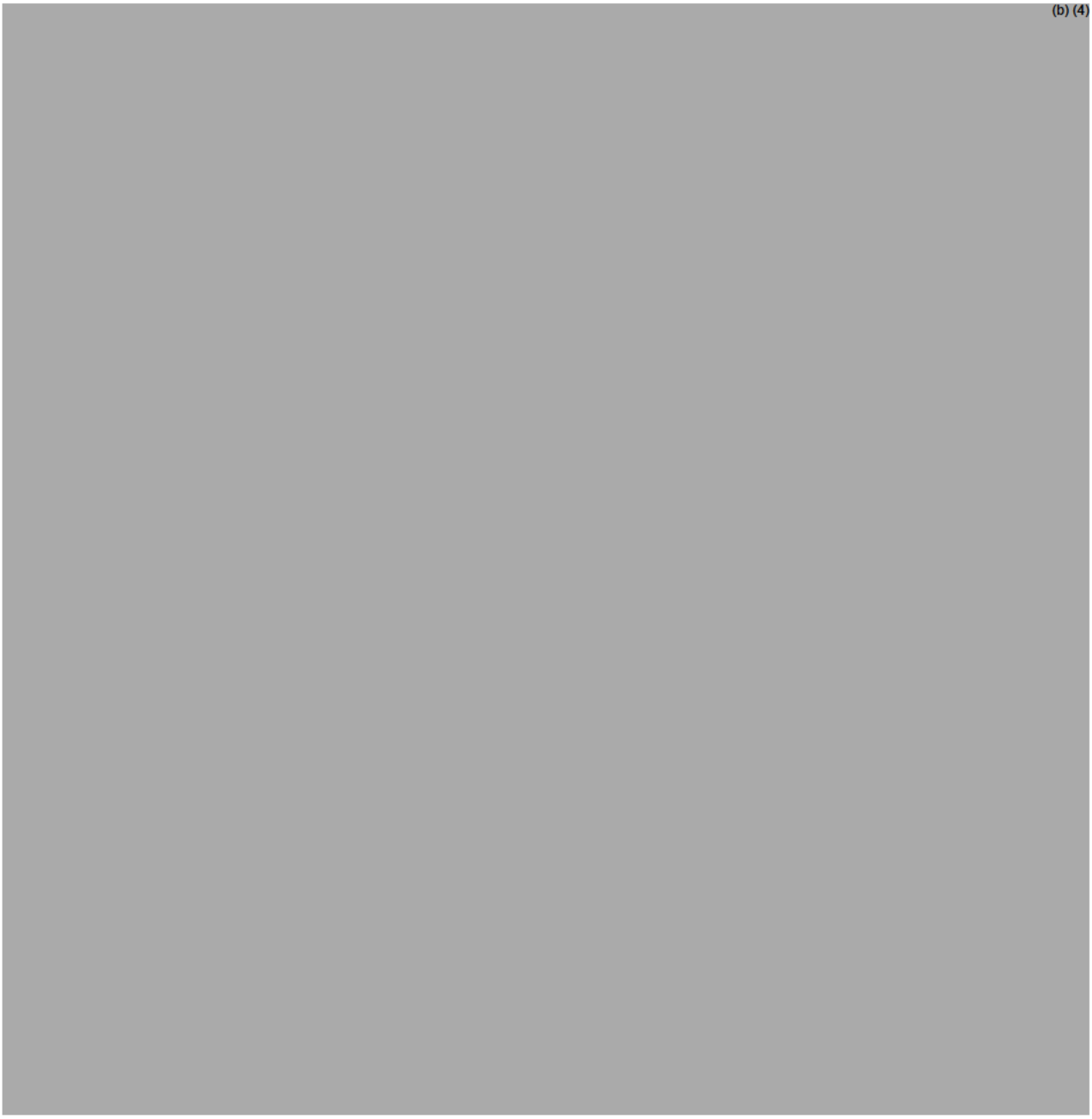
Based on the findings of this study, Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atorvastatin were concluded to be negative for the induction of structural and numerical chromosome aberrations in both non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

Table 7. Atorvastatin calcium was tested in the absence of impurities in the chromosome aberration test.

(b) (4)



Table 14. Atorvastatin calcium was tested in the presence of impurities in the chromosome aberration test.



Under the conditions of the assay described in this report, Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4) % (b) (4) and (b) (4) % (b) (4) Impurities of Atorvastatin were concluded to be negative for the induction of structural and numerical chromosome aberrations in both non-activated and S9-activated test systems in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes.

In summary, Sponsor by providing a 2-week toxicity study in rats with the atorvastatin with impurities (spiked with (b) (4) and (b) (4) in the atorvastatin calcium drug product) vs without impurities, as well as by conducting two geno-toxicity studies (Ames and chromosome aberration assay) has qualified the impurities in atorvastatin calcium, and these are acceptable. Thus from the pharmacology/toxicity point of view, the proposed levels of (b) (4) and (b) (4) impurities in the atorvastatin calcium drug product are qualified based on toxicity studies.

Following toxicity studies have been conducted to support the (b) (4) impurity in the atorvastatin calcium drug product

A 2-Week Oral Toxicity Study of atorvastatin calcium containing (b) (4)% of (b) (4) impurity in Rats (Study No. G7008)

The purpose of this repeated dose 14 day toxicity study in Wistar rats was to assess the toxic potential of test item (Atorvastatin Calcium) without impurities and with impurities (b) (4) impurity) when administered daily by oral gavage. This study is intended to provide information on major toxic effects on target organs and an estimate of a "No Observed Effect Level (NOEL)"

Study no: G7008
Volume #, and page #: eCTD submission dated 8/4/10

Conducting laboratory and location: (b) (4)
Date of study initiation: 12/23/2009
GLP compliance: Yes
QA report: yes (X) no ( )

Drug lot #, and % purity:
Atorvastatin (without impurities) batch # ACO160708, manufactured by Matrix Laboratories in India on 11/07; purity was (b) (4)%

Atorvastatin (with impurities) batch # ATC-ARL (A-489) 51B, manufactured by Matrix Laboratories Ltd. on 11/09; purity was (b) (4)%. Following COA was provided on the drug with impurity, the percentage of impurity present in the drug was (b) % as stated in Table 1 below.

APPENDIX 11 contd. Certificate of Analysis / Technical Data Sheet

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

TECHNICAL DATA SHEET

(b) (4)

[redacted]

Formulation/vehicle:. 1% sodium carboxy methyl cellulose (NaCMC-low viscosity). Dosing volume was 10 ml/kg.

Methods (unique aspects):

Male and female Wistar rats were assigned to five groups and each group comprised 10 rats /sex. Each treatment group was administered with respective dose formulation (40 and 80 mg / kg Bwt) at the dose volume of 10 mL/kg Bwt. Animals in the vehicle control group were administered with the vehicle [1.0 % sodium salt of carboxy methylcellulose(low viscosity) in Milli Q water] at the dose volume of 10 mL/kg Bwt. The test items were prepared as two separate dose suspensions, without impurities (Atorvastatin Calcium) and with impurity [redacted] Impurity).

Two dose levels of 40 (G2a) and 80 (G3a) mg/kg of test item without impurity (Atorvastatin Calcium) have been selected. In additions, the two dose levels of 40 (G2b) and 80 (G3b) mg/kg of test item with impurity [redacted] Impurity) has been selected.

Required quantities of each of the test item were calculated as below:

a) API calculation (for G2a and G3a groups):

$$\text{Amount of Atorvastatin calcium (mg)} = \frac{\text{Required concentration (mg/mL) x Total volume (mL) x 100}}{\text{\% Purity of Atorvastatin Calcium}}$$

b) API calculation (for G2b and G3b groups):

$$\text{Amount of Atorvastatin calcium (mg)} = \frac{\text{Required concentration (mg/mL) x Total volume (mL) x 99.00}}{\text{\% Purity of Atorvastatin Calcium}}$$

c) Impurity caluculation (for G2b and G3b groups):

$$\text{Amount of [redacted] Impurity (mg)} = \frac{\text{Required concentration (mg/mL) x Total volume (mL) x 1.00}}{\text{\% Purity of [redacted] Impurity}}$$

Doses in administered units: 0, 40, 80 mg/kg/day with and without impurities were administered to rats (8 weeks of age, BW males 243-248 g /females 170-171 g) by gavage orally for 14 consecutive days.

Table 1.

Groups	G1	G2a	G3a	G2b	G3b
Doses (mg/kg Bwt / day)	0	40	80	40	80
Total test item required (mg)-API	0	401.7	803.2	397.7	795.3
Total impurity added@ (mg)	0	-	-	[redacted]	
Premix volume(mL)	-	20	20	20	20
Total volume made up with vehicle (mL)	100	100	100	100	100
Stirring Time(Min)	15	15	15	15	15
Concentration(mg/mL)	0	4	8	4	8

@[redacted]% of total API

Experimental design and parameters measured are shown in the Table below:

TABLE 1. Details of Experimental Design, Treatment regime, Clinical Pathology Investigations, Pathology and Sacrifice Schedule

Group No.	Dose (mg/kg Bwt/day)	No. of rats per group		Treatment Period-oral gavage (Days)		Clinical Pathology investigations			Pathology		Sacrifice schedule	
		M	F	M	F	Haematology	Clinical chemistry	Urinalysis	Gross pathology	Histopathology	M	F
G1	0	10	10	14	14	+	+	+	+	+	Day 15	Day 15
G2a	40	10	10	14	14	+	+	+	+	a	Day 15	Day 15
G3a	80	10	10	14	14	+	+	+	+	+	Day 15	Day 15
G2b	40	10	10	14	14	+	+	+	+	a	Day 15	Day 15
G3b	80	10	10	14	14	+	+	+	+	+	Day 15	Day 15

+: Yes, a: Liver only

Each animal in the experiment was observed for clinical signs, mortality, ocular abnormalities, neurological effects and changes in the body weights and food intake. The laboratory investigations such as haematology, clinical chemistry and urinanalysis were performed at the end of the treatment period.

Gross pathology: At sacrifice.

Organs weighed: Following organs were weighed as shown in the Table below.

Histopathology: This was performed at sacrifice in control and high dosed animals in organs listed in histopathology Table below.

Histopathological examination was carried out on the preserved organs of vehicle control (G1), high dose without impurities (G3a) and high dose with impurity (G3b) group rats. In addition, all gross lesions from all the animals were examined microscopically. As Liver was showing test item related histopathological changes in high dose groups (G3a and G3b), it was examined in respective the low dose group rats (G2a and G2b).

b. Tissue collection

The following organs and tissues (indicated as X) were collected from all rats and preserved in 10% Neutral Buffered Formalin (NBF):

Sl. No.	Tissue	Organ Weights	Collection Preservation	Microscopic Examination
1	Adrenal glands	X	X	X
2	Aorta		X	X
3	Bone marrow smear		X	X

Sl. No.	Tissue	Organ Weights	Collection Preservation	Microscopic Examination
4	Brain including medulla/pons, cerebellum and cerebrum	X	X	X
5	Cecum		X	X
6	Colon		X	X
7	Duodenum		X	X
8	Epididymides	X	X	X
9	Esophagus		X	X
10	Eyes with optic nerve*		X	X
11	Mammary gland		X	X
12	Femur bone with joint**		X	X
13	Heart	X	X	X
14	Ileum with Peyer's patches		X	X
15	Jejunum		X	X
16	Kidneys	X	X	X
17	Lacrimal glands		X	X
18	Larynx		X	X
19	Liver	X	X	X
20	Lungs (with bronchi and bronchioles) #	X	X	X
21	Mesenteric lymph nodes		X	X
22	Mandibular lymph nodes		X	X
23	Ovaries	X	X	X
24	Oviducts		X	X
25	Pancreas		X	X
26	Pituitary		X	X
27	Prostate$	X	X	X
28	Rectum		X	X
29	Salivary glands		X	X
30	Sciatic nerves		X	X
31	Seminal vesicles and coagulating glands $	X	X	X
32	Skin		X	X
33	Skeletal muscle		X	X
34	Spinal cord at 3 levels - cervical, mid thoracic and lumbar.		X	X
35	Spleen	X	X	X
36	Sternum with marrow**		X	X
37	Stomach		X	X
38	Testes@	X	X	X
39	Thymus	X	X	X
40	Thyroid with Parathyroids***	X	X	X
41	Tongue		X	X
42	Trachea		X	X
43	Urinary bladder		X	X
44	Ureters		X	X
45	Uterus with Cervix	X	X	X
46	Vagina		X	X

#: Lungs inflated with 10%NBF before fixation
*: Collected in Davidson's fluid.
@: Collected in modified Davidson's fluid.
X: Activity carried out.
**: Decalcified prior to sectioning

Results:

Mortality: No treatment related mortality was observed.

Clinical signs: No drug related effects were observed.

Functional observation Battery (FOB): Significant findings were noted with atorvastatin vs the control in some FOB tests as seen below, but no significant drug related effects were observed between atorvastatin with or without impurities. The RLD was not used in this study to know if these effects were unique to this drug product.

Neuromuscular observations:

Grip Strength: At 80 mg / kg Bwt / day, hindlimbs grip strength was significantly higher in G3a males and G3b males whereas in G3b females, fore limbs grip strength were significantly higher and were considered to be incidental as the observed changes are marginal (3 to 8%).

Motor Activity: At 80 mg / kg Bwt / day, significantly higher horizontal and total activity scores were seen in G3a males and horizontal, vertical and total activity scores in G3b males whereas in females, significantly higher vertical activity scores were observed in G3a group animals.

At 80 mg / kg Bwt / day, significantly higher rectal body temperature was observed in G3b females as compared to the vehicle control group. The change seen in rectal body temperatures was considered to be incidental as the observed change is marginal(less than 1%).

TABLE 4 contd. Summary of Functional Observation Battery

Group No. Dose (mg/kg)		Neuromuscular observations						Refer Appendices 3 & 4 Physiological Observation
		Grip strength (kg)			Motor activity score			
		Forelimbs Average	Hindlimbs Average	Hindlimb footsplay (cms) Average	Horizontal score	Vertical score	Total score	Body temperature (°F)
Males								
G1	Mean	0.989	0.495	5.36	776.20	606.50	1382.70	98.59
0	SD	0.02	0.03	1.22	344.23	248.21	586.18	0.79
	N	10	10	10	10	10	10	10
			+		+		+	
G3a	Mean	1.002	0.527	5.19	1074.00	756.60	1830.60	98.73
80	SD	0.03	0.02	0.72	160.43	94.29	238.16	0.38
	N	10	10	10	10	10	10	10
Females								
G1	Mean	0.826	0.439	5.41	1295.10	762.00	2057.10	100.01
0	SD	0.02	0.03	0.94	159.05	129.54	276.99	0.46
	N	10	10	10	10	10	10	10
						+		
G3a	Mean	0.844	0.442	5.06	1246.00	905.00	2151.00	99.92
80	SD	0.02	0.03	0.82	94.04	163.10	179.20	0.40
	N	10	10	10	10	10	10	10

N: No. of observations
+ : Significantly higher (+) than the vehicle control group

TABLE 4 contd. Summary of Functional Observation Battery

Refer Appendices 3 & 4

Group No. Dose (mg/kg)		Neuromuscular observations						Physiological Observation
		Grip strength (kg)			Motor activity score			
		Forelimbs Average	Hindlimbs Average	Hindlimb footsplay (cms) Average	Horizontal score	Vertical score	Total score	Body temperature (°F)
Males								
G1	Mean	0.989	0.495	5.36	776.20	606.50	1382.70	98.59
0	SD	0.02	0.03	1.22	344.23	248.21	586.18	0.79
	N	10	10	10	10	10	10	10
			+		+	+	+	
G3b	Mean	0.994	0.535	5.31	1079.30	804.20	1883.50	98.41
80	SD	0.03	0.02	0.66	165.91	134.21	287.47	0.60
	N	10	10	10	10	10	10	10
Females								
G1	Mean	0.826	0.439	5.41	1295.10	762.00	2057.10	100.01
0	SD	0.02	0.03	0.94	159.05	129.54	276.99	0.46
	N	10	10	10	10	10	10	10
		+						+
G3b	Mean	0.858	0.462	5.35	1218.90	767.00	1985.90	100.58
80	SD	0.03	0.03	0.74	87.00	156.30	216.11	0.48
	N	10	10	10	10	10	10	10

N: No. of observations
+ : Significantly higher (+) than the vehicle control group

Body weights: In males, body weight gains were higher with the impurity at a HD (15.3, 18.9, 19.4* at 0, 40, 80 mg/kg/day, *p<0.05), while these were not higher without impurities (15.3, 18.9, 17.6 respectively).

Table 7 shows the body weight gains in males without impurities.

TABLE 7. Summary of Cumulative Net Body Weight Gains (g) – Males

Refer Appendix: 7

G1 vs G2a & G3a

Body Weight Gain (g)

				Days					
		Base Weight Day	From:	1	4	8	11	Abs Gain 1	% Gain 1
Group	Sex	1	To:	4*	8*	11	14	14	14
G1	M	248.208	Mean	5.765	12.590	12.663	6.848	37.866	15.26
		14.056	S.D.	3.656	3.859	3.449	3.661	6.056	2.34
		10	N	10	10	10	10	10	10
G2a	M	245.241	Mean	9.072	18.508*	9.542	9.074	46.196	18.85
		15.991	S.D.	2.455	3.973	4.103	2.248	5.693	2.21
		10	N	10	10	10	10	10	10
G3a	M	243.356	Mean	10.918*	13.147	10.757	8.088	42.910	17.61
		16.239	S.D.	4.409	4.639	3.362	3.365	7.254	2.60
		10	N	10	10	10	10	10	10

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level;

Abs Gain = absolute bodyweight gain between base period and end of the analysis period
% Gain = percentage bodyweight gain between base period and end of the analysis period

Group G1 - G1 0 Group G2a - G2a 40 Group G3a - G3a 80

G1 vs G2b & G3b

Table below shows the body weight gains in males with impurities.

Body Weight Gain (g)

Group	Sex	Base Weight Day 1		Days From: 1	4	8	11	Abs Gain 1	% Gain 1
			To:	4*	8*	11	14	14	14
G1	M	248.208	Mean	5.765	12.590	12.663	6.848	37.866	15.26
		14.056	S.D.	3.656	3.859	3.449	3.661	6.056	2.34
		10	N	10	10	10	10	10	10
G2b	M	245.702	Mean	11.040*	15.557	9.916	9.822	46.335	18.85
		16.526	S.D.	3.461	7.920	3.480	4.252	11.047	4.32
		10	N	10	10	10	10	10	10
G3b	M	243.957	Mean	10.367*	16.709	10.552	9.528	47.156*	19.41*
		15.846	S.D.	2.150	3.477	5.741	3.209	8.125	3.63
		10	N	10	10	10	10	10	10

Statistics Test: 1 Way Analysis of Variance: * - 5% significance level;

Abs Gain = absolute bodyweight gain between base period and end of the analysis period
% Gain = percentage bodyweight gain between base period and end of the analysis period

Group G1 - G1 0 Group G2b - G2b 40 Group G3b - G3b 80

Food consumption: Food consumption (FC) was not significantly altered

Ophthalmoscopy: No drug related effects were observed.

Hematology: Some subtle differences were observed between two products, for example all doses of the drug with impurities decreased prothrombin (PT) time in rats (16.6, 15.1*, 15.4* seconds at 0, 40, 80 mg/kg/day respectively) vs this was noted only at a HD without impurities (16.6, 16.4, 14.5* sec respectively).

Sponsor states following changes in the hematological parameters. Basically they state that similar findings were observed with both products.

> Increase in Mean Corpuscular Haemoglobin Concentration (5%) in high dose (G3b) males was considered insignificant as the percent change was minimal and was within the physiological variations.
>
> Minimal increase in haematocrit values (7%) and decrease in Mean Corpuscular Haemoglobin Concentration (3%) in high dose (G3a) females were also considered insignificant as the percent changes were within physiological variation.

- Decrease in Prothrombin Time in high dose (G3a:-12%) females
- Decrease in Prothrombin Time in high and low dose (G2b:-9 % G3b:-17%) females

TABLE 1. Summary of Haematological Values at Termination – Males

Refer Appendix 1

Group No. Dose (mg/kg)		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV f/l	MCH pg	MCHC g/l	Plat G/l	P.T. s	APTT s	Neut %	Lymp %	Mono %	Eosi %	Baso %	Retic %
G1	Mean	8.40	8.59	158.20	0.495	57.72	18.40	318.40	1200.30	16.78	11.73	19.61	74.54	2.67	1.78	0.21	3.29
0	SD	2.48	0.43	14.32	0.017	1.76	1.42	20.95	191.20	1.89	2.47	14.02	17.43	0.59	3.46	0.09	0.41
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
G2a	Mean	7.47	8.58	159.50	0.492	57.48	18.62	324.30	1271.30	17.08	11.93	23.48	69.34	3.56	2.11	0.24	3.46
40	SD	1.48	0.47	5.66	0.025	2.99	0.77	11.46	75.90	0.69	2.37	6.08	7.64	1.08	2.12	0.12	0.46
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
G3a	Mean	9.53	8.88	163.70	0.504	56.73	18.43	325.00	1325.90	15.87	10.88	21.54	71.58	3.41	1.98	0.28	3.45
80	SD	1.85	0.42	8.90	0.031	1.34	0.29	8.96	98.73	1.30	2.47	7.07	8.20	1.21	2.11	0.08	0.48
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
G2b	Mean	9.54	8.32	157.70	0.474	57.00	18.96	332.60	1277.50	15.44	11.32	22.00	72.77	2.97	1.11	0.21	3.46
40	SD	2.21	0.32	6.67	0.019	1.72	0.79	8.49	152.23	1.18	1.75	4.26	4.48	0.49	1.03	0.09	0.42
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
								* (+5)									
G3b	Mean	8.58	8.80	164.70	0.493	56.06	18.73	333.90	1385.40	16.73	11.31	19.14	75.39	3.16	1.11	0.23	3.41
80	SD	2.21	0.47	11.51	0.034	1.48	0.66	8.60	155.82	1.03	1.52	4.54	4.78	1.15	0.43	0.05	0.69
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

*: Significantly higher than the vehicle control group
Values in parenthesis indicate % change

TABLE 2. Summary of Haematological Values at Termination – Females

Refer Appendix 2

Group No. Dose (mg/kg)		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV f/l	MCH pg	MCHC g/l	Plat G/l	P.T. s	APTT s	Neut %	Lymp %	Mono %	Eosi %	Baso %	Retic %
G1	Mean	5.54	8.12	151.90	0.459	56.56	18.71	330.90	1293.20	16.62	13.56	16.44	78.67	2.80	0.97	0.17	3.43
0	SD	0.76	0.25	6.87	0.020	1.77	0.81	7.99	90.70	0.51	2.03	4.37	5.26	0.77	0.41	0.07	0.54
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
											* (-25)						
G2a	Mean	6.37	8.31	153.10	0.469	56.47	18.47	326.70	1348.30	16.43	10.14	15.34	79.58	2.25	1.57	0.21	3.80
40	SD	1.63	0.30	7.19	0.018	2.13	0.80	7.45	75.87	0.68	1.79	4.35	4.45	0.44	1.17	0.12	0.82
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
					* (+7)			* (-3)		* (-12)							
G3a	Mean	6.53	8.43	157.40	0.491	58.22	18.68	320.80	1309.90	14.55	11.23	20.69	72.12	2.45	3.67	0.22	3.49
80	SD	2.39	0.37	6.06	0.021	1.37	0.50	8.38	154.63	0.71	3.01	9.01	11.68	0.96	3.78	0.09	0.59
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
										* (-9)							
G2b	Mean	6.24	8.31	152.90	0.463	55.75	18.40	330.30	1216.80	15.14	10.37	14.46	80.75	2.55	1.09	0.21	3.65
40	SD	1.63	0.32	6.08	0.015	1.65	0.42	9.45	133.98	0.83	2.86	3.96	4.50	0.43	0.86	0.07	0.52
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
										* (-17)							
G3b	Mean	7.76	8.43	156.60	0.470	55.81	18.59	333.30	1360.30	15.43	12.26	15.88	76.70	3.48	2.48	0.23	3.86
80	SD	2.61	0.38	7.14	0.026	1.83	0.62	9.64	136.78	1.19	3.40	4.31	8.91	1.09	5.04	0.11	0.79
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

*: Significantly higher / lower than the vehicle control group
Values in parenthesis indicate % change

Clinical chemistry: ALP levels in females were higher with all doses of the drug with impurities in rats (71, 98*, 98* U/L at 0, 40, 80 mg/kg/day respectively), not so without impurities. (71, 81, 89

U/L sec respectively). LDH and serum sodium levels were similarly higher with impurities in females than without it, see below. The following changes were observed on clinical chemistry parameters.

Males

TABLE 3. Summary of Clinical Chemistry Values at Termination – Males

Refer Appendix 3

Group No. Dose (mg/kg)		Glu mmol/l	BUN mmol/l	T.Pro g/l	AST U/l	ALT U/l	ALP U/l	GGT^ U/l	T-Bil# µmol/l	Creat# µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	T.Chol mmol/l
G1	Mean	6.58	5.81	62.03	92.70	36.40	140.90	-	1.96	25.33	41.09	2.56	2.75	1.50
0	SD	1.16	0.75	2.22	21.88	7.85	33.52		0.21	2.60	1.21	0.22	0.16	0.15
	n	10	10	10	10	10	10		5	9	10	10	10	10
					* (+177)	* (+349)					* (+6)		* (-7)	* (+27)
G2a	Mean	5.69	5.97	61.97	256.80	163.60	166.80	-	2.53	24.40	43.61	2.67	2.56	1.91
40	SD	0.50	0.62	3.26	143.87	120.98	38.02		0.48	3.24	1.20	0.42	0.09	0.41
	n	10	10	10	10	10	10		9	10	10	10	10	10
			* (+21)		* (+268)	* (+375)	* (+58)				* (+7)		* (-13)	* (+29)
G3a	Mean	5.95	7.01	61.57	341.20	173.00	222.70	-	2.31	26.40	44.10	2.39	2.39	1.93
80	SD	1.54	1.14	3.04	252.11	122.90	73.52		0.51	4.53	1.81	0.16	0.14	0.47
	n	10	10	10	10	10	10		7	10	10	10	10	10
					* (+104)	* (+187)				* (-12)	* (+5)		* (-14)	
G2b	Mean	6.40	5.80	62.69	188.90	104.40	146.60	-	1.92	22.40	43.28	2.38	2.37	1.99
40	SD	0.53	0.94	2.08	142.31	97.73	31.43		-	2.46	1.39	0.21	0.17	0.22
	n	10	10	10	10	10	10		1	10	10	10	10	10
			* (+15)		* (+203)	* (+278)	* (+53)				* (+9)	* (-11)	* (-18)	
G3b	Mean	5.94	6.69	61.41	281.10	137.70	216.20	-	2.05	23.80	44.81	2.29	2.26	1.93
80	SD	0.83	0.77	2.08	127.22	66.88	43.20		0.24	1.99	1.26	0.18	0.10	0.78
	n	10	10	10	10	10	10		7	10	10	10	10	10

^: GGT: Lower Limit of Quantification (LLOQ): 3U/l and this parameter not analysed.
#: T Bil: Lower Limit of Quantification (LLOQ): 1.71µmol/l. Creat: Lower Limit of Quantification: 18µmol/l. Values below LLOQ were not considered for Statistical analysis. Values in parenthesis indicate % change.
*: Significantly higher / lower than the vehicle control group.

TABLE 3 contd. Summary of Clinical Chemistry Values at Termination – Males

Refer Appendix 3

Group No. Dose (mg/kg)		Glob g/l	A/G -	Trig mmol/l	CK U/l	LDH U/l	Na mEq/l	K mEq/l	Cl mEq/l
G1	Mean	20.94	1.97	0.50	425.50	245.10	142.03	3.84	91.33
0	SD	1.21	0.08	0.07	205.57	187.53	4.17	0.41	3.12
	n	10	10	10	10	10	10	10	10
		* (-12)	* (+23)	* (-20)			* (+3)		* (+4)
G2a	Mean	18.36	2.42	0.40	307.50	194.10	146.58	3.66	95.37
40	SD	2.77	0.36	0.04	115.54	49.60	3.09	0.67	1.80
	n	10	10	10	10	10	10	10	10
		* (-17)	* (+30)	* (-24)			* (+4)		* (+7)
G3a	Mean	17.47	2.57	0.38	356.10	235.80	147.24	3.90	97.57
80	SD	2.35	0.40	0.07	89.37	91.34	1.66	0.60	2.88
	n	10	10	10	10	10	10	10	10
			* (+14)	* (-14)	* (-37)		* (+4)		* (+6)
G2b	Mean	19.41	2.24	0.43	267.30	176.70	147.04	3.65	96.70
40	SD	1.62	0.20	0.05	73.12	39.61	1.83	0.25	2.20
	n	10	10	10	10	10	10	10	10
		* (-21)	* (+39)	* (-22)	* (-46)		* (+4)		* (+8)
G3b	Mean	16.60	2.73	0.39	228.90	189.40	147.12	3.66	98.55
80	SD	1.82	0.29	0.04	64.32	23.26	6.29	0.50	4.12
	n	10	10	10	10	10	10	10	10

+/-: Significantly higher/lower than the vehicle control group.
Values in parenthesis indicate % change.

Females

TABLE 4. Summary of Clinical Chemistry Values at Termination – Females

Refer Appendix 4

Group No. Dose (mg/kg)		Glu mmol/l	BUN mmol/l	T.Pro g/l	AST U/l	ALT U/l	ALP U/l	GGT^ U/l	T-Bil# µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	T.Chol mmol/l
G1	Mean	6.28	6.23	63.32	79.70	29.30	70.80	-	2.31	26.20	44.82	2.24	2.71	1.53
0	SD	0.45	0.82	1.70	8.04	6.06	18.15		0.43	2.30	2.22	0.28	0.09	0.24
	n	10	10	10	10	10	10		9	10	10	10	10	10
G2a	Mean	6.12	6.23	63.35	90.60	35.60	80.70	-	2.09	25.50	45.29	2.17	2.58	1.76
40	SD	0.60	1.11	2.75	14.79	14.33	18.74		0.25	2.92	1.64	0.22	0.14	0.35
	n	10	10	10	10	10	10		7	10	10	10	10	10
				* (+4)	* (+40)	* (+67)					* (+6)		* (-10)	* (+31)
G3a	Mean	5.73	6.58	65.99	111.50	48.80	89.10	-	2.17	25.50	47.38	2.25	2.43	2.01
80	SD	0.75	1.20	2.71	29.09	10.08	27.74		0.28	2.55	1.73	0.24	0.16	0.40
	n	10	10	10	10	10	10		8	10	10	10	10	10
				* (+5)	* (+18)		* (+38)				* (+6)		* (-12)	
G2b	Mean	6.34	6.79	66.32	93.70	33.80	97.70	-	2.22	28.70	47.37	2.12	2.38	1.83
40	SD	0.40	1.27	1.92	8.55	4.24	17.90		0.30	5.17	1.95	0.37	0.15	0.34
	n	10	10	10	10	10	10		5	10	10	10	10	10
				* (+7)	* (+66)	* (+152)	* (+38)				* (+8)		* (-14)	* (+40)
G3b	Mean	5.94	7.29	67.77	132.00	73.70	97.70	-	2.64	29.00	48.16	2.13	2.32	2.14
80	SD	0.93	0.87	1.29	25.95	20.52	23.13		0.41	3.06	1.64	0.17	0.12	0.52
	n	10	10	10	10	10	10		6	10	10	10	10	10

^: GGT: Lower Limit of Quantification (LLOQ): 3U/l and this parameter not analysed.
#: T Bil: Lower Limit of Quantification (LLOQ): 1.71µmol/l. Values below LLOQ were not considered for Statistical analysis.
Values in parenthesis indicate % change. *: Significantly higher / lower than the vehicle control group.

TABLE 4 contd. Summary of Clinical Chemistry Values at Termination – Females

Refer Appendix 4

Group No. Dose (mg/kg)		Glob g/l	A/G -	Trig mmol/l	CK U/l	LDH U/l	Na mEq/l	K mEq/l	Cl mEq/l
G1	Mean	18.50	2.45	0.39	335.20	148.10	142.40	3.72	93.13
0	SD	1.54	0.31	0.03	140.37	22.03	5.39	0.68	4.11
	n	10	10	10	10	10	10	10	10
G2a	Mean	18.06	2.53	0.37	358.90	159.50	143.00	3.65	94.58
40	SD	1.70	0.23	0.03	130.47	48.15	2.78	0.61	1.96
	n	10	10	10	10	10	10	10	10
				* (-10)					* (+6)
G3a	Mean	18.61	2.56	0.35	418.80	279.70	147.20	3.64	98.43
80	SD	1.67	0.21	0.03	259.23	275.02	6.40	0.74	2.61
	n	10	10	10	10	10	10	10	10
							* (+5)		* (+8)
G2b	Mean	18.95	2.51	0.38	282.00	222.30	149.30	3.55	100.65
40	SD	1.32	0.23	0.02	73.53	72.23	4.40	0.72	3.96
	n	10	10	10	10	10	10	10	10
						* (+143)	* (+6)		* (+8)
G3b	Mean	19.61	2.47	0.39	313.40	360.50	150.84	3.85	100.88
80	SD	1.12	0.20	0.06	93.99	253.02	5.01	0.64	4.31
	n	10	10	10	10	10	10	10	10

Values in parenthesis indicate % change.
+/-: Significantly higher/lower than the vehicle control group.

The following significant changes in clinical chemistry parameters were considered test-item related changes.

	MALES				FEMALES			
Analyte	ATORVASTATIN CALCIUM		(b) (4) IMPURITY		ATORVASTATIN CALCIUM		(b) (4) IMPURITY	
	G2a	G3a	G2b	G3b	G2a	G3a	G2b	G3b
	40 mg/kg	80 mg/kg	40 mg/kg	80 mg/kg	40 mg/kg	80 mg/kg	40 mg/kg	80 mg/kg
ALT	↑ 4.5 fold	↑ 4.7 fold	↑ 2.9 fold	↑ 3.8 fold	-	↑ 1.7 fold	-	↑ 2.5 fold
AST	↑ 2.8 fold	↑ 3.7 fold	↑ 2 fold	↑ 3 fold	-	↑ 1.4 fold	-	↑ 1.7 fold
ALP	-	↑ 58%	-	↑ 53%	-	↑ 25%	-	↑ 38%
Total Cholesterol	↑ 27%	↑ 29%	↑ 32%	↑ 29%	↑ 15%	↑ 31%	↑ 20%	↑ 40%
Triglycerides	↓20%	↓24%	↓14%	↓22%	-	↓10%	-	-
Calcium	↓7%	↓13%	↓14%	↓18%	↓5%	↓10%	↓12%	↓14%

-Indicates that values are not considered meaningfully different from controls
↑: Increase ↓: Decrease

ALT and AST increase in all the treated males and high dose females (G3a & G3b) and ALP increase in high dose males and females (G3a & G3b) was considered test-item related change as microscopically it was associated with hepatocyte single cell necrosis and degeneration.

Urinalysis: No drug related effects were observed.

Organ weights: Liver weights were increased in females at a HD with both products, i.e. with impurities (6.6* vs 5.8 g in controls, *p<0.05) and without impurities (6.4* vs 5.8 g in controls).

Increase in absolute and relative weights of liver (ratio to body weight) in high dose females (G3a &G3b) was considered test-item related change as microscopically hepatocyte single cell necrosis and degeneration were observed.

TABLE 11. Summary of Terminal Fasting Body Weights and Organ Weights – Females

Refer Appendix 9

Sex: Female		Terminal Fasting BW (g) 1 Way ANOVA (Automatic)	Adrenals (g) 1 Way ANOVA (Automatic)	Brain (g) 1 Way ANOVA (Automatic)	Heart (g) 1 Way ANOVA (Automatic)	Kidneys (g) 1 Way ANOVA (Automatic)	Liver (g) 1 Way ANOVA (Automatic)	Lungs (g) 1 Way ANOVA (Automatic)
		Day 15	Day 15	Day 15	Day 15	Day 15	Day 15	Day 15
G1 0	Mean	176.86	0.090	1.836	0.630	1.392	5.776	1.066
	SD	8.43	0.015	0.081	0.043	0.090	0.501	0.090
	N	10	10	10	10	10	10	10
G2a 40	Mean	176.01	0.088	1.806	0.637	1.365	5.676	1.013
	SD	11.57	0.013	0.090	0.057	0.120	0.415	0.067
	N	10	10	10	10	10	10	10
G3a 80	Mean	176.06	0.087	1.842	0.659	1.402	6.403 *(+11)	1.080
	SD	11.71	0.013	0.068	0.051	0.139	0.479	0.095
	N	10	10	10	10	10	10	10

*: Significantly higher than the vehicle control group (at 5% level of significance)

TABLE 13. Summary of Terminal Fasting Body Weights and Organ Weights – Females

Refer Appendix 9

Sex: Female		Terminal Fasting BW (g) 1 Way ANOVA (Automatic)	Adrenals (g) 1 Way ANOVA (Automatic)	Brain (g) 1 Way ANOVA (Automatic)	Heart (g) 1 Way ANOVA (Automatic)	Kidneys (g) 1 Way ANOVA (Automatic)	Liver (g) 1 Way ANOVA (Automatic)	Lungs (g) 1 Way ANOVA (Automatic)
		Day 15	Day 15	Day 15	Day 15	Day 15	Day 15	Day 15
G1	Mean	176.86	0.090	1.836	0.630	1.392	5.776	1.066
0	SD	8.43	0.015	0.081	0.043	0.090	0.501	0.090
	N	10	10	10	10	10	10	10
G2b	Mean	175.06	0.087	1.873	0.634	1.340	5.523	1.056
40	SD	10.31	0.009	0.082	0.066	0.069	0.442	0.108
	N	10	10	10	10	10	10	10
G3b	Mean	176.78	0.087	1.818	0.650	1.484	6.566 *(+14)	1.069
80	SD	12.97	0.011	0.084	0.072	0.151	0.642	0.108
	N	10	10	10	10	10	10	10

*: Significantly higher than the vehicle control group (at 1% level of significance)

Gross pathology: No drug related effects were observed.

Histopathology: The following drug related effects were observed.

Hepatocyte single cell necrosis and hepatocyte degeneration observed in all the treated males and high dose females (G3a & G3b) were considered test-item related changes. These microscopic changes had (increase in ALT, AST and ALP) clinical chemistry correlates.

TABLE 16 contd. Summary of Histopathological Findings

Refer Appendix 11 and 12

Observations: Non Neo-Plastic	MALES					FEMALES				
Removal Reason: TERMINAL SACRIFICE	G1	G2a	G3a	G2b	G3b	G1	G2a	G3a	G2b	G3b
	0	40	80	40	80	0	40	80	40	80
Number of Animals on Study :	10	10	10	10	10	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
LIVER;										
Examined	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Within Normal Limits	7	0	0	2	0	9	9	1	9	0
Hepatocellular necrosis; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
mild	0	0	0	0	1	0	0	0	0	0
Hepatocyte degeneration	(0)	(1)	(6)	(1)	(4)	(0)	(0)	(1)	(0)	(1)
minimal	0	1	4	1	2	0	0	1	0	1
mild	0	0	2	0	2	0	0	0	0	0
Hepatocytic single cell necrosis	(0)	(10)	(10)	(8)	(10)	(0)	(0)	(7)	(0)	(10)
minimal	0	9	8	8	7	0	0	7	0	10
mild	0	1	2	0	3	0	0	0	0	0
Increased mitotic acitivity; hepatocyte	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(0)	(0)
minimal	0	0	0	0	1	0	0	1	0	0
Portal leukocytic infiltration	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(2)	(0)	(0)
minimal	0	0	0	0	1	0	0	2	0	0
Pigmented kupffer cells; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0	0	0
Chronic inflammatory focus(i)	(2)	(0)	(0)	(1)	(0)	(1)	(1)	(0)	(1)	(0)
minimal	2	0	0	1	0	1	1	0	1	0
LYMPH NODE, MESENTERIC;										
Examined	(10)	(0)	(10)	(0)	(10)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	10	0	10	0	10	10	0	10	0	10
MAMMARY GLANDS;										
Examined	(8)	(0)	(8)	(0)	(9)	(10)	(0)	(10)	(0)	(10)
Within Normal Limits	8	0	8	0	9	10	0	10	0	10
Not Examined: Not Present	2	0	2	0	1	0	0	0	0	0

The following microscopic changes in liver were considered test-item related.

Microscopic change	MALES					FEMALES				
	ATORVASTATIN CALCIUM			[redacted] (b) (4) IMPURITY		ATORVASTATIN CALCIUM			[redacted] (b) (4) IMPURITY	
	G1	G2a	G3a	G2b	G3b	G1	G2a	G3a	G2b	G3b
mg/kg/day	0	40	80	40	80	0	40	80	40	80
Hepatocyte Single cell necrosis	0/10	10/10	10/10	8/10	10/10	0/10	0/10	7/10	0/10	10/10
Hepatocyte Degeneration	0/10	1/10	6/10	1/10	4/10	0/10	0/10	1/10	0/10	1/10

Sponsor's conclusions are provided below

The results of this study indicated that the 14 day repeated oral administration of the test item-without impurities (Atorvastatin Calcium) and with impurities [redacted] (b) (4) Impurity) to Wistar rats at the dose levels of 40 (G2a/G2b) and 80 (G3/G3b) mg/kg Bwt/day did not cause any moralities and did not elicit any effect on general health status, growth and food consumption of the animals. No treatment-related changes were observed in the functional observation tests. There were no test item-related alterations in hematology, coagulation and urinalysis parameters in both sexes. Treatment with test items resulted increased plasma ALT and AST levels in all the test items treated group males and in high dose females (80 mg/kg - G3a & G3b).The increases were also seen in plasma ALP level of high dose groups (80 mg/kg - G3a & G3b) and total cholesterol at all the test item treated groups in both sexes whereas decreases were seen in triglycerides level of all the test item treated males and high dose group females (80 mg/kg - G3a) and also decreases were seen in plasma calcium level in all the test items treated groups in both sexes. Increased absolute and relative weights of liver (ratio to body weight) were seen in high dose females (80 mg/kg - G3a &G3b) and these changes were associated with histological changes observed in the liver (hepatocyte single cell necrosis/degeneration). Microscopically, hepatocyte single cell necrosis/ degeneration observed in all the treatment group males and high dose females (80 mg/kg - G3a & G3b) and these changes were associated with increased in plasma ALT, AST and ALP level.

CONCLUSION

In view of the results discussed above, it is apparent that the observed findings in rats treated with Atorvostatin Calcium-without impurity were similar and no novel toxicity was seen when compared to Atorvastatin Calcium ([redacted] (b) (4) Impurity) with impurities. Further no changes of toxicological significance were noted among female Wistar rats that received a dose of 40 mg/kg body weight/day for test items Atorvostatin Calcium-without impurity or Atorvastatin Calcium ([redacted] (b) (4) Impurity) with impurities, hence this dose level is considered as No Observed Effect Level (NOEL) for the females and NOEL/NOAEL could not be established for males treated with test item alone or with the impurity under the test conditions and doses employed.

In summary: In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurity to rats. The impurity was (b) (4) (b) (4), present at (b) (4)% of API. The TK parameters (such as Cmax and AUC values) of the drug were not measured in this study. The drug (with and without impurity) produced some neuromuscular changes in the functional observation battery (such as grip strength and motor activity), but since RLD was not used, it is unclear if these were unique to the current drug product. Both products had no effects on clinical signs. BW gains in male rats were higher with impurity at a HD (19.4* vs 15.3 g in controls), *p<0.05) than without the impurity (17.6 vs 15.3 g in controls). In hematological/coagulation parameters, prothrombin time was decreased at all doses of the drug with impurity (16.6, 15.1*, 15.4* sec at 0, 40, 80 mg/kg/day respectively, *p<0.05), vs only at a HD without impurity. Similarly, ALP levels were increased at all doses of the drug with impurity (71, 98, 98 IU/L at 0, 40, 80 mg/kg/day respectively), these were not increased in the drug product without impurity. The histopathological changes were in general similar in the liver (i.e. with or without impurities in the drug). No NOAEL could be established in this study since even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one.

Genetic toxicology studies

Following gene-toxicity studies have been conducted with the (b) (4) (at concentration of (b) (4)%) to qualify this impurity.

1) AMES test was conducted with atorvastatin calcium, without and with (b) (4)% of (b) (4) impurity. As seen below, atorvastatin calcium was negative in the AMES test at doses up to 5000 ug/plate in the presence and absence of impurities (report # G7009). The study was conducted by (b) (4) (completed on 3/9/10).

Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted] (b) (4) impurity was tested for its mutagenic potential in the bacterial reverse mutation assay. The study was conducted using TA 98, TA 100, TA 1535 and TA 1537 strains of *Salmonella typhimurium* and WP2 uvrA (pKM 101) strain of *Escherichia coli*. The study consisted of a preliminary toxicity test and two mutation assays (trials) comprising four independent experiments. The bacterial tester strains were exposed to the test item in the presence and absence of metabolic activation system (S-9 fraction prepared from Aroclor 1254 induced rat liver).

The test items were found to be soluble at the required concentration of 50000 µg/mL in [redacted] (b) (4) The test item was also found to be stable for at least 6 hours in [redacted] (b) (4)

In a preliminary toxicity test, the mean number of revertant colonies and the intensity of the bacterial background lawn was comparable to the solvent control up to 5000 µg/plate, both in the presence and absence of metabolic activation. Hence, it was decided to test a maximum of 5000 µg/plate in the mutation assay.

In the first mutagenicity assay, the test items were exposed in triplicate to 50, 158, 500, 1581 and 5000 µg/plate test concentrations in the presence and absence of metabolic activation using direct plate incorporation procedure. In the confirmatory (second) assay, the test items were exposed in triplicate to concentrations of 100, 266, 707, 1880 and 5000 µg/plate in the presence and absence of metabolic activation using direct plate incorporation procedure. The solvent control [redacted] (b) (4) and the appropriate positive controls were tested simultaneously. The mean and standard deviation of numbers of revertant colonies were calculated for each test concentration and the controls for all the tester strains.

All formulations of the test doses from the mutation assay were analysed and the API concentrations were well within the acceptable range.

The results of the study, from the first as well as from the confirmatory assays showed that the mean numbers of revertant colonies neither doubled for strains TA 98, TA 100 and WP2 uvrA (pKM 101) nor tripled for strains TA 1535 and TA 1537 when compared to the respective solvent control plates, either in the presence or in the absence of the metabolic activation at any of the tested concentrations.

Under identical test conditions, there was a statistically significant increase in the mean numbers of revertant colonies in the positive controls, demonstrating the sensitivity of the assay procedure used.

The study indicated that the test items, Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted] (b) (4) - [redacted] (b) (4) impurity, were not mutagenic in this Bacterial Reverse Mutation Assay up to the highest tested concentration of 5000 µg/plate.

Purity as per Certificate of Analysis	:	Atorvastatin Calcium: [redacted] (b) (4) % on [redacted] (b) (4) basis [redacted] (b) (4) [redacted] (b) (4) impurity ATC ARL(A-489) 13-D: [redacted] (b) (4) % ATC ARL(A-489) 51B: [redacted] (b) (4) %
Batch No.	:	Atorvastatin Calcium: AC0160708 [redacted] (b) (4) [redacted] (b) (4) impurity: ATC ARL(A-489) 51B

TABLE 3. Summary Results of Bacterial Reverse Mutation Test (Trial 1)

Refer Appendix 2

Group	Treatment [µg/plate]	No. of revertants/plate*/ Presence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - [redacted] (b) (4) 100 µL)	24	4	97	5	12	3	14	1	135	3
G2	50	23	3	105	5	12	2	13	2	136	4
G3	158	22	0	104	6	+ 17	2	13	2	147	15
G4	500	23	1	111	2	9	1	13	1	130	6
G5	1581	22	2	+ 115	6	9	1	12	2	128	6
G6	5000	23	4	111	11	9	1	13	4	131	4
G7	50	22	3	104	10	11	2	14	2	132	5
G8	158	22	2	97	8	9	1	11	2	130	3
G9	500	26	2	99	8	14	1	11	3	137	6
G10	1581	23	2	110	8	13	2	14	1	141	7
G11	5000	23	1	+ 116	2	15	3	13	2	143	7
G12	Positive control	+ 538	11	+ 769	4	+ 137	4	+ 116	6	+ 575	13

*: Values are means of three replicates and are rounded off to the nearest whole number.
+ : Significantly higher than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with [redacted] (b) (4) Impurity.
Group No. G12 had respective positive controls.

TABLE 3. contd. Summary Results of Bacterial Reverse Mutation Test (Trial 1)

Refer Appendix 3

Group	Treatment [µg/plate]	No. of revertants/plate*/ Absence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - [redacted] (b) (4) 100 µL)	20	2	114	7	11	3	13	3	128	9
G2	50	25	3	- 80	9	9	2	9	2	121	1
G3	158	21	2	95	13	9	3	11	2	129	8
G4	500	22	2	103	9	13	1	11	3	135	10
G5	1581	25	5	102	9	12	2	13	2	117	18
G6	5000	20	4	97	11	14	2	13	3	117	4
G7	50	20	4	102	13	11	3	12	1	118	11
G8	158	21	4	103	4	12	5	13	1	122	3
G9	500	21	6	128	15	11	1	12	2	124	10
G10	1581	22	4	112	1	13	3	14	1	137	7
G11	5000	19	4	110	6	11	4	11	1	129	11
G12	Positive control	+ 232	10	+ 552	8	+ 127	9	+ 120	5	+ 575	8

*: Values are means of three replicates and are rounded off to the nearest whole number.
+/- : Significantly higher/lower than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with [redacted] (b) (4) mpurity.
Group No. G12 had respective positive controls.

TABLE 4. Summary Results of Bacterial Reverse Mutation Test (Trial 2)

Refer Appendix 4

Group	Treatment [µg/plate]	No. of revertants/plate*/ Presence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - (b) (4) (100 µL)	18	3	123	16	11	2	15	4	117	4
G2	100	20	2	- 106	3	10	1	15	3	115	4
G3	266	24	5	- 104	2	14	3	11	1	116	3
G4	707	23	3	114	2	12	3	15	2	116	4
G5	1880	24	3	108	7	9	2	14	1	122	4
G6	5000	23	4	111	7	11	4	13	1	120	8
G7	100	22	5	- 106	6	10	3	11	1	122	3
G8	266	19	1	108	5	12	3	11	2	127	7
G9	707	19	2	112	5	11	3	13	2	121	5
G10	1880	18	3	- 100	3	14	2	13	2	121	9
G11	5000	19	2	- 105	4	11	3	14	2	130	8
G12	Positive control	+ 537	8	+ 721	17	+ 148	3	+ 125	4	+ 579	4

*: Values are means of three replicates and are rounded off to the nearest whole number.
+/- : Significantly higher/lower than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with (b) % of (b) (4) impurity.
Group No. G12 had respective positive controls.

TABLE 4. contd. Summary Results of Bacterial Reverse Mutation Test (Trial 2)

Refer Appendix 5

Group	Treatment [µg/plate]	No. of revertants/plate*/ Absence of Metabolic activation									
		TA 98		TA 100		TA 1535		TA 1537		WP2 uvrA (pKM 101)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
G1	Solvent control - (b) (4) (100 µL)	22	7	112	8	10	2	12	2	116	4
G2	100	23	2	108	2	13	2	13	1	115	3
G3	266	18	2	112	7	14	3	14	2	122	6
G4	707	19	2	107	4	13	4	13	3	123	5
G5	1880	23	6	108	6	13	4	11	2	115	3
G6	5000	22	3	111	4	15	3	12	2	115	2
G7	100	21	5	102	3	11	2	12	2	122	3
G8	266	24	4	109	6	13	2	13	1	121	5
G9	707	21	4	113	3	10	1	13	1	122	4
G10	1880	19	2	107	4	13	2	13	1	115	3
G11	5000	19	1	113	4	14	1	13	2	118	3
G12	Positive control	+ 237	19	+ 553	7	+ 130	9	+ 125	5	+ 577	8

*: Values are means of three replicates and are rounded off to the nearest whole number.
+ : Significantly higher than the solvent control

Group Nos. G2 to G6 had five test concentrations of Atorvastatin Calcium. Group Nos. G7 to G11 had five test concentrations of Atorvastatin Calcium spiked with (b) % of (b) (4) impurity.
Group No. G12 had respective positive controls.

Conclusion: Thus as noted above, atorvastatin calcium drug product was negative in the AMES test at doses up to 5000 ug/plate in the absence and presence of [(b) (4)]% of [(b) (4)] impurity (report # G7009)

2. In vitro chromosomal aberration test in Peripheral blood lymphocytes:. Atorvastatin calcium spiked with [(b) (4)]% [(b) (4)] impurity was tested in an 'in vitro cultured Chinese Hamster ovary (CHO) cell in the mammalian chromosome aberration test. The drug was negative in the above assay with and without impurities (study # G7010). This assay was conducted at [(b) (4)] .

The details on the drug product and the study are provided below:

Purity as per Certificate of Analysis	:	Atorvastatin Calcium: [(b) (4)]% on [(b) (4)] basis [(b) (4)] [(b) (4)] impurity ATC ARL(A-489) 13-D: [(b) (4)]% ATC ARL(A-489) 51B: [(b) (4)]%
Batch No.	:	Atorvastatin Calcium: AC0160708 [(b) (4)] [(b) (4)] impurity: ATC ARL(A-489) 13-D and ATC ARL(A-489) 51B
Manufactured date	:	Atorvastatin Calcium: Nov 2007 [(b) (4)] [(b) (4)] impurity: Nov 2009

The clastogenic potential of the test items, Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted] impurity, to induce chromosome aberrations in mammalian cells was evaluated using cultured Chinese Hamster Ovary (CHO) cells.

The study consisted of a preliminary toxicity test and a chromosome aberration assay comprising three independent experiments, one each in the presence and absence of metabolic activation and a confirmatory experiment in the absence of metabolic activation. CHO cells were exposed to the test items in the presence and absence of metabolic activation system (S-9 fraction prepared from Aroclor 1254 induced rat liver).

Both the test items formed a solution in [redacted] at the tested concentration of 50 mg/mL. The dose formulations of the test items at 450 µg/mL and 50000 µg/mL were found to be homogeneous and stable in [redacted] for at least 6 hours at room temperature. The test items did not cause any appreciable change in the pH of the test medium at the end of 3-hour exposure to treatment either in the presence or in the absence of metabolic activation.

In a preliminary cytotoxicity test for the selection of test doses, a significant reduction in the growth of CHO cells was observed at and above 150 µg/mL both in the presence and absence of metabolic activation in 3-hour exposure and at 150 µg/mL in 21-hour exposure in the absence of metabolic activation compared to the [redacted] control with Atorvastatin Calcium and spiked Atorvastatin Calcium.

In the definitive chromosome aberration assay, CHO cells were exposed for 3 hours to Atorvastatin Calcium and spiked Atorvastatin Calcium in duplicate at the concentrations of 12, 36 and 108 µg/mL of the medium in the presence of metabolic activation and at 14, 44 and 140 µg/mL of the medium the absence of metabolic activation. Similarly, CHO cells were

exposed in duplicate at concentrations of 9, 28 and 90 μg/mL for 21 hours in the absence of metabolic activation.

In a similar way, concurrent solvent control and the positive controls, cyclophosphamide monohydrate in the presence of metabolic activation and ethylmethanesulphonate in the absence of metabolic activation were also tested in triplicate.

In each case, the cells in C-metaphase were harvested at 21 hours after the start of the treatment from the solvent control, test concentrations and the positive controls.

At the highest tested concentration of Atorvastatin Calcium, the reduction in the cell growth was 53% in the presence of metabolic activation, 57 and 58% in the absence of metabolic activation with 3 and 21-hour exposure, respectively, compared to the solvent control.

Similarly, at the highest tested concentration of spiked Atorvastatin Calcium, the reduction in the cell growth was 55% in the presence of metabolic activation, 56 and 56% in the absence of metabolic activation with 3 and 21-hour exposure, respectively, compared to the solvent control.

A total of 200 metaphases per dose level from triplicate cultures from the solvent control, treatment and the positive control were evaluated for chromosome aberrations. The data from the treatment groups and the positive control were statistically compared with the solvent control.

There was no evidence of induction of chromosome aberrations, either in the presence or in the absence of metabolic activation in any of the tested concentrations either including or excluding gaps.

In each of these experiments, the respective positive control substances produced a large and statistically significant increase in aberrant metaphases, under identical conditions.

The study indicated that Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) - (b) (4) Impurity do not have the potential to cause chromosome aberrations at the concentrations tested and under the conditions of testing.

TABLE 5. Summary Results of *In vitro* Mammalian Chromosome Aberration Test in the Presence of Metabolic Activation (Experiment 1)

Refer Appendices 2 and 3

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
(b) (4) (300 µL)	200	0	2 (1.0)	0	1 (0.5)	0	0	0	2 (1.0)	1 (0.5)	-
12	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	5
36	200	0	0	0	0	0	0	0	0	0	26
108	200	0	1 (0.5)	0	0	0	0	0	1 (0.5)	0	53
12	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	17
36	200	1 (0.5)	2 (1.0)	0	0	0	0	0	3 (1.5)	0	22
108	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	55
CPA 55	200	20 (10.0)	33 (16.5)	1 (0.5)	18 (9.0)	61 (30.5)	41 (20.5)	0	+ 122 (61.0)	+ 98 (49.0)	21

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations
Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome CPA: Cyclophosphamide monohydrate
+: Significantly higher than control ($p \leq 0.05$) by Fisher exact test
Groups G2 to G4 represents Atorvastatin Calcium and groups G5 to G7 represents spiked Atorvastatin Calcium

TABLE 6. Summary Results of *In vitro* Mammalian Chromosome Aberration Test in the Absence of Metabolic Activation (Experiment 2)

Refer Appendices 2 and 4

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
(b) (4) (300 µL)	200	0	2 (1.0)	1 (0.5)	1 (0.5)	0	0	0	4 (2.0)	2 (1.0)	-
14	200	0	3 (1.5)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	22
44	200	0	4 (2.0)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	29
140	200	0	2 (1.0)	2 (1.0)	2 (1.0)	0	0	0	5 (2.5)	4 (2.0)	57
14	200	0	4 (2.0)	0	4 (2.0)	0	0	0	5 (2.5)	4 (2.0)	27
44	200	1 (0.5)	3 (1.5)	1 (0.5)	2 (1.0)	0	0	0	5 (2.5)	3 (1.5)	36
140	200	1 (0.5)	2 (1.0)	0	1 (0.5)	0	0	0	3 (1.5)	1 (0.5)	56
EMS 600	200	18 (9.0)	57 (28.5)	51 (25.5)	42 (21.0)	32 (16.0)	25 (12.5)	1 (0.5)	+ 127 (63.5)	+ 99 (49.5)	21

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations
Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome EMS: Ethylmethane sulphonate
+: Significantly higher than control ($p \leq 0.05$) by Fisher exact test
Groups G2 to G4 represents Atorvastatin Calcium and groups G5 to G7 represents spiked Atorvastatin Calcium

TABLE 6. Summary Results of *In vitro* Mammalian Chromosome Aberration Test in the Absence of Metabolic Activation (Experiment 2)

Refer Appendices 2 and 4

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
(b) (4) (300 µL)	200	0	2 (1.0)	1 (0.5)	1 (0.5)	0	0	0	4 (2.0)	2 (1.0)	-
14	200	0	3 (1.5)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	22
44	200	0	4 (2.0)	0	2 (1.0)	0	0	0	5 (2.5)	2 (1.0)	29
140	200	0	2 (1.0)	2 (1.0)	2 (1.0)	0	0	0	5 (2.5)	4 (2.0)	57
14	200	0	4 (2.0)	0	4 (2.0)	0	0	0	5 (2.5)	4 (2.0)	27
44	200	1 (0.5)	3 (1.5)	1 (0.5)	2 (1.0)	0	0	0	5 (2.5)	3 (1.5)	36
140	200	1 (0.5)	2 (1.0)	0	1 (0.5)	0	0	0	3 (1.5)	1 (0.5)	56
EMS 600	200	18 (9.0)	57 (28.5)	51 (25.5)	42 (21.0)	32 (16.0)	25 (12.5)	1 (0.5)	+ 127 (63.5)	+ 99 (49.5)	21

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations
Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome EMS: Ethylmethane sulphonate
+: Significantly higher than control ($p \leq 0.05$) by Fisher exact test
Groups G2 to G4 represents Atorvastatin Calcium and groups G5 to G7 represents spiked Atorvastatin Calcium

Conclusion: Atorvastatin calcium spiked with (b) (4)% (b) (4) impurity was tested in an 'in vitro cultured Chinese Hamster ovary (CHO) cell in the mammalian chromosome aberration test. The drug was negative in the above assay with and without impurities.

L-Arginine safety assessment

In the previous consult review on L-arginine (see DARRTs, signed off on 6/16/09), we had recommended that the sponsor establish the safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), at levels intended ((b) (4)) for chronic use.

As indicated previously, L-arginine has been approved by FDA in injectable drug products in antibiotics, as an aid to solubilize the drug (at doses up to of 780 mg per gram of the drug, NDA 50-580, NDA 50-632, NDA 50-679 or Maxipime), these antibacterial drugs are not for a chronic use. Maxipime is dosed up to 2 g every 8 hours (the lowest dose is 500 mg every 12 hours). At these doses, L-arginine exposure with Maxipime will range from 1.5 g to 4.35 g/day, this dose is much higher than the dose that will be used in the atorvastatin calcium drug product ((b) (4)). However, L-arginine has not been approved by FDA in any oral drug products.

There is a study conducted at John's Hopkins in post-myocardial infarction patients taking L-arginine 3 g, three times a day (TID), for 6 months. This study reported that these high doses of L-arginine did not have a beneficial effect on cardiac outcomes and in fact had a detrimental effect {JAMA 2006 295(1):58-64}. In this study, L-arginine use was associated with higher post-infarction mortality (3 g TID). This study suggests that L-arginine should not be recommended following acute myocardial infarction.

Therefore, there is published clinical literature suggesting that patients with cardiovascular disease may have adverse outcomes from L-arginine. Patients with frank and underlying disease as well as those with cardiovascular (CV) risk are given atorvastatin to lower cholesterol (and implied CV risk) in combination of various drugs. Safe levels of L-arginine have not been established in this patient population. The literature supports the safety of L-arginine in an otherwise healthy population and more importantly reports significant adverse outcomes with L-arginine in patients with CV risk without establishing a safe level. The information provided by the sponsor does not address this body of literature at all.

Note that nonclinical studies may not address or establish the risk because they are performed in otherwise healthy animals. Animal CV disease models have a tenuous association to human risk and it is unclear which CV models are most relevant to this situation. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population i.e. subjects with CV disease. There may be data available from patients with CV disease that have received a particular level of L-arginine chronically in other approved drugs at levels intended for use here ((b) (4)). While this may be supportive, additive effects of other co-administered medications with L-arginine can not be excluded. There are known drug interactions with L-arginine and common medications in this patient population (e.g. potassium sparing diuretics, ACE inhibitors etc.).

In conclusion, the long term effects of oral L-arginine (the semi-essential amino acid) are unknown. The current generic drug product atorvastatin calcium would be used by patients for many years. Because the patient population in ANDA (b) (4) is very different (i.e. patients with frank and underlying diseases, as well as those with cardiovascular risk), and there's cause for heightened concern in patients with CV disease based on clinical literature, which is the intended patient population for atorvastatin; safe levels of L-arginine in the patient population have not been established. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), as well as the additive effects of other co-administered medications with L-arginine. This data may be available from the literature from

patients with CV disease that have received a particular level of L-arginine chronically in other approved drugs at levels intended for use here ([(b) (4)]).

We had provided following recommendations on 6/16/2009:
The long term effects of oral L-arginine are unknown. The generic atorvastatin calcium is for chronic use, it is important to know at what doses it produces toxicity, especially in patients with cardiovascular (CV) risk. Therefore, sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease). This data may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use here ([(b) (4)]).

In the current submission (4/8/2010), sponsor has provided more justification for use of the inactive ingredient L-Arginine, in their atorvastatin calcium drug product. Sponsor in response to our recommendation has provided a summary of published and unpublished studies from the Medline/toxline search as stated below.

Sponsor has provided following summary of studies on L-Arginine:

> The purpose of this document is to review the available clinical safety information on L-Arginine to provide an assessment of the safe use in the proposed product in cardiovascular disease subjects. This review was based on available published and unpublished information. The published clinical information was identified through searching the internet as well as the National Library of Medicine databases (MEDLINE/TOXLINE) back to 1965. The CAS number and the generic names/synonyms were used in the database searches. The search resulted in the identification of a large number of publications including a number of review articles which include assessments of safety and efficacy in patient populations for a number of cardiovascular diseases as well as associated risk factors. Collectively, these publications demonstrate the strong acceptability of the use of L-Arginine supplementation in subjects with cardiovascular disease and indicate good tolerability at doses far exceeding the proposed limit of [(b) (4)] in Matrix's atorvastatin calcium drug product formulation.
>
> ***Hypertension:*** NO plays a crucial role in regulating blood pressure; thus, L-Arginine or NO deficiency results in hypertension in animals and humans. Much research has shown that intravenous or oral L-Arginine administration increases NO synthesis and prevents endothelial dysfunction in animal models of pulmonary hypertension or salt-induced hypertension. The same beneficial effect of L-Arginine has been observed in most studies involving hypertensive patients, who exhibit elevated plasma levels of ADMA and reduced NO synthesis.

Summary reviews have been previously published and established the safety and efficacy in these cardiovascular conditions (Cheng, 2001; Bode-Boger, 2006; Shao 2008).

L- Arginine in clinical trials

Based on observations from experimental clinical studies, which showed vasodilation and enhanced NO production after administration of L-Arginine, a series of clinical trials have been performed to investigate the potential of this amino acid to improve the symptoms of cardiovascular disease. The first clinical application of L-Arginine in an attempt to improve vascular function in patients with cardiovascular disease was published almost 20 years ago. Since then, there have been many studies with L-Arginine in healthy human subjects or in patients with various cardiovascular conditions.

L-Arginine has generally been well tolerated by healthy volunteers and patients when administered via the intravenous or oral route in doses <30 g. When high doses of L-Arginine are given intravenously, local irritation and phlebitis may occur because of the high osmolality of the solution.

The following trails are aimed at determining the efficacy and safety of L-Arginine administered in long- term clinical trails as summarized below.

1. Bednarz et al, 2005 examined 792 patients with acute ST-segment elevation myocardial infarction admitted within 24h after the onset of symptoms. This multicenter, randomized, double-blind, placebo-controlled study examined the effects of placebo or 3 grams of L-Arginine orally in capsules three times daily for a period of 30 days. The end point which was the composite of 30 day cardiovascular death, reinfarction, successful resuscitation, shock/pulmonary edema or recurrent myocardial ischemia occurred in 24% patients treated with L-Arginine and 27% with placebo. These results demonstrated a beneficial trend in patients with an acute MI while also demonstrating that 9 grams of L-Arginine orally is safe and well tolerated.
2. Gutman and colleagues (2005) studied the effects of L-Arginine supplementation 45 patients with multiple risk factors or evidence of vascular disease. The study was a randomized, double-blind assessment of 6 grams of L-Arginine or placebo daily for 6 months. The results demonstrated that L-Arginine supplementation is well tolerated and serves to reduce systolic blood pressure and increase large artery elasticity.
3. Lucotti et al, 2009 studied the effect of oral L-Arginine supplementation (6.4 grams per day) in 32 non-diabetic cardiopathic patients following aortocoronary bypass in a six month duration placebo controlled clinical trail. The results of this study conclude that L-Arginine supplementation (6.4 grams per day) in Non-diabetic cardiopathic patients improved glucose tolerance in coronary artery bypass grafted (CABG) patients; this was achieved through significant improvement of Serum Insulin (SI) levels, endothelial function. There was no added risk when L-Arginine was added in the therapy, and on the contrary there was a significant benefit as explained above.
4. Koga Y et al 2006 evaluated the effects of administration of L-Arginine in 15 young patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS) and 20 control subjects in long term study after administration of L-Arginine orally in a dose range of 4-24 g/day for at least a 24 months treatment period. The outcome of the study indicated that the frequency and severity of clinical symptoms of stroke-like episodes decreased without serious adverse effects.
5. Lerman A, et al 1998 evaluated the effects of L-Arginine supplementation in a long-term placebo controlled study after administration of L-Arginine orally 3g TID for 6 months treatment period in 26 patients without coronary artery disease (CAD). The outcome of the study indicated that the L-Arginine supplementation for 6 months in human improves coronary small vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentrations. Update
6. Hambrecht, et al 2000 evaluated the effects of L-Arginine supplementation and exercise in a short term placebo controlled study after administration of L-Arginine orally 8g/day in chronic heart failure patients with endothelial dysfunction. Forty patients were studied in a crossover fashion in 4 groups receiving L-Arginine with or without exercise and a control group without L-Arginine and exercise for 4 weeks in each period with a one week washout with each treatment. The outcome of the study indicated that the L-Arginine

supplementation for 4 weeks leads to a fourfold increase in endothelium dependent vasodilatation in patients with CHF after four weeks of treatment.

7. Martina and colleagues (2008) studied the effects of L-Arginine in 24 male subjects with hypertension and Type 2 Diabetes. The study was a randomized, double-blind, placebo-controlled study which evaluated 1200 mg of L-Arginine once daily and 600 mg n-acetylcysteine twice daily for 6 months. In this study, N-acetylcysteine and L-Arginine were demonstrated to improve endothelial function by improving NO bioavailability via a reduction of oxidative stress and increase in NO production without any adverse effects.
8. Reul et al. 2008 studied the effects of L-Arginine and vascular endothelial growth factor or placebo for 3 months in 19 severe diffuse coronary artery disease patients. Subjects were randomized in 2 X 2 factorial fashion to receive ten 200-mg injections of vascular endothelial growth factor-165 plasmid DNA or placebo in the anterior myocardium along the proximal and mid-left anterior descending arteries, plus oral L-Arginine supplementation at a dose of 6 g per day or placebo for 3 months. Patients who received the combination of vascular endothelial growth factor and L-Arginine had improved anterior wall perfusion on positron emission tomography (P=0.02), a trend toward smaller perfusion defects (P=0.10), and better anterior wall contractility (P=0.02, Kruskal–Wallis) at 3 months vs. baseline. In this study L-Arginine administration was not associated with any major adverse events.
9. The Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) published by Schulman (2006) was a single-center, randomized, double-blind, placebo-controlled trail examining the effects of L-Arginine (3g tid) or matching placebo in 153 myocardial infarction subjects for 6 months. In this study, L-Arginine added to standard postinfarct medications did not reduce noninvasive measures of vascular stiffness, improve ejection fraction, or improve clinical outcomes. Six-month clinical events, including death, myocardial infarction, and hospitalization for heart failure, occurred in 12 (16.7%) patients in the L-Arginine group compared with 7 (10.1%) patients in the placebo group. However, 6 participants (8.6%) in the L-Arginine group died during the 6-month study period vs. none in the placebo group (*P*=.01). Because of the safety concerns, the data and safety monitoring committee closed enrollment.
10. The Nitric Oxide in Peripheral Arterial Insufficiency (known as the NO-PAIN study) published by Wilson (2007) was a single center, randomized, double-blind, placebo-controlled trail examining the effects of L-Arginine (3/day) or matching placebo in 133 patients with Peripheral Artery Disease for 6 months. In this trial oral L-Arginine supplementation significantly increased plasma L-Arginine levels, however, measures of nitric oxide were reduced or not improved compared with placebo. There were 9 adverse events reported in each group that were considered serious including 1 death in both the placebo and L-Arginine, however, no group differences existed in serious or total adverse events.

Note that none of the studies provided above are standard toxicity studies. The studies provided are clinical publications using higher doses in CV patients for 6 months. Pharmacology /toxicology can not make this safety call on the summary of some clinical literature in subjects with CV disease from a literature search, this needs to be determined by the medical officer. As indicated earlier, the patient population from the Johns Hopkins study with 3 g L-arginine was associated with increased mortality in subjects with post acute myocardial infarction (MI, see reference 9 on page 59 by Schulman JAMA 295:58, 2006). Note that although (b) (4) is considerably less, we do not have any data that suggests that the long-term use at this dose is safe in patients with MI, who will likely be given atorvastatin chronically.

We have a concern, because the literature studies provided are not adequate to support the levels of L-arginie in their atorvastatin drug product. Thus, proposed generic atovastatin calcium may not be "the same as Lipitor" based on the L-arginine being present. The 2-week toxicity studies provided by the sponsor (to qualify the impurities) or the 13-week toxicity study (from this reviewer's literature search) are not sufficient to establish safety for a chronic use product with a potential safety risk in the patient population its indicated for.

Safety Evaluation

1. Qualification of (b) (4) and (b) (4) impurities in the atorvastatin calcium drug product.

Sponsor has conducted a 2-week toxicity study and two in vitro geno-toxicity studies to qualify above impurities in their drug product. The summary of these studies are provided below.

In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurities to rats. The impurities were (b) (4) (b) (4) (at concentration of (b) (4)%) and (b) (4) (at concentration of (b) (4)%), both relative to atorvastatin calcium drug product. The TK parameters of the drug (such as Cmax and AUC values) were not measured in this study. The drug had no effects on clinical signs and BWs with and without the impurities. Food consumption was not significantly altered with both. Hematological parameters, such as hemoglobin and hematocrit were increased at all doses of the drug (with or without impurities); since the reference listed drug (RLD) was not used in the study, it is hard to know if these toxicities were unique to the current drug product. In clinical chemistry parameters, similar effects were observed on liver enzymes, etc. with or without impurities. The histopathological changes in the liver were also in general similar in the presence or absence of impurities in the drug. No NOAEL could be established in this study, as even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. However, toxicity of both products (with or without impurities) were in general similar.

Mutagenicity: Atorvastatin calcium without and with impurity (spiked with (b) (4)% of (b) (4) (b) (4) and (b) (4)% of (b) (4) in the atorvastatin calcium drug product) was not mutagenic/cytogenic in the following 2 tests: Ames test at doses up to 5000 ug/plate, and in vitro in chromosomal aberration assay in human peripheral blood lymphocytes at concentration up to 150-300 ug/ml with 50% mitotic index.

2. Qualification of (b) (4) impurity in the atorvastatin calcium drug product.

Sponsor has conducted a 2-week toxicity study and two in vitro geno-toxicity studies to qualify above impurity in their drug product. The summary of these studies are provided below.

In summary: In a 2-week oral gavage toxicity study of atorvastatin calcium, doses of 0, 40, 80 mg/kg/day were administered without and with impurity to rats. The impurity was (b) % (b) (4) in the drug product. The TK parameters (such as Cmax and AUC values) of the drug were not measured in this study. The drug (with and without impurity) produced some neuromuscular changes in the functional observation battery (such as grip strength and motor activity), but since RLD was not used, it is unclear if these were unique to the current drug product. Both products had no effects on clinical signs. BW gains in male rats were higher with impurity at a HD (19.4* vs 15.3 g in controls, *p<0.05); which was not seen without the impurity (17.6 vs 15.3 g in controls). In hematological/coagulation parameters, prothrombin time was decreased at all doses of the drug with impurity (16.6, 15.1*, 15.4* sec at 0, 40, 80 mg/kg/day respectively, *p<0.05), vs only at a HD without impurity. Similarly, ALP levels were increased at all doses of the drug with impurity (71, 98, 98 IU/L at 0, 40, 80 mg/kg/day respectively), these were not increased in the drug product without impurity. The histopathological changes were in general similar in the liver (i.e. with or without impurities in the drug). No NOAEL could be established in this study since even at the lowest dose of 40 mg/kg/day, toxicity was noted in the liver with both products. Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one, so this study has limited value. Thus, although some subtle differences in toxicity of the drug with impurities vs without impurities were observed as noted above, the toxicity of both products (without or with (b) (4) impurity) were in general similar.

Mutagenicity: Atorvastatin calcium without and with impurity (spiked with (b) % (b) (4) impurity in the atorvastatin calcium drug product) was not mutagenic/cytogenic in the following 2 tests: Ames test at doses up to 5000 ug/plate, and in vitro in chromosomal aberration assay in cultured Chinese Hamster Ovary (CHO) cells at concentration up to 108-140 ug/ml.

In summary, Sponsor by providing 2-week toxicity study in one species (rats) with the atorvastatin with impurities (spiked with (b) (4) and (b) (4) in the atorvastatin calcium drug product, as well as with (b) (4) impurity) and without impurities, as well as by conducting two geno-toxicity studies (Ames and chromosome aberration assay) has qualified the impurities in their atorvastatin calcium, and these are acceptable.

3. Safety of L-arginine: In the current submission, sponsor has provided additional clinical studies to support the (b) (4) of L-arginine in 80 mg of atorvastatin drug product. Pharmacology /toxicology can not evaluate the safety of clinical literature summaries in subjects with CV disease, this needs to be determined by the medical officer.

The 2-week toxicity studies provided by the sponsor (to qualify the impurities) or the 13-week toxicity study (from this reviewer's literature search on L-arginine) are not sufficient to establish safety for a chronic use product with a potential safety risk in the patient population its indicated for. At present the proposed generic atovastatin calcium may not be "the same as Lipitor" based on the L-arginine being present.

Internal Recommendations:

From the pharmacology/toxicologyy point of view, the proposed levels of [redacted] (b) (4) and [redacted] (b) (4) impurities, as well as [redacted] (b) (4) impurity in the atorvastatin calcium drug product are qualified, based on submitted toxicity studies.

As far as the safety of L-arginine is concerned, pharmacology /toxicology can not determine the safety of the summary of clinical studies provided by the sponsor in subjects with CV disease from a literature search, these need to be assessed by the medical officer. The proposed generic atovastatin calcium may not be "the same as Lipitor" based on the L-arginine being present. The 2-week toxicity studies provided by the sponsor (to qualify the impurities) or the 13-week toxicity study (from this reviewer's literature search) are not sufficient to establish safety for a chronic use product with a potential safety risk in the patient population it's indicated for.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/aljuburi/TranTrang/Leigh Ann Bradford/Ripper, L
File name: ANDA 91226-10-OGD consult (atorvastatin- Matrix)

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/s/

INDRA ANTONIPILLAI
09/29/2010
Please see the internal pharmacology/toxicology recommendations.

KAREN L DAVIS BRUNO
09/29/2010

Labeling comments

ANDA 91226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Mylan Pharmaceuticals Inc.
U.S. Agent for Matrix Laboratories LTD.

TEL: 304-599-5899

FAX: 304-285-6407

ATTN: Keith Giunta

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20mg, 40 mg and 80 mg.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:
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/

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

ANDA Number: 91226 Date of Submission: August 12, 2010

Applicant's Name: Matrix Laboratories Ltd.

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

---

Labeling Deficiencies:

1. CONTAINER (all strengths in bottles of 90s and 500s):

   Acceptable in final print

2. INSERT

   FULL PRESCRIBING INFORMATION: CONTENTS

   Revise to read:

   2.1 Hyperlipidemia [delete “Heterozygous...IIb]

   2.2 Heterozygous Familial...Patients [delete “10 to 17....Age]

   14.2 Hyperlipidemia and Mixed Dyslipidemia [delete “Heterozygous Familial...Nonfamilial” and “Frederickson Types... IIb]

   14.3 Hypertriglyceridemia [delete “Fredrickson Type IV]

   14.4 Dysbetalipoproteinemia [delete Fredrickson Type III]

3. PATIENT INFORMATION SHEET:

   Acceptable in final print.

Submit labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

THUYANH VU
09/10/2010

JOHN F GRACE
09/20/2010
for Wm Peter Rickman

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: September 14, 2010

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director,
Document Control Room
7620, Standish Place,
Rockville, Maryland 20857

Gratuitous Labeling Amendment

Subject: ANDA # 91-226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Dr. Webber:

Reference is made to the subject under-review ANDA of Matrix Laboratories Limited, India. The objective of this labeling amendment is to provide updated insert labeling for revision in the drug substance description to be consistent with the Chemistry, Manufacturing and Controls section of the application. To facilitate review, a side by side comparison of revised proposed labeling against the last submitted labeling with differences annotated and explained, is being submitted with this amendment. Other label/labeling components (PIL, container labels) remain unaltered.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Consultation from: Office of Generic Drugs/OGD/RSB (HFD-615)

Reviewer: James M. Willard Ph.D. Pharm/Tox Reviewer

Through: Albert Defelice Ph.D., DCaRP Pharm/Tox Team Leader

Norman Stockbridge M.D., DCaRP Division Director

Document Date: 4/8/2010

Date: 9/8/2010

Due Date: 9/9/2010

ANDA No.: 91226

Drug Name: Atorvastatin Calcium

Reason for Consult: OGD is requesting a pharm/tox review. "Impurities listed are higher than the RLD." Please evaluate the amendment ANDA in EDR Module 3 (See attached documents for reference),

Review:

Introduction:

Atorvastatin is a HMG-CoA inhibitor that blocks production of cholesterol primarily in the liver. It is a member of the statin group, all of which have a primary mode of action in this area. Statins are under the purview of the Division of Metabolic and Endocrine Products, however, this consult was submitted to the Division of Cardiovascular and Renal Products. The primary issues are related to 3 impurities/degradation products: 1) (b) (4)

The primary issues associated with this submission are the higher levels of the (b) (4) (b) (4) and (b) (4) along with the (b) (4) impurity in the preparation. Sponsor sought to qualify the compounds with bacterial reverse mutation studies, in vitro

mammalian chromosome aberration studies, and a 14 day repeat dose oral toxicity study for the (b) (4) impurity.

Additionally, the sponsor did a safety assessment of L-arginine, which is added as a (b) (4) and is approximately (b) (4)% of the capsule contents, with the projected highest exposure to be (b) (4) with the 80 mg capsules (L-arginine supplements can be purchased over the counter in 500 mg or larger capsules).

Toxicology:

(b) (4)

(b) (4)

Structure of Atorvastatin

(b) (4)



Mechanism:

Atorvastatin is one of the HMG-CoA inhibitors that block cholesterol synthesis in the liver.

Genotoxicity of the [redacted] and [redacted] Impurities:

1. Bacterial Reverse Mutation Assay for Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted]% [redacted] and [redacted]% [redacted] impurities of Atorvastatin
    a. Study was done following typical methodology and using US GLP standards.
    b. Compound used was from the following batches:

[redacted] Code Number	Test Article / Impurity ID	Batch No.	Purity (per protocol)	Test Article Description	Storage Conditions
AC27KV	Atorvastatin Calcium	AC0160708	[redacted]%	White powder	-15 to -40°C, stored in the dark with desiccant
AC27KW	[redacted] Impurity of Atorvastatin	ADL/941(149)/1008	[redacted]%	[redacted]	
AC27KX	[redacted] Impurity of Atorvastatin	ATC/Imp/918/118	[redacted]%		

c. Positive controls were typical for this assay system:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535 and TA1537	Rat	2-aminoanthracene (b) (4) Lot No. 03403ED Exp. Date 22-Jan-2012 CAS No. 613-13-8 Purity (b) (4) %	1.0
TA100			2.0
WP2 *uvr*A			10

d. Bacterial strains were standard for the assay system:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98	None	2-nitrofluorene (b) (4) Lot No. 03319JD Exp. Date 28-Feb-2011 CAS No. 607-57-8 Purity (b) (4) %	1.0
TA100, TA1535		sodium azide (b) (4) Lot No. G24R025 Exp. Date 10-Feb-2010 CAS No. 26628-22-8 Purity (b) (4) % min.	1.0
TA1537		9-aminoacridine (b) (4) Lot No. 106F06682 Exp. Date 08-Nov-2009 CAS No. 90-45-9 Purity (b) (4) %	75
WP2 *uvr*A		methyl methanesulfonate (b) (4) Lot No. 06823KH Exp. Date 04-Jun-2011 CAS No. 66-27-3 Purity (b) (4) %	1,000

e. Results: Atorvastatin plus impurities was negative in the bacterial genotoxicity testing.

2. Bacterial Reverse Mutation Assay with the (b) (4) impurity:
   a. Assay was done using typical methods and under GLP standards
   b. Conditions and cultures and positive controls were similar to the previous study.
   c. Results: no positive genotoxicity results were seen.

3. In vitro mammalian chromosome aberration test report for Atorvastation Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) (b) (4) impurities of Atorvastatin:
    a. Results for Atorvastatin alone are seen in the following table:

Treatment Time (hours)	Recovery Time (hours)	Harvest Time (hours)	S9	Mitotic Index Reduction[1] at dose scored (µg/mL)	LED[2] for Structural Aberrations (µg/mL)	LED[2] for Numerical Aberrations (µg/mL)
4	16	20	-	52% at 300	None	None
20	0	20	-	58% at 150	None	None
4	16	20	+	54% at 250	None	None

[1] relative to the solvent control at high dose evaluated for chromosome aberrations
[2] LED = lowest effective dose level

    b. Results for Atorvastatin plus impurites are seen in this table:

Treatment Time (hours)	Recovery Time (hours)	Harvest Time (hours)	S9	Mitotic Index Reduction[1] at dose scored (µg/mL)	LED[2] for Structural Aberrations (µg/mL)	LED[2] for Numerical Aberrations (µg/mL)
4	16	20	-	50% at 125	None	None
20	0	20	-	51% at 100	None	None
4	16	20	+	57% at 150	None	None

[1] relative to the solvent control at high dose evaluated for chromosome aberrations
[2] LED = lowest effective dose level

    c. Assays were done by (b) (4) following OECD protocols and using GLP standards.
    d. Assays were negative at up through concentrations which markedly decreased mitotic index.

4. In Vitro mammalian chromosome aberration test report – (b) (4) impurity:
    a. Assays were done by (b) (4) following OECD protocols and using GLP standards
    b. Assays were negative.

Repeat Dose Toxicology Studies:

14-day Repeat dose oral toxicity study by gavage in wistar rats- [redacted] impurity:

Assay was done to GLP standards

Results: Minor liver damage with mild necrosis/degeneration was the only histopathology reported in all males and the high and mid-dose females treated with Atorvastatin *per se* or combined with [redacted] impurity. The impurity did not promote lesion severity.

Conclusion: The [redacted] impurity, in combination with Atorvastatin, neither exacerbated the liver histopathology observed with the statin *per se* nor provoked other gross or microscopic lesions in this study. Accordingly, at the dosages tested, there was no extra overt toxicologic pathology to attribute to the impurity.

A 14-Day Toxicity Study of Atorvastatin Calcium Administered by Oral Gavage to Rats: [redacted] and [redacted] impurities

Experimental Design

Group No.	No. of Toxicity Animals		Test Material	Atorvastatin Dose Level (mg/kg/day)	Atorvastatin Dose Concentration (mg/mL)	Atorvastatin Dose Volume (mL/kg)	Atorvastatin Adjusted Dose Concentration[a] (mg/g[b])
	Male	Female					
1	10	10	[redacted] CMC	0	0	10	0
2	10	10	Atorvastatin Calcium	40	4	10	4.136
3	10	10	Atorvastatin Calcium + impurities[c, d]	40	4	10	4.136
4	10	10	Atorvastatin Calcium	80	8	10	8.272
5	10	10	Atorvastatin Calcium + impurities[c, d]	80	8	10	8.272

[a]Expressed as [redacted] concentration. Correction factor of [redacted] applied (based on [redacted]
[b]The dose concentrations were based on an approximate density of 1 g/mL.
[c]The [redacted] impurity was adjusted by [redacted] for purity.
[d]The Atorvastatin Calcium and [redacted] impurity was combined at a ratio of [redacted] [redacted]% concentration of [redacted] impurity relative to Atorvastatin Calcium). This provided an approximate [redacted] impurity concentration of [redacted]% relative to Atorvastatin Calcium.

Assay was done to GLP standards. No additional toxicity that could be attributed to the [redacted] and [redacted] impurities could be seen in the assay. Toxicities seen with Atorvastatin and Atorvastatin plus impurities were similar.

L-Arginine Safety Assessment:

Sponsor points out that L-Arginine at [redacted]% of any formulation is considered GRAS (Generally Regarded As Safe) by the FDA,. It comprises [redacted]% of the proposed formulation.. L-Arginine is available as a supplement in 500 mg and 1,000 mg capsules.

In my opinion, the exposure to L-Arginine contained in the Atorvastatin product is of little toxicological concern.

Summary and Recommendations:

OGD requested a review of studies qualifying 3 impurities from Atorvastatin Calcium, a generic replacement for Lipitor®. Genotoxicity assays were done for Atorvastatin per se and Atorvastatin plus either the (b) (4) and (b) (4); and Atorvastatin plus the (b) (4) impurity. All 3 combinations were negative in the bacterial reverse mutation assay and in the mammalian chromosomal aberration assays. In addition, 14 day toxicology studies were done on Atorvastatin per se, or in combination with impurities.. These studies showed no differences between Atorvastatin neat versus Atorvastatin spiked with either the (b) (4) or a combination of the (b) (4) and (b) (4) impurities. The human exposure, on a mg/Kg basis, to the various impurities at the highest dose (80 mg) and at up to Sponsor's limits will be approximately (b) (4) times less than the dosages used in the toxicology studies (see below):

Impurity	% in	Tox study Exposure per 60	Actual Exposure per 60
(b) (4)			

This demonstrates a reasonable safety margin for the tested impurities. Since no degradant –related excess toxicity was observed, the maximum NOAEL are greater than the sub-toxic dosage tested, and the (b) (4) safety margins are conservative.

The impurities from the Atorvastatin synthesis do not show toxicity at the concentrations and dosages studied *in vitro* and *in vivo*, respectively.,, There is some concern that the release specifications for the finished product allow up to (b) (4)-(b) (4)% (w/w) of the (b) (4) and (b) (4) impurities, i.e., levels that are appreciably higher than measured in the batches of drug substance ((b) (4)-(b) (4)%, w/w; see table below.. Sponsor needs to provide sufficient reasoning for the liberal NMT limits.

Impurities control in Drug Substance ATORVASTATIN CALCIUM

TEST	RESULTS		SPECIFICATION
	AC0090408 (DS Manufacturer)	1004608 (DP Manufacturer)	
Related Substances (by HPLC)			(b) (4)

Impurities control in Drug Product

Impurities limit in Finished Product Specification- Atorvastatin Calcium Tablets, 10 mg, 20, 40 and 80 mg.

Test	Specification	
	Release	Shelf life
Related Substances (by HPLC)		(b) (4)

Please feel free to contact me if you have any questions or need clarification on any issue.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

JAMES M WILLARD
09/10/2010

ALBERT F DEFELICE
09/10/2010

NORMAN L STOCKBRIDGE
09/10/2010

BIOEQUIVALENCE AMENDMENT

ANDA 091226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Matrix Laboratories Limited TEL: (304) 554-5899

ATTN: Keith Giunta FAX: (304) 285-6407

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 30, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendment dated September 30, 2009.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence SOPs **Bioequivalence Response to Information Request**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

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/

Please submit your response in electronic format. This will improve document availability to review staff.

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BIOEQUIVALENCE DEFICIENCIES

ANDA:	091226
APPLICANT:	Matrix Laboratories Limited, India
DRUG PRODUCT:	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. For your pre-study method validation, please specify the salt form of the Ethylenediaminetetraacetic Acid(EDTA), the anticoagulant used in the blank human plasma of the method validation samples.

2. Your repeat analysis for both fasting and fed study is incomplete. Please provide the following:

    1) For the fasting study (study No. 022-08), please provide the quality control (QC) data of the run for the samples of subject No. 09 to show clearly that the batch was rejected due to the QC data not meeting the acceptance criteria.

    2) For the fed study (study No. 162-08), please provide the original concentrations of atorvastin of subject No. 25 for further evaluation.

    3) Please provide the Standard Operation Procedures (SOP) for the re-integration of the chromatograms. In addition, please provide the concentrations of the three analytes of subject No. 42 and No. 43 in fasting study and subject No. 01 and No. 02 in fed study, obtained using the original integration parameters that were used for other batches in the fasting and fed study, respectively.

3. For the clinical report of the fed study, please explain why some elevated creatine phosphokinase (CPK) levels obtained in some subjects during the post-study lab assessment were listed as adverse events (For example, increased CPK levels of 310 U/L in Subject #3), while some other similar increased CPK levels obtained during the washout period were not listed as adverse events (For example, the CPK level of 410 U/L in Subject #16 and the CPK level of 342 U/L in

Subject #49). Please provide a complete list of abnormal laboratory results obtained during the washout and post-study assessment even if the results were not considered clinically significant.

4. For the original fed bioequivalence study (Study No. 023-08), please submit the complete study report, which should include the clinical report (with complete adverse events and clinical laboratory results), bioanalytical report and statistical analysis report as well as the study datasets in SAS Transport format.

5. The following recommendation is for your future submissions:

   Please note that the concentrations of the long-term stability samples should be compared to the mean of back-calculated values for the fresh QC at the appropriate concentrations from the first day of the long-term stability testing, as recommended in the Guidance for Industry: Bioanalytical Method Validation, issued 2001.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	ATORVASTATIN CALCIUM

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

/s/

DALE P CONNER
09/07/2010

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: August 12, 2010

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director,
Document Control Room
7620, Standish Place,
Rockville, Maryland 20857

Gratuitous Labeling Amendment

Subject: ANDA # 91-226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Dr. Webber:

Reference is made to the subject under-review ANDA of Matrix Laboratories Limited, India. This labeling amendment provides for minor editorial changes in labeling and labels per current standard format, correction in description section of labeling to be consistent with the CMC section and minor typographical errors. To facilitate review, a side by side comparison of proposed labels and labeling against the last submitted labels and labeling with differences annotated and explained, is also being submitted with this amendment.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

for ----------

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2010-0443**	
TO *(Division/Office)* DCRP - HFD 110 Thru: Devi Kozeli, ODE I - HFD 101			FROM: Leigh Ann Bradford	
DATE: 8/10/2010	IND NO.	ANDA NO. 091226	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 4/8/2010,
NAME OF DRUG ATORVASTATIN CALCIUM		PRIORITY CONSIDERATION 30 days	CLASSIFICATION OF DRUG Lipid Lowering Agent	DESIRED COMPLETION DATE 9/9/2010

NAME OF FIRM MATRIX LABS LTD

REASON FOR REQUEST

I. GENERAL

✆ NEW PROTOCOL	✆ PRE NDA MEETING	✆ RESPONSE TO DEFICPENCY LETTER
✆ PROGRESS REPORT	✆ END OF PHASE II MEETING	✆ FINAL PRINTED LABELING
✆ NEW CORRESPONDENCE	✆ RESUBMISSION	✆ LABELING REVISION
✆ DRUG ADVERTISING	✆ SAFETY/EFFICACY	✆ ORIGINAL NEW CORRESPONDENCE
✆ ADVERSE REACTION REPORT	✆ PAPER NDA	✆ FORMULATIVE REVIEW
✆ MANUFACTURING CHANGE/ADDITION	✆ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
✆ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW	✆ CHEMISTRY
✆ END QF PHASE II MEETING	✆ PHARMACOLOGY
✆ CONTROLLED STUDI ES	✆ BIOPHARMACEUTICS
✆ PROTOCOL REVIEW	✆ OTHER
✆ OTHER	

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review. "Impurities listed are higher than the RLD." Please evaluate the amendment ANDA in EDR Module 3 (see attached documents for reference). Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Bradford, HFD-617 (Leigh.bradford@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Pharm-Tox consults-ANDA 91226CR02, Amendment submitted April 8, 2010.

HFD-630/W.Jiang/CR/07/10/10
HFD-630/L. Nagavelli/TL
HFD-617/L.A.Bradford/PM

Location: Edr: 91226, 08-APR-2010, m3 folder:

Baterial Reverse Mutation Assay for Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atrovastatin (89 page)

In Vitro Mammalian Chromosome Aberration Test Report- (b) (4) impurity (93 page)

In Vitro Mammalian Chromosome Aberration Test Report for Atorvastatin Calcium and Atorvastatin Calcium spiked with (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities of Atrovastatin (129 page)

The purpose of this repeated dose 14 day toxicity study in Wistar rats was to assess the toxic potential of test item (Atorvastatin Calcium) without impurities and with impurities (b) (4) (b) (4) Impurity) when administered daily by oral gavage. This study is intended to provide information on major toxic effects on target organs and an estimate of a "No Observed Effect Level (NOEL)"

14-Day Toxicity Study of Atorvastatin Calcium Administered by Oral Gavage to Rats (493 page) to qualify (b) (4) and (b) (4) impurities in the DP at the (b) (4)% and (b) (4)% level, respectively.

The purpose of this study was to qualify (b) (4) and (b) (4) impurities in the atorvastatin drug product at the (b) (4) and (b) (4)% level, respectively. The study was designed in compliance with ICH Q3A(R2) to allow comparison of qualified and unqualified material following once daily oral gavage to rats for 14 days. The study design was as follows (see report).

L-Arginine Safety Assessment (47 page).

Impurities information:



(b) (4)

Impurities control in Drug Substance ATORVASTATIN CALCIUM

TEST	RESULTS		SPECIFICATION
	AC0090408 (DS Manufacturer)	1004608 (DP Manufacturer)	
Related Substances (by HPLC)			
(b) (4)			

Impurities control in Drug Product

Impurities limit in Finished Product Specification- Atorvastatin Calcium Tablets, 10 mg, 20, 40 and 80 mg.

Test	Specification	
	Release	Shelf life
Related Substances (by HPLC)		
(b) (4)		

Chemical names of the impurities:

(b) (4)

Location: Edr: 91226, 08-APR-2010, m3 folder:

The firm submits 3 reports for (b) (4) impurity for DP specification ((b) (4) % for release and (b) (4) % for stability).

1. Bacterial Reverse Mutation Test Report – [redacted] impurity (93 page)
2. In Vitro Mammalian Chromosome Aberration Test Report- [redacted] impurity (93 page)
3. 14-Day repeated dose oral toxicity study by Gavage in wistar rats- [redacted] impurity (373 page)

The firm submits 2 reports for [redacted] and [redacted] Impurities for DS and DP specification (see attached for specification).

1. Baterial Reverse Mutation Assay for Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted]% [redacted] and [redacted]% [redacted] Impurities of Atrovastatin (89 page)

2. In Vitro Mammalian Chromosome Aberration Test Report for Atorvastatin Calcium and Atorvastatin Calcium spiked with [redacted]% [redacted] and [redacted]% [redacted] Impurities of Atrovastatin (129 page)

The firm submits 1 report for L-Arginie Safety Assessment.

1. L-Arginine Safety Assessment (47 page).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	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/

LEIGH A BRADFORD
08/10/2010

TRANG Q TRAN
08/10/2010

QUALITY DEFICIENCY - MINOR

ANDA 091226

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: Matrix Laboratories Limited TEL: (304) 554-5899

ATTN: Keith Giunta FAX: (304) 285-6407

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 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendment dated April 8, 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 **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
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/*

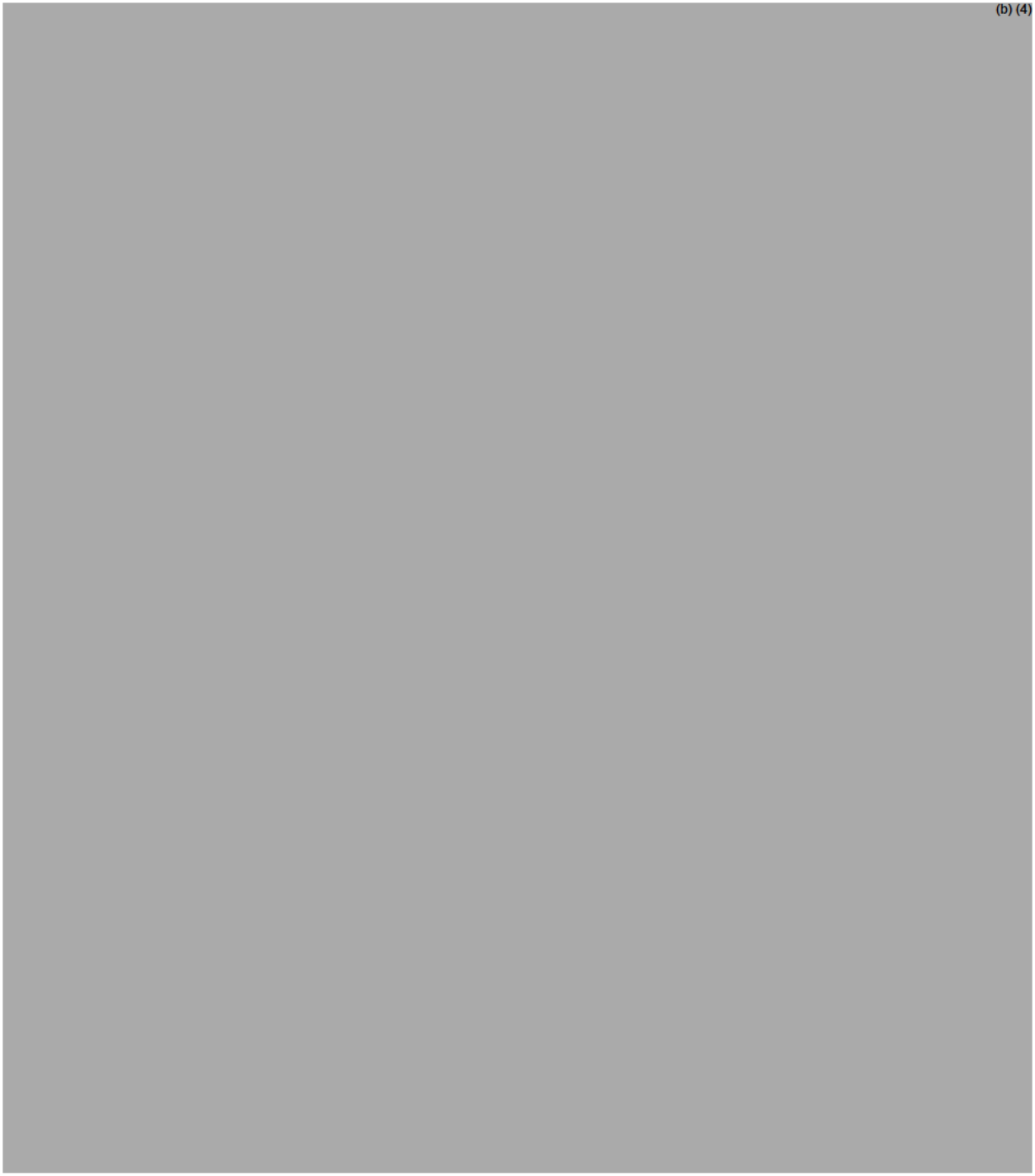
THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, 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: 091226 **APPLICANT:** Matrix Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.



(b) (4)

B. Please acknowledge and respond to the following comments:

1. Please provide all available long-term stability data.

2. Please be informed that the toxicological studies provided for L-Arginine have been forwarded to the Pharmocology-Toxicology Division for evaluation. Additional questions may be asked after their review is complete

3. Please be informed that the toxicological studies provided for (b) (4)% (b) (4) and (b) (4)% (b) (4) Impurities are forwarded to the Pharmocology-Toxicology Division for evaluation. Additional questions may be asked after their review is complete. In addition, the pharm-tox needs to be evaluated for the drug product stability specification limits of (b) (4)% and (b) (4)% for (b) (4) and (b) (4) impurity respectively.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	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/

SUHAS J PATANKAR on behalf of LAXMA R NAGAVELLI
08/03/2010

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003. India
Tel : 91-40-27700363, 66327722. Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: April 8, 2010

To:
Office of Generic Drugs, CDER, FDA
Keith Webber, Ph.D, Acting Director
Document Control Room
Metro Park North II
7500, Standish Place, Room 150
Rockville MD 20855-2773

Minor CMC Amendment

Subject: ANDA # 91-226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Dr. Webber:

Reference is made to CMC review comments dated August 28, 2009, during review of the subject ANDA of Matrix Laboratories Limited, India (Matrix). In this amendment we respond fully to all of the questions. For each item, we first restate the question **(in bold)** and then present our response.

This amendment is being submitted through FDA's Electronic Submissions Gateway. Please note that Mylan previously submitted a letter of Non-Repudiation on April 17, 2006. Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: October 20, 2009

To:
Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500, Standish Place, Room 150
Rockville MD 20855-2773

Telephone Labeling Amendment

Subject: ANDA # 91-226,
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Buehler:

This is in reference to Telephone Fax labeling deficiency dated May 14, 2009 upon review of the subject ANDA of Matrix Laboratories Limited, India. In this amendment, we respond fully to all the comments and provide the revised labeling. We first restate the question (in bold) and then provide our response.

This telephone amendment includes an archival (blue) copy and a CD containing electronic form of the proposed labeling and related information. Additionally, a desk copy of this submission is also being submitted.

Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

Nitin Bhattad Oct 20, 2009
Regulatory Affairs
Matrix Laboratories Limited, India

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

Cc: Jeanne Skanchy, Project Manager, OGD, CDER, FDA
Ann Vu, OGD, CDER, FDA

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Date: September 30, 2009

To:
Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500, Standish Place, Room 150
Rockville MD 20855-2773

Bioequivalency Amendment

Subject: ANDA # 91-226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Buehler:

Reference is made to bioequivalence comments dated June 22, 2009 received upon review of subject ANDA of Matrix Laboratories Limited, India. In this amendment, we fully respond to all of the questions. We first restate the question **(in bold)** and then provide our response.

This amendment includes two copies, an archival (blue) copy, and a review (orange) copy. We are also submitting an electronic copy of this amendment as requested by the Agency. Additionally, a desk copy of this submission is also being submitted.

Should you require any additional information, please contact Keith J Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

---------- Sep 30, 2009.

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

---------- KJG

Keith J Giunta
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited, India

Cc: Jeanne Skanchy, Project Manager, OGD, CDER, FDA.
Diana Solana-Sodeinde, DBE, OGD, CDER, FDA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
MATRIX LABORATORIES LIMITED	**September 30, 2009**
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
0091-40-66269994	**0091-40-27700343**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
1-1-151/1, 4th Floor **Sairam Towers, Alexander Road** **Secunderabad – 500 003** **Andhra Pradesh (AP)** **India**	**Keith Giunta, Associate Director, Regulatory Affairs** **Mylan Pharmaceuticals Inc.** **781 Chestnut Ridge Road, P.O. Box 4310** **Morgantown, WV 26504-4310** **Tel: (304) 554-5899 or (800) 848-0461, ext. 5899** **Fax: (304) 285-6407**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **91-226**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Atorvastatin Calcium Tablets	**N/A**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
[R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, (b) (4)

CODE NAME *(If any)*: **N/A**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	**10 mg, 20 mg, 40 mg and 80 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
Indicated in the prevention of cardiovascular disease and hypercholesterolemia

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug **Lipitor®** Holder of Approved Application **Pfizer**

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to Agency Correspondence Dated June 22, 2009

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED **1** THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* **Response to Agency Correspondence Dated June 22, 2009**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Keith Giunta, Associate Director Regulatory Affairs	**September 30, 2009**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504-4310	**(304) 554-5899**

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Response to Bioequivalence deficiency dated June 22, 2009

RESPONSE: BIOEQUIVALENCE DEFICIENCY DATED JUNE 22, 2009

ANDA # : 91-226
APPLICANT : Matrix Laboratories Limited
DRUG PRODUCT : Atorvastatin Calcium Tablets, 10mg, 20mg, 40mg and 80mg
FDA CONTACT : Diana Solana-Sodeinde

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver requests will be conducted at a later date. The following deficiencies have been identified:

1. **Your dissolution testing using the FDA-recommended method is acceptable. However, your proposed specification of not less than (b) (4) % (Q) in (b) (4) minutes is not acceptable. Based on the dissolution data you submitted, the DBE recommends a different but more appropriate specification for your test product. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:**

   Medium: 0.05 M Phosphate buffer, pH 6.8
   Apparatus:II (Paddle)
   RPM: 75
   Volume: 900 mL
   Specification: Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin is dissolved in 15 minutes.

   Response:

   We acknowledge the Agency's recommendation for the dissolution method and specification. Kindly note, the dissolution method followed at Matrix is the same as recommended by the Agency.

   Based on the Agency's recommendation the dissolution specification for Atorvastatin calcium tablets has been revised as follows:

   Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin is dissolved in 15 minutes. A copy of the revised finished product specifications is enclosed as **Attachment # 1**.

   ---

2. **The Long Term Storage Stability Data you provided are not sufficient to cover the storage period of the bio-study samples for your fasting bioequivalence study (Study Number 022-08). Please provide Long Term Storage Stability data to cover a storage period of at least 81 days.**

Response:

As requested, long-term sample storage stability data for Atorvastatin and its metabolites in human plasma demonstrating stability for 405 days -70 ± 15ºC and -20 ± 5ºC is enclosed as **Attachment # 2.** "Table # 4, Bioanalytical Method Validation" of the standard template for BE summary has been updated to include this information and is also enclosed.

BIOEQUIVALENCE AMENDMENT

ANDA 91-226

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: Matrix Laboratories Limited TEL: (304) 554-6551

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 30, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review,** nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 91-226

APPLICANT: Matrix Laboratories Limited, India

DRUG PRODUCT: Atorvastatin Calcium Tablets;
10mg, 20mg, 40mg, and 80 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver requests will be conducted at a later date. The following deficiencies have been identified:

1. Your dissolution testing using the FDA-recommended method is acceptable. However, your proposed specification of not less than (b) (4) % (Q) in (b) (4) minutes is ***not acceptable***. Based on the dissolution data you submitted, the DBE recommends a different but more appropriate specification for your test product. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

   Medium: 0.05 M Phosphate buffer, pH 6.8
   Apparatus: II (Paddle)
   RPM: 75
   Volume: 900 mL
   Specification: Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin is dissolved in 15 minutes.

2. The Long Term Storage Stability Data you provided are not sufficient to cover the storage period of the bio-study samples for your fasting bioequivalence study (Study Number 022-08). Please provide Long Term Storage Stability data to cover a storage period of at least 81 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Dale Conner
6/22/2009 10:05:40 AM

(b) (4)

S. No.	Test	Specification

(b) (4)

39 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Table 4 Bioanalytical Method Validation (Amended to updated stability data)

Information Requested	Data		
Bioanalytical method validation report location	Study No:022-08; Volume 19; Page:5928 Study No:162-08;Volume 15 ;Page:11208		
Analyte	**Atorvastatin**	**O-OH-Atorvastatin**	**P-OH-Atorvastatin**
Internal standard (IS)	Atorvastatin D5	Atorvastatin D5	Atorvastatin D5
Method description	Liquid-Liquid Extraction (method description is detailed in method SOP attached as appendix 1)	Liquid-Liquid Extraction (method description is detailed in method SOP attached as appendix 1)	Liquid-Liquid Extraction (method description is detailed in method SOP attached as appendix 1)
Limit of quantitation	0.250 ng/mL	0.250 ng/mL	0.050 ng/mL
Average recovery of drug (%)	70.00% (LQC), 65.43% (M2QC) & 70.31% (HQC)	77.61% (LQC), 70.26% (M2QC) & 71.48% (HQC)	75.40% (LQC), 68.62% (M2QC) & 71.90% (HQC)
Average recovery of IS (%)	71.41%	71.41%	71.41%
Standard curve concentrations (units/mL)	0.250, 0.500, 5.010, 15.040, 50.130, 100.250, 150.380, 200.500, 250.630 ng/mL	0.250, 0.500, 2.480, 9.930, 29.780, 59.550, 84.360, 114.140, 148.880 ng/mL	0.050, 0.100, 0.500, 0.990, 1.990, 3.980, 5.960, 7.950, 9.940 ng/mL
QC concentrations (units/mL)	0.250 ng/mL (LLOQQC), 0.740 ng/mL (LQC), 24.560 ng/mL (M1QC), 78.600 ng/mL (M2QC), 176.850 ng/mL (HQC)	0.250 ng/mL (LLOQQC), 0.750 ng/mL (LQC), 19.900 ng/mL (M1QC), 49.750 ng/mL (M2QC), 104.480 ng/mL (HQC)	0.050 ng/mL (LLOQQC), 0.150 ng/mL (LQC), 1.490 ng/mL (M1QC), 3.480 ng/mL (M2QC), 7.160 ng/mL (HQC)
QC Intraday precision range (%)	1.44% to 6.07%	2.06% to 7.08%	1.67% to 7.26%
QC Intraday accuracy range (%)	83.12% to 109.56%	86.40% to 102.87%	96.42% to 107.40%
QC Interday precision range (%)	1.79 % to 7.72%	2.67% to 7.25%	4.25% to 12.72%
QC Interday accuracy range (%)	94.32% to 110.49%	93.20% to 102.71%	96.87% to 103.93%
Bench-top stability (hrs)	5 hrs	5 hrs	5 hrs
Stock stability (days)	Drug - 74 days & 72 days at 2-10ºC ISTD- 74 days & 68 days at 2-10ºC	Drug - 74 days & 72 days at 2-10ºC ISTD- 74 days & 68 days at 2-10ºC	Drug - 74 days & 72 days at 2-10ºC ISTD- 74 days & 68 days at 2-10ºC
Processed stability (hrs)	Auto Sampler about 46 hrs 20 min at 5ºC Dry Extract 23 hrs at 2-10ºC	Auto Sampler about 46 hrs 20 min at 5ºC Dry Extract 23 hrs at 2-10ºC	Auto Sampler about 46 hrs 20 min at 5ºC Dry Extract 23 hrs at 2-10ºC
Freeze-thaw stability (cycles)	4 Cycles	4 Cycles	4 Cycles
Long-term storage stability (days)	405 days@-20±5ºC and -70±15ºC	405 days@-20±5ºC and -70±15ºC	405 days@-20±5ºC and -70±15ºC
Dilution integrity	1/2 dilution – 1.88% (precision) 1/4 dilution – 11.28% (precision)	1/2 dilution – 2.84% (precision) 1/4 dilution – 11.78% (precision)	1/2 dilution – 4.78% (precision) 1/4 dilution – 11.22% (precision)
Selectivity	No interfering peaks were observed at the retention time of Drug and ISTD	No interfering peaks were observed at the retention time of Drug and ISTD	No interfering peaks were observed at the retention time of Drug and ISTD

Iser, Robert

From: Iser, Robert
Sent: Wednesday, September 09, 2009 11:16 AM
To: 'Keith.Giunta@mylan.com'
Cc: Nguyen, Sarah; Jiang, Weiqin; Skanchy, Jeanne
Subject: RE: Matrix Labs ANDA 91-226 - Deficiency clarification

Keith,

Good Morning,

With respect to your question regarding Section A, Comment 6:

All of the information provided was taken into consideration during the pharmacology – toxicology (pharm-tox) review. Based on the information provided and additional information available in the literature, the pharm-tox reviewer expressed concerns with respect to the proposed level of L-arginine based on the chronic use of the product and possible additive effects with co-administered medications. Additional information cited by the pharm-tox reviewer included:

1. Published clinical literature is available suggesting that patients with cardiovascular disease may have adverse outcomes from L-arginine, including a study conducted at John's Hopkins in post-myocardial infarction patients taking L-arginine, 3 g (TID) for 6 months. This study reported that these high doses of L-arginine did not have a beneficial effect on cardiac outcomes and in fact had a detrimental effect {JAMA 2006 295(1):58-64}. In this study, L-arginine use was associated with higher post-infarction mortality (3 g TID).

2. Patients on statins may be on anti-hypertensive / anti-diabetic / diuretic and other treatments, and it is not known if the proposed level of L-arginine following a chronic use over time will exacerbate some of the above conditions, either due to drug-drug interactions or changes in parameters (such as electrolytes, sugar, BUN/creatinine levels, etc.) in the compromised patients (diabetics, cardiovascular diseases, etc.). Additive effects of other co-administered medications with L-arginine cannot be excluded. There are known drug interactions with L-arginine and common medications in this patient population (e.g. potassium sparing diuretics, ACE inhibitors, etc.).

Therefore, the pharm-tox reviewer recommended that safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease) should be established; and that there may be data available in the literature from patients with CV disease that have received a particular level of L-arginine, chronically, in other approved drugs at levels intended for use in this ANDA ((b) (4)).

Regards

Robert Iser

Team Leader (Team 12)
Office of Generic Drugs
Division of Chemistry III
MPN-2, HFD-630, Rm E131

Phone: 240-276-8481
Fax: 240-276-8474

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: Keith.Giunta@mylan.com [mailto:Keith.Giunta@mylan.com]
Sent: Friday, September 04, 2009 10:05 AM
To: Skanchy, Jeanne
Cc: Iser, Robert; Nguyen, Sarah; Jiang, Weiqin
Subject: RE: Matrix Labs ANDA 91-226 - Deficiency clarification

Thanks, Jeanne.

I have one more request for clarification regarding Section A, Comment 6 (pasted below):

6. Based on the pharmacology / toxicology consult with respect to the proposed amount of L-arginine, the following recommendation is made:

   As the long term effects of oral L-arginine are unknown and atorvastation calcium is for chronic use, it is important to know at what doses it produces toxicity, especially in patients with cardiovascular risk. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population. This data may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use (i.e. (b) (4)

Matrix provided a report in Module 3.2.P.1 which espouses the safety of L-arginine at levels well above the (b) (4) proposed by Matrix, including a clinical study with MI patients (the intended patient population). Was this study considered during your review and found to be insufficient or could it have been overlooked during review?

Thanks,

Keith

"Skanchy, Jeanne" <Jeanne.Skanchy@fda.hhs.gov>

09/04/2009 07:45 AM

To Keith.Giunta@mylan.com
cc "Nguyen, Sarah" <Sarah.Nguyen@fda.hhs.gov>, "Jiang, Weiqin" <Weiqin.Jiang@fda.hhs.gov>, "Iser, Robert" <Robert.Iser@fda.hhs.gov>
Subject RE: Matrix Labs ANDA 91-226 - Deficiency clarification

Dear Keith,

I will contact the DMF holder to see if the deficiency letter needs to be re-faxed. Thank you for the notification.

Sincerely,

Jeanne Skanchy, R.Ph., LCDR, USPHS
Project Manager, Team 12
Division of Labeling and Program Support
Office of Generic Drugs/Division of Chemistry III
Center for Drug Evaluation and Research
Food and Drug Administration
p (240) 276-8467
f (240) 276-8474
MPN2, Room E116
jeanne.skanchy@fda.hhs.gov

From: Keith.Giunta@mylan.com [mailto:Keith.Giunta@mylan.com]
Sent: Thursday, September 03, 2009 3:56 PM
To: Iser, Robert
Cc: Skanchy, Jeanne; Nguyen, Sarah; Jiang, Weiqin
Subject: RE: Matrix Labs ANDA 91-226 - Deficiency clarification

Thanks, Robert.

One other request:

Matrix Laboratories (API group) informed us that they haven't received the DMF deficiency yet. Could you confirm if it has been sent? If so, please forward another copy to them (their fax number is 973.761.1680). If not, please let me know how long it will be until they do receive it.

Thanks,

Keith

"Iser, Robert" <Robert.Iser@fda.hhs.gov>

09/03/2009 12:34 PM

To Keith.Giunta@mylan.com
cc "Nguyen, Sarah" <Sarah.Nguyen@fda.hhs.gov>, "Jiang, Weiqin" <Weiqin.Jiang@fda.hhs.gov>, "Skanchy, Jeanne" <Jeanne.Skanchy@fda.hhs.gov>
Subject RE: Matrix Labs ANDA 91-226 - Deficiency clarification

Keith,

Good Afternoon. With respect to your question on Section B, Comment 8, our intent was with respect to the change in criteria (specifications) recommended by DBE, and was not intended to imply that there were any additional change in the method recommendations.

Best Regards

Robert Iser

Team Leader (Team 12)
Office of Generic Drugs
Division of Chemistry III
MPN-2, HFD-630, Rm E131

Phone: 240-276-8481
Fax: 240-276-8474

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: Keith.Giunta@mylan.com [mailto:Keith.Giunta@mylan.com]
Sent: Wednesday, September 02, 2009 12:16 PM
To: Nguyen, Sarah
Subject: Matrix Labs ANDA 91-226 - Deficiency clarification

Dear Sarah,

On 28 August 2009, you provided us with a deficiency letter related to Matrix Laboratories' ANDA 91-226 for Atorvastatin Tablets. We also received a bioequivalence deficiency (22 June 2009) in which DBE requested a change in Matrix's dissolution specification, but identified the method as acceptable.

Point B-8 of your CMC deficiency (pasted below), indicates a change in dissolution method and criteria.

> 8. Please be informed that since there was a change in dissolution method and criteria 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.

I'd like to clarify if your intention with respect to this was just a change in criteria (specification) only or if it also entailed a change in the method (parameters) as well.

Thanks,

Keith

Keith Giunta
Associate Director, Regulatory Affairs
Mylan Pharmaceuticals, Inc.

==========
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	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
09/09/2009

Iser, Robert

From: Iser, Robert
Sent: Thursday, September 03, 2009 12:34 PM
To: 'Keith.Giunta@mylan.com'
Cc: Nguyen, Sarah; Jiang, Weiqin; Skanchy, Jeanne
Subject: RE: Matrix Labs ANDA 91-226 - Deficiency clarification

Keith,

Good Afternoon. With respect to your question on Section B, Comment 8, our intent was with respect to the change in criteria (specifications) recommended by DBE, and was not intended to imply that there were any additional change in the method recommendations.

Best Regards

Robert Iser

Team Leader (Team 12)
Office of Generic Drugs
Division of Chemistry III
MPN-2, HFD-630, Rm E131

Phone: 240-276-8481
Fax: 240-276-8474

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: Keith.Giunta@mylan.com [mailto:Keith.Giunta@mylan.com]
Sent: Wednesday, September 02, 2009 12:16 PM
To: Nguyen, Sarah
Subject: Matrix Labs ANDA 91-226 - Deficiency clarification

Dear Sarah,

On 28 August 2009, you provided us with a deficiency letter related to Matrix Laboratories' ANDA 91-226 for Atorvastatin Tablets. We also received a bioequivalence deficiency (22 June 2009) in which DBE requested a change in Matrix's dissolution specification, but identified the method as acceptable.

Point B-8 of your CMC deficiency (pasted below), indicates a change in dissolution method and criteria.

8. Please be informed that since there was a change in dissolution method and criteria 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.

I'd like to clarify if your intention with respect to this was just a change in criteria (specification) only or if it also entailed a change in the method (parameters) as well.

Thanks,

Keith

Keith Giunta
Associate Director, Regulatory Affairs
Mylan Pharmaceuticals, Inc.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91226	ORIG-1	MATRIX LABORATORIES LTD	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
09/03/2009

COMPLETE RESPONSE -- MINOR

ANDA 91-226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

TO: Mylan Pharmaceuticals, Inc.,
U.S. Agent for Matrix Laboratories Limited

TEL: (304) 599-2595

FAX: (304) 285-6407

ATTN: S. Wayne Talton

FDA CONTACT PHONE: (240)-276-8467

FROM: Sarah Nguyen

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (**6** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
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CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 91-226 **APPLICANT:** Matrix Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

[redacted]

3 pages have been withheld as b4 (CCI/TS) immediately following this page

8. Please be informed that since there was a change in dissolution method and criteria 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.

9. Please provide all available long-term stability data.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L ISER
08/28/2009
signed for Vilayat Sayeed

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

MI notice filed Suits filed 1:2009cv-00441 & 1:09-cv-79 S. Mobley 10/5/09

ORIG-1 / SD-6

Date: August 12, 2009

To:

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Patent Amendment
(Informing litigation within 45 days)

Subject: ANDA # 91-226,
Atorvastatin Calcium Tablets; 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Buehler:

Reference is made to the patent amendment to the subject ANDA dated May 01, 2009 wherein Matrix informed the Agency that an appropriate notification as required under 21 CFR § 314.95(a) has been provided to each of the patent holder(s) and the New Drug Application holder.

This amendment provides documentation of receipt of notice as required under 21 CFR § 314.95(e), as it pertains to the Paragraph IV patent certification contained in Matrix's subject ANDA. Please find enclosed documentation of the receipts by the owner(s) of the patent and the holder of the application for the listed drug claimed by said patent(s). Matrix had FDA's prior permission to serve the required notice by Federal Express (Mr. Martin Shimer).

Proof of delivery by FedEx substantiates receipt of notice by:

1. Pfizer Inc., New York, on May 04, 2009
2. Warner Lambert Company dba Pfizer Ann Arbor, MI on May 04, 2009
3. Warner Lambert Company dba Pfizer Morris Plains, NJ on May 04, 2009

On June 15, 2009 Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company and Warner-Lambert Company LLC commenced litigation against Mylan Inc., Matrix Laboratories Limited and Matrix Laboratories Inc., in the United States District Court for the District of Delaware (Civil Action No. 1:2009cv 00441) and in the Northern District of West Virginia (Civil Action No. 1:09-cv-79), and is captioned:

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AUG 13 2009
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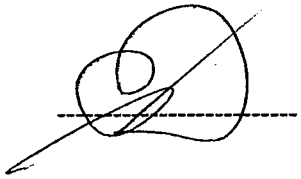
Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003. India
Tel : 91-40-27700363, 66327722. Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Pfizer Inc, Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner Lambert Company LLC (Plaintiffs) Vs Mylan Inc, Matrix Laboratories Limited, and Matrix Laboratories Inc., (Defendents)

A copy each of said complaints is enclosed for your reference.

Should you need any additional information, please contact Mylan Pharmaceuticals, Attention, Keith Giunta at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India.



Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India.

Cc: Jeanne Skanchy, Project Manager, OGD, CDER, FDA

CONNOLLY BOVE LODGE & HUTZ LLP
ATTORNEYS AT LAW

WILMINGTON, DE

The Nemours Building
1007 North Orange St.
P.O. Box 2207
Wilmington, DE 19899
TEL: (302) 658 9141
FAX: (302) 658 5614
WEB: www.cblh.com

Jeffrey B. Bove
Partner

TEL (302) 888-6241
FAX (302) 656-9072
EMAIL jbove@cblh.com
REPLY TO Wilmington Office

RECEIVED
JUL 30 2009
OGD

July 8, 2009

BY CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
HFD-600
5600 Fishers Lane
Rockville, MD 20857

ORIG- 1 / SD-005

Re: ANDA No. 91-226
Notice of Filing Legal Action for Patent Infringement

Dear Sir or Madam:

We represent Plaintiffs Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company and Warner-Lambert Company LLC, (collectively referred to as "Pfizer") who have brought suit against Mylan Inc, Matrix Laboratories, Inc. and Matrix Laboratories Ltd. (collectively "Mylan") for infringement of United States Letters Patent Nos. 5,969,156 ("the '156 patent"), by the submission of the Matrix's ANDA No. 91-226 for a generic Lipitor® product. The '156 patent expires on July 8, 2016, and is subject to a period of pediatric exclusivity expiring January 8, 2017.

Pursuant to 21 CFR § 314.107(f)(2), Pfizer provides notification as follows:

(i) The ANDA number is 91-226;

(ii) The name of the abbreviated new drug applicant is Matrix Laboratories Ltd.;

(iii) The notice from Mylan Inc. to Pfizer about the ANDA filing provided an established name for the ANDA drug product as atorvastatin, in the form of tablets, which contain the equivalent of 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin as the active ingredient.

(iv) We certify that the above-referenced patent infringement suits were filed under Civil Action No. 09-441-JJF in the United States District Court for the District of Delaware on June 15, 2009, and Civil Action No. 09-79 in the United States District Court for the Northern District of West Virginia. A copy of the summonses and complaints are enclosed.

Pfizer received notice dated May 1, 2009, pursuant to § 505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA. Accordingly, pursuant to § 505(j)(5)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30-month period beginning from Pfizer's receipt of such notice, i.e., until November 1, 2011, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Jeffrey B. Bove

JBB\
Enclosures

cc: Janet Woodcock, M.D., Director (w/ enclosures)
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-001, Room 6133
White Oak Bldg. 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Jane A. Axelrad (w/ enclosures)
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-005, Room 6140
White Oak Bldg. 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Jeffrey M. Senger, Esquire (w/ enclosures)
Deputy Chief Counsel
Food and Drug Administration
GCF-1, Room 6-57
Parklawn Bldg.
5600 Fishers Lane
Rockville, MD 20857

698250_1.DOC

BIOEQUIVALENCE AMENDMENT

ANDA 91-226

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: Matrix Laboratories Limited TEL: (304) 554-6551

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 30, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 91-226

APPLICANT: Matrix Laboratories Limited, India

DRUG PRODUCT: Atorvastatin Calcium Tablets;
10mg, 20mg, 40mg, and 80 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and waiver requests will be conducted at a later date. The following deficiencies have been identified:

1. Your dissolution testing using the FDA-recommended method is acceptable. However, your proposed specification of not less than (b)(4) % (Q) in (b)(4) minutes is ***not acceptable***. Based on the dissolution data you submitted, the DBE recommends a different but more appropriate specification for your test product. Please acknowledge your acceptance of the following FDA-recommended dissolution method and specification:

Medium:	0.05 M Phosphate buffer, pH 6.8
Apparatus:	II (Paddle)
RPM:	75
Volume:	900 mL
Specification:	Not less than (b)(4) % (Q) of the labeled amount of Atorvastatin is dissolved in 15 minutes.

2. The Long Term Storage Stability Data you provided are not sufficient to cover the storage period of the bio-study samples for your fasting bioequivalence study (Study Number 022-08). Please provide Long Term Storage Stability data to cover a storage period of at least 81 days.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Dale Conner

6/22/2009 10:05:40 AM

Signed off in DFS on 6/16/09

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 91-226
Date of submission: 4/16/09 (from OGD). OGD is requesting the pharmacology /toxicology consult on the ingredient L-Arginine in the atorvastatin calcium drug product under ANDA 91-226.

Review Number: 1

Drug Names: Atorvastatin Calcium, 10, 20, 40, 80 mg tablets.

Consult #: 20009-0324 for atorvastatin calcium tablets.

Consult from: Saundra Middleton, and Theresa Liu. Request date: 4/16/09 (desired completion date is 6/15/09)

Generic drug name: Atorvastatin calcium tablets. OGD wants to know if the proposed levels of L-arginine from Matrix laboratories, Inc. are acceptable in the abbreviated NDA (ANDA) 91-226.

Drug class: Statins (generic atorvastatin).

Indication: To lower cholesterol.

Type of document: Electronic submission by OGD. In the current submission, Mylan Laboratories has consulted with [redacted] (b) (4) (a senior consultant for pharmacology/toxicology), who has provided the safety assessment of the oral use of L-Arginine.

Subject of Consult: OGD is requesting a pharmacology/toxicology consult for the inactive ingredient L-Arginine, which is present at doses of [redacted] (b) (4) in the sponsor's 80 mg dosage form atorvastatin calcium tablets. This ingredient has only been used in approved injectable drug products and has never been used in oral products before, they want to know if these levels are safe in their drug product (in ANDA 91-226).

The consult comments are stated below:

OGD is requesting a Pharm/Tox Review. The firm submitted information regarding the use of L-Arginie in the drug product. They are using a max of [redacted] (b) (4) of L-Arginie per tablet. This inactive has only been used in injectables, never in an oral product. Please review their submission and provide comment if these levels are safe for human use. **NOTE** a consult was sent for the same ingredient under [redacted] (b) (4) and found acceptable. Pls. confirm if the proposed level and data submitted by Matrix is also acceptable.

Reviewer name: Indra Antonipillai, Ph.D., Pharmacology Reviewer.

Division: Division of Metabolic and Endocrinology products.

Review completion date: 6/16//2009.

Introduction and drug history:

Arginine is considered a semi-essential amino acid for adults because even though the body normally makes enough of it, supplementation is sometimes needed. For example, people with protein malnutrition, excessive ammonia production, excessive lysine intake, burns, infections, peritoneal dialysis, rapid growth, urea synthesis disorders, or sepsis may not have enough arginine. Symptoms of arginine deficiency include poor wound healing, hair loss, skin rash, constipation, and fatty liver. However, L-Arginine is an essential amino acid for infants and growing children.

L-Arginine is a substrate for at least five enzymes identified in mammals, including nitric oxide synthase (NOS), arginase, arginine-glycine transaminase, kyotorphine synthase, and arginine decarboxylase.

As stated above, L-arginine is the substrate for the enzyme nitric oxide synthase (NOS), which is responsible for the production of nitric oxide (NO), an endogenous messenger molecule involved in many of the processes associated with the development of atherosclerosis. Acute and chronic administration of L-arginine has been shown to improve endothelial function in animal models of hyper-cholesterolemia and atherosclerosis.

L-arginie is available as a dietary supplement, it is also available through internet. Several oral preparations are available in recommended doses from 500 mg to 5000 mg/day. There are many uses of this amino acid, including its use in patients with inborn error of urea synthesis, healing of wounds, body building, removing ammonia from the body, coronary artery disease, angina, critical illness, heart failure, migraine headache, burns, chest pain, dental pain, diabetes, high blood pressure, respiratory infections, etc, but safety and effectiveness have not always been proven.

Many different doses have been used, and studies suggest that 0.5-16 g of arginine have been taken daily by mouth for up to 6 months. Adverse events (AEs) have been observed with L-Arginine including severe allergy like anaphylaxis (with injections), as well as rash, itching or shortness of breath. L-arginine is generally well tolerated by most people but stomach discomfort (including nausea, stomach cramps, an increased number of stools) and also worsening of asthma have been observed. Other potential side effect include low blood pressure, and changes in electrolytes, high BUN, high creatinine etc. (see L-arginine-MayoClinic.com).

L-Arginine is currently approved in the injectable antibiotic drug products, doses up to 780 mg/gram of the drug are approved under NDA 50-580/NDA 50-632. Similarly, doses of 725 mg per gram of the drug are approved under NDA 50-679. However these drugs are not for chronic use since these are antibiotics and both above products are injectable formulations. It has never been used in oral drug products before. No toxicity studies were conducted with L-Arginine in above NDAs or the current ANDA 91-226.

OGD has requested a pharmacology/toxicology consult and wants to know if (b) (4) of L-Arginine in the 80 mg tablet (a high dose tablet) of atorvastatin calcium are safe. No standard pharmacology/toxicity studies have been conducted by the sponsor on L-Arginine. However, sponsor has provided literature data, and the approved labels on the above two marketed anti-bacterial injectable drug products (NDA 50-580 or azactam, NDA 50-679 or Maxipime) to support the levels used in their ANDA.

The sponsor states the following:

In a pilot clinical trial conducted in Poland, 792 patients with acute myocardial infarction (MI) were given either placebo or 3 grams of L-Arginine orally in capsules three times daily for a period of 30 days. The results of the study showed a beneficial trend in patients with an acute MI while also demonstrating that 9 grams of L-Arginine orally is safe and well tolerated.[5]

The level of L-Arginine in Matrix's atorvastatin calcium tablets 80 mg is identified as (b) (4) per tablet and which is given once daily to patients. This level is far below the level found in common foods and the amounts given parenterally to sick patients with bacterial infections and orally to patients with acute MI. It would therefore seem prudent for the US FDA to accept the inclusion of L-Arginine at (b) (4) per tablet in this drug product given what is known about this semi-essential amino acid and the recognition of a very low risk to safety of the drug-ingesting patient.

Note that toxicity studies are very useful in evaluating the safety of an excipient/ingredient. The literature search by this reviewer led to a published 13-week dietary toxicity study in rats (International J. of Toxicology 23: 101-105, 2004). This study was conducted in Japan in rats (n=12/sex/group, 6-weeks of age) for 13 weeks, followed by a 5-week of the drug free recovery period.

Methods: In this study, rats were administered with L-Arginine in a standard diet (ad libitum) at doses of 1.25%, 2.5% and 5% w/w. The actual doses of L-arginine ingested in males were 840, 1690, 3300 mg/kg/day respectively; these values in females were 975, 2005, 3880 mg/kg/day respectively (see Table below). The study was conducted in compliance with GLP. Following parameters were observed in rats: clinical signs, body weights, diet intake, water intake, ophthalmologic exams, hematology, blood chemistry and histopathology.

Average intake of L-arginine (Arg) ingested throughout the 13-week-long administration period

	Average intake (mg/kg/day)	
	Males	Females
Standard diet		
+ Arg (1.25%)	842.7 ± 33.8	975.3 ± 29.5
+ Arg (2.50%)	1688.9 ± 58.6	2005.9 ± 103.3
+ Arg (5.00%)	3318.1 ± 110.2	3879.0 ± 167.7

Note. Means ± *SD* of 12 rats are shown.

Results showed no effects on clinical signs, body weights, ophthalmology exams. Urine analysis in week-5 at a high dose showed a slightly elevated levels of urinary glucose in 6/12 males and in 1/12 females, however these differences were not seen in week 13 and following 5-weeks of the drug free recovery period, suggesting that these findings were reversible. Some minor changes in hematology/clinical chemistry were observed as shown below, which were again reversible (following 5-weeks of the drug free recovery period). No drug related effects on gross pathology, absolute organ weights, or histopathology were observed. NOAEL was considered 3.3 g/kg/day in male rats, and 3.9 g/kg/day in female rats.

Hematology and Blood Chemistry

The following significant changes were observed at the end of the administration period in the male 5.0% concentration group, an increase in the hemoglobin (controls, 15.5 ± 0.4 g/dl; 5.0% group, 16.1 ± 1.1 g/dl), an increase in the prothrombin time (controls, 12.3 ± 0.5 s; 5.0% group, 12.9 ± 0.3 s), and a decrease in urea nitrogen (controls, 19.2 ± 1.5 mg/dl; 5.0% group, 17.3 ± 1.0 mg/dl). In females of the 5.0% concentration group, a significant drop in the orthochromatic erythroblast ratio (controls, 7.7% ± 1.2%; 5.0% group, 5.8% ± 1.4%), and a significant increase in the mast cell ratio at the end of the administration period (controls, 0.1% ± 0.1%; 5.0% group, 0.3% ± 0.2%) were seen.

At the end of the recovery period, a significant decline in red blood cell count (799.2 ± 16.5 $10^4/mm^3$; 5.0% group, 764.8 ± 18.2 $10^4/mm^3$) and reticulocyte ratio (30.0% ± 5.3%; 5.0% group, 22.7% ± 4.0%) was seen in females in the 5.0% concentration group.

Thus, the above 3-month published toxicity study did not show any significant toxicity of L-Arginine in rats. The clinical dose of L-Arginine in an 80 mg tablet of atorvastatin calcium tablet will be (b) (4) or (b) (4) (or (b) (4)), assuming a 60 kg subject. The doses of 3300-3900 mg/kg/day used in the above 13-week rat study, will provide (b) (4) fold safety margin in rats to humans for L-Arginine, based on body surface area in both rats and humans.

As stated before, L-arginine has been well tolerated by most people. Side effects include stomach discomfort such as nausea, and stomach cramps. However, serious adverse events (AEs) have also been observed with L-Arginine, such as worsening of asthma (due to allergy from L-arginine), low blood pressure, increased blood glucose levels, increased risk of bleeding, etc. Changes in numerous chemicals and electrolytes have been reported with the use of L-arginine, and patients with liver or kidney diseases may be especially sensitive to L-arginine.

OVERALL SUMMARY AND EVALUATION:

In the current consult, OGD wants to know if (b) (4) of L-arginine in the oral atorvastatin calcium drug product is safe. This amino acid has been previously approved only in injectable antibacterial drug products at dose of up to 780 mg per gram of the drug; but these drugs are used for limited time in patients. In contrast, atorvastatin calcium is for a chronic use, and patients probably will use it for many years. No standard pharmacology/toxicity studies have been conducted by the sponsor on L-arginine. Sponsor has provided the published literature data and approved drug labels for two injectable antibiotic drugs, which contain L-Arginine, this is to support the levels of L-arginine used in their ANDA.

This reviewer found a published 13-week rat toxicity study conducted in Japan, which did not show any significant toxicological effects of L-arginine in rats at doses up to 3300-3900 mg/kg/day when administered to rats in a diet. These doses provide (b) (4) fold safety margin in rats to humans, both based on the body surface area (and based on the highest dose of (b) (4) of L-arginine/day in humans).

Note that the above study is not a standard toxicity study and as stated earlier that adverse events and some serious have been observed with L-arginine in the literature. We do not know at what level L-Arginine can cause alterations in blood glucose, glucagon, changes in

electrolytes, etc. Patients on statins (such as atorvastatin) may be on the anti-hypertensive /anti-diabetic/diuretic and other treatments, and we do not know if these levels of L-arginine following a chronic use over time will exacerbate some of the above conditions, either due to drug-drug interactions or changes in parameters (such as electrolytes, sugar, BUN/creatinine levels, etc.) in the compromised patients (diabetics, cardiovascular diseases, etc.). The approval of generic atorvastatin will mean patients can technically receive a generic atorvastatin with or without L-arginine indiscriminately. If patients start having problems with their BP or glucose, it may not be traced back to an excipient in their generic atorvastatin.

Note that L-arginine has been approved by FDA in injectable drug products in antibiotics, as an aid to solubilize the drug (at doses up to of 780 mg per gram of the drug, NDA 50-580, NDA 50-632, NDA 50-679 or Maxipime), these antibacterial drugs are not for a chronic use. Maxipime is dosed up to 2 g every 8 hours (the lowest dose is 500 mg every 12 hours). At these doses, L-arginine exposure with Maxipime will range from 1.5 g to 4.35 g/day, this dose is much higher than the dose that will be used in the atorvastatin calcium drug product ((b) (4)). However, L-arginine has not been approved by FDA in any oral drug products.

There is a study conducted at John's Hopkins in post-myocardial infarction patients taking L-arginine 3 g, three times a day (TID), for 6 months. This study reported that these high doses of L-arginine did not have a beneficial effect on cardiac outcomes and in fact had a detrimental effect {JAMA 2006 295(1):58-64}. In this study, L-arginine use was associated with higher post-infarction mortality (3 g TID). This study suggests that L-arginine should not be recommended following acute myocardial infarction.

Therefore, there is published clinical literature suggesting that patients with cardiovascular disease may have adverse outcomes from L-arginine. Patients with frank and underlying disease as well as those with cardiovascular (CV) risk are given atorvastatin to lower cholesterol (and implied CV risk) in combination of various drugs. Safe levels of L-arginine have not been established in this patient population. The literature supports the safety of L-arginine in an otherwise healthy population and more importantly reports significant adverse outcomes with L-arginine in patients with CV risk without establishing a safe level. The information provided by the sponsor does not address this body of literature at all.

Note that nonclinical studies may not address or establish the risk because they are performed in otherwise healthy animals. Animal CV disease models have a tenuous association to human risk and it is unclear which CV models are most relevant to this situation. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population i.e. subjects with CV disease. There may be data available from patients with CV disease that have received a particular level of L-arginine chronically in other approved drugs at levels intended for use here ((b) (4)). While this may be supportive, additive effects of other co-administered medications with L-arginine can not be excluded. There are known drug interactions with L-arginine and common medications in this patient population (e.g. potassium sparing diuretics, ACE inhibitors etc.).

In conclusion, lhe long term effects of oral L-arginine (the semi-essential amino acid) are unknown. The current generic drug product atorvastatin calcium would be used by patients for many years. Because the patient population in ANDA (b) (4) is very different (i.e. patients with frank and underlying diseases, as well as those with cardiovascular risk), and there's cause for heightened concern in patients with CV disease based on clinical literature, which is the intended patient population for atorvastatin; safe levels of L-arginine in the patient population have not been established. Therefore, the sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease), as well as the additive effects of other co-administered medications with L-arginine. This data may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically in other approved drugs at levels intended for use here ((b) (4)).

Recommendations:
The long term effects of oral L-arginine are unknown. The generic atorvastatin calcium is for chronic use, it is important to know at what doses it produces toxicity, especially in patients with cardiovascular (CV) risk. Therefore, sponsor needs to establish safe levels of L-arginine in the intended patient population (i.e. subjects with CV disease). This data may be available from the literature from patients with CV disease that have received a particular level of L-arginine chronically, at levels intended for use here (b) (4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/aljuburi/Saundra middleton/Teresa Liu/Ripper, L
File name: ANDA 91226-OGD consult (atorvastatin- Matrix)

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

/s/

Indra Antonipillai
6/16/2009 03:15:35 PM
PHARMACOLOGIST
Please see the recommendations from the pharm/tox consult
Please see the pharm/tox recommendations

Karen Davis-Bruno
6/16/2009 04:31:05 PM
PHARMACOLOGIST
safety concern for intended treatment population

Telephone Fax

ANDA 91-226

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Mylan Pharmaceuticals Inc.
U.S. Agent for Matrix Laboratories LTD.

TEL: 304-599-2595 ext. 6551

FAX: 304-285-6407

ATTN: Wayne Talton

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20mg, 40 mg and 80 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: 91-226 Date of Submission: December 30, 2008

Applicant's Name: Matrix Laboratories Ltd.

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

---

Labeling Deficiencies:

1. CONTAINER (all strengths in bottles of 90s and 500s):

   a. Storage temperature statement- please relocate the period between the two phrases to the end of the bracket, e.g. “Store at 20 to 25°C (68 to 77°F) [See USP for Controlled Room Temperature].”

   b. Since this drug product is associated with a patient package insert, we encourage you to add to the principal display panel: “Pharmacist: please dispense with patient package insert”.

2. INSERT

   ADVERSE REACTIONS, Postintroduction Reports- add “and hepatic failure” after “tendon rupture”.

3. PATIENT INFORMATION SHEET:
   a. Please submit the patient package insert. We refer you to the RLD, 20-702/S-046 approved on 6/23/06 at the Drugs@FDA website.
   b. Please state the number of sheets you intend on providing in order for each patient to receive one.

Submit labels and labeling electronically. We refer you to the website http://www.fda.gov/oc/datacouncil/spl.html for further guidance.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
5/14/2009 11:04:02 AM
for Wm Peter Rickman

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722. Fax : 27700343
E-mail:matrix@matrixlabsindia.com

AA Notice sent to holder S. Miller 6/11/09 5/11/09

Date: May 1, 2009

To:
Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Patent Amendment
(Notice sent to NDA and patent holder)

N/XP

Subject: ANDA # 91-226,
Atorvastatin Calcium Tablets; 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Buehler:

Reference is made to the subject Abbreviated New Drug Application (ANDA) of Matrix Laboratories Limited India (Matrix).

In accordance with Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act, and 21 C.F.R. § 314.95(b), Matrix certifies that on this date, it has provided notice to each owner of the patents which are the subject of a Paragraph IV certification (U.S. Patent #s 5,686,104; 5,969,156; & 6,126,971) or their representatives, and also to the holder of the approved application for the referenced drug claimed by said patents. Said notice complies with the requirements set forth in 21 C.F.R. § 314.95(c) with respect to the content of the notice.

Further, in accordance with 21 C.F.R. § 314.95(e), Matrix commits to amend this application to provide documentation that the notifications sent to each owner of the patent(s) and application holder have been received.

Should you require any additional information, please contact Mylan Pharmaceuticals, Attention, Ronald T. Groman at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India.

Ronald T. Groman

For Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India.

RECEIVED
MAY 04 2009
OGD

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2009-0324	
TO *(Division/Office)* DMEP - HFD-510 Thru: Leah Ripper, ODEII - HFD 102			FROM: Saundra Middleton	
DATE: 4/16/2009	IND NO.	ANDA NO. 091226	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 12/30/2008,
NAME OF DRUG ATORVASTATIN CALCIUM		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG LIPID ALTERING AGENTS	DESIRED COMPLETION DATE 6/15/2009

NAME OF FIRM MATRIX LABS LTD

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICPENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

□ DISSOLUTION
□ PROTOCOL-- BIOPHARMACEUTICS
□ IN--VIVO WAIVER REQUEST
□ DEFICIENCY LETTER RESPONSE
□ BIOAVAILABILITY STUDIES
□ PHASE IV STUDIES

IV.DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
□ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
□ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS

OGD is requesting a Pharm/Tox Review. The firm submitted information regarding the use of L-Arginie in the drug product. They are using a max of (b) (4) of L-Arginie per tablet. This inactive has only been used in injectables, never in an oral product. Please review their submission and provide comment if these levels are safe for human use. **NOTE** a consult was sent for the same ingredient under ANDA (b) (4) and found acceptable. Pls. confirm if the proposed level and data submitted by Matrix is also acceptable.

Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 91-226 **FIRM NAME**: MATRIX LABORATORIES INC.

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM

DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Random Queue: 12

Chem Team Leader: Iser, Robert Chem PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Nam Chuh

Letter Date: DECEMBER 30, 2008 **Received Date**: DECEMBER 31, 2008

Comments: EC- 4 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Saundra T. Middleton	**Recommendation:**
Date 3/18/2009	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date: ____**

ADDITIONAL COMMENTS REGARDING THE ANDA:

3/18/2009 – Requested the Pharm/Tox informationfor L-Arginine be submitted electronically in the interim. NOTE: The use of L-Arginine was used in the formulation. L-Arginine has never been used in an approved drug product before. Matrix has submitted Pharm/Tox information on L-Arginine and this will be sent for consult.

Ronald Groman was advised with regards to future submission that patent and exclusivity statement should be separated out.

3/18/2009 – electronic copy was requested from Mylan and received 3/24/2009

3/23/2009 – Mr. Groman was asked to address the newly issued patent RE40667. Addressed 3/25/2009

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 30, 2008	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PIII to '893 and '995 and PIV to '104, '156 and '971 3/25/2009 patent amendment – PIII to RE 40667 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 1-08-2017 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES - will not market until I-523 has expired	☒

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	Delist Requested
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 8, 2016	Y			
020702	004	5969156*PED	Jan 8, 2017				
020702	004	6126971	Jan 19, 2013		Y		
020702	004	6126971*PED	Jul 19, 2013				
020702	004	RE40667	Dec 28, 2010	Y	Y	U-162	
020702	004	RE40667*PED	Jun 28, 2011				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020702	004	I-471	Sep 21, 2008
020702	004	I-523	Mar 2, 2010

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-161	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT
U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA
U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA

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

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES # 21477 b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒
1.12.11	**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 or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use **YES** 2. Active ingredients **YES** 3. Inactive ingredients **YES** 4. Route of administration **YES** 5. Dosage Form **YES** 6. Strength **YES**	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒

1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES – 10 mg, 20 mg and 40 mg	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Electronic **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained **YES** **1.14.1.3** 1 package insert (content of labeling) submitted electronically **YES** ***Was a proprietary name request submitted? **NO** (If yes, send email to Labeling Reviewer indicating such.) The container labeling is presented for following configurations: **Sr. No.** / **Strength** / **Bottle Packs** / **Bulk Shipment Packs** 1 / 10 mg / 90's count, 500's count / (b) (4) 2 / 20 mg / 90's count, 500's count / (b) (4) 3 / 40 mg / 90's count, 500's count / (b) (4) 4 / 80 mg / 90's count, 500's count / (b) (4)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained **YES** **1.14.3.3** 1 RLD label and 1 RLD container label **YES**	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF YES** **Word Processed e.g., MS Word YES** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR) YES** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) YES** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product YES** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF YES** **Word Processed e.g., MS Word YES** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary **YES** Table 4. Bioanalytical Method Validation **YES** Table 6. Formulation Data **YES** **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **YES** **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies **YES** Table 3. Statistical Summary of the Comparative BA Data **YES** **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **YES** **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies **YES**	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) **YES** 2. Function or Responsibility **YES** 3. Type II DMF number for API **YES # 21477** 4. CFN or FEI numbers **YES**	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) **YES** **3.2.S.4.2 Analytical Procedures YES** **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples **YES** 2. Samples-Statement of Availability and Identification of: a. Drug Substance **YES** b. Same lot number(s) **YES** **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) **YES** 2. Applicant certificate of analysis **YES** **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems – IN DMF**	☒
3.2.S.7	**Stability – IN DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition **YES** 2. Inactive ingredients and amounts are appropriate per IIG **YES – except for the use of L-Arginine which has never been used before in an approved drug product. Pharm/Tox data was submitted by Matrix and will be sent for consult.**	☐
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report **YES**	☒

3.2.P.3

Manufacture

3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)

1. Name and Full Address(es)of the Facility(ies) **YES**
2. CGMP Certification: YES
3. Function or Responsibility **YES**
4. CFN or FEI numbers **YES**

3.2.P.3.2 Batch Formula YES

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process **YES**
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4)

Batch Size

A comparison of the exhibit and intended commercial batch sizes is shown below. The commercial batch size is (b) (4) of the exhibit batch size.

Strength	Exhibit Batch size*		Intended Commercial Batch size	
	kg	units	kg	units
(b) (4)				(b) (4)
10 mg				
20 mg				
40 mg				
80 mg				

* For exhibit batches, one batch of (b) (4) was prepared and subdivided for (b) (4) of 10 mg ((b) (4)), 20 mg ((b) (4)), 40 mg (b) (4)) and 80 mg (b) (4) strengths.

3. If sterile product: Aseptic fill / Terminal sterilization NA
4. Reprocessing Statement **YES**

3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

1. Microbiological sterilization validation NA
2. Filter validation (if aseptic fill) NA

3.2.P.4

Controls of Excipients (Inactive Ingredients)

Source of inactive ingredients identified **YES**

3.2.P.4.1 Specifications

1. Testing specifications (including identification and characterization) **YES**
2. Suppliers' COA (specifications and test results) **YES**

3.2.P.4.2 Analytical Procedures

3.2.P.4.3 Validation of Analytical Procedures

3.2.P.4.4 Justification of Specifications

Applicant COA

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s) YES** **3.2.P.5.2 Analytical Procedures YES** **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form **YES** 2. Same lot numbers **YES** **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form **YES** **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) **YES** 2. Components Specification and Test Data **YES** 3. Packaging Configuration and Sizes **YES** 4. Container/Closure Testing **YES** 5. Source of supply and suppliers address **YES**	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted **YES** 2. Expiration Dating Period **YES –** (b)(4) **MONTHS** **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments **YES** **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data **YES** 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation **YES – SEE BELOW** **3.2.R.1.P.2 Information on Components YES** **3.2.R.2.P Comparability Protocols NO** **3.2.R.3.P Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

· **What is the reconciliation of the exhibit batch?**

Please see tabulated below the reconciliation of the exhibit batch.

SUMMARY OF YIELD RECONCILIATION

Product Name: (b) (4) for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Batch #: 1004885

Batch Size: (b) (4)

#	**Particulars**	(b) (4) (D) (4)
1	Theoretical Qty (Kg)	
2	Actual Qty (Kg)	
3	Samples @ (kg)	
4	Actual Yield (%) = (2) x 100 / (1)	

Division of (b) (4)

The (b) (4) of Batch # 1004885 was divided, for (b) (4) into 4 strengths details of which are presented below :

Strength & Batch #	(b) (4)	
	Actual quantity	Theoretical quantity
10 mg (Batch # 1004888)	(b) (4)	
20 mg (Batch # 1004889)		
40 mg (Batch # 1004890)		
80 mg (Batch # 1004891)		

@ Samples drawn for testing / evaluation purposes.

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 10 mg
Batch #: 1004888
Batch size: (b) (4)

MANUFACTURING		
#	Particulars	(b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	
4	Rejections Non-recoverable @@	
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING	
Particulars	(b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes
@@ In-process checks or known losses accounted during processing

(b) (4)

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 20 mg
Batch #: 1004889
Batch size: (b) (4)

MANUFACTURING

#	Particulars	(b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	
4	Rejections Non-recoverable @@	
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING

Particulars	(b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes
@@ In-process checks or known losses accounted during processing

(b) (4)

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 40 mg
Batch #: 1004890
Batch size: (b) (4)

MANUFACTURING		
#	Particulars	(b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	
4	Rejections Non-recoverable @@	
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING	
Particulars	(b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes
@@ In-process checks or known losses accounted during processing

(b) (4)

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 80 mg
Batch #: 1004891
Batch size: (b) (4)

MANUFACTURING		
#	Particulars	(b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	

4	Rejections Non-recoverable @@	(b) (4)
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING	
Particulars	(b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes

@@ In-process checks or known losses accounted during processing

(b) (4)

MODULE 5

CLINICAL STUDY REPORTS ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) **YES** b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **NA** **2. Lot Numbers of Products used in BE Study(ies):** Study # 022-08 and 162-08 Lot number **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **YES** 2. Summary Bioequivalence tables: Table 10. Study Information **YES** Table 12. Dropout Information **YES** Table 13. Protocol Deviations **YES** **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information **YES** Table 16. Composition of Meal Used in Fed Bioequivalence Study **YES** **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples **YES** Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses **YES** Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **YES** **5.3.7** **Case Report Forms and Individual Patient Listing YES**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) Fed and Fasting on the 80 mg 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **YES – see below** 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: **YES**	☒

Table 3A Statistical Summary of the Comparative Bioavailability Data

a) Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (Study No. 022-08)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max} (ng/mL)	78.6529	73.2673	107.35	94.47 – 121.99
AUC_{0-t}	325.1762	308.0635	105.55	99.01 – 112.53
AUC_{0-INF}	329.3475	312.2741	105.47	98.97 – 112.39

Table 3B Statistical Summary of the Comparative Bioavailability Data

a) Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 162-08)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max} (ng/mL)	47.3025	49.3465	95.86	86.49 - 106.23
AUC_{0-t} (ng*h/mL)	249.3969	262.2604	95.10	88.88 – 101.74
AUC_{0-INF} (ng*hr/mL)	254.7854	268.3049	94.96	88.84 – 101.50

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008

Table 6 Formulation Data

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet
	10 mg	20 mg	40 mg	80 mg	
[redacted]					(b) (4)
Atorvastatin Calcium					(b) (4)
Microcrystalline cellulose (b) (4)					
Colloidal silicon dioxide (b) (4)					
Sodium carbonate anhydrous					
L-Arginine					
Anhydrous lactose (b) (4)					
Croscarmellose sodium (b) (4)					
Hydroxypropyl cellulose (b) (4)					
Magnesium stearate (b) (4)					
[redacted]					(b) (4)
[redacted]					(b) (4)

(b) (4)

Inactive ingredient confirmation per unit for 91-226:

CELLULOSE, MICROCRYSTALLINE (b) (4)

SILICON DIOXIDE, COLLOIDAL (b) (4)

(b) (4)

L-ARGININE – NOT FOUND – PHARM/TOX DATA SUBMITTED BY MATRIX – WILL BE SENT FOR CONSULT

LACTOSE, ANHYDROUS (b) (4)

CROSCARMELLOSE SODIUM (b) (4)

HYDROXYPROPYL CELLULOSE (b) (4)

MAGNESIUM STEARATE (b) (4)

(b) (4)

SAFETY ASSESSMENT FOR ORAL USE OF L-ARGININE

MEMORANDUM

To: **Jeffrey P. Smith, PhD, Director, Pharmacology and Toxicology**
Mylan Laboratories

From: [redacted] (b) (4)

Subject: L-Arginine in Atorvastatin Calcium Tablets 80 mg, Matrix/Mylan

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L-arginine is an α-amino acid and is considered to be semi-essential depending upon the health and developmental status of the organism. With the exception of infants, L-Arginine can be synthesized by the human body and, therefore, may not be a necessary component of the diet. However, it is present to a great extent in foods (animal protein such as beef, poultry, milk etc., seafood such as lobster, salmon, shrimp, etc. and many vegetable sources such as nuts, seeds, wheat flour, etc.).

Some of the foods that contain the highest amount of L-Arginine (values per 200 calorie serving or approximately 100 g[1,2]) are:

- Sesame flour---4465 mg
- Soy protein isolate, K type ---4156 mg
- Gelatins, dry powder, unsweetened---3951 mg
- Crustaceans, Alaska King raw---3805 mg
- Crustaceans, Dungeness cooked---3538 mg
- Crustaceans, Shrimp raw---3349 mg
- Poultry, Turkey raw---2866 mg
- Pork Chops---2348 mg

L-Arginine has essential roles in the healing of wounds, removing ammonia from the body, immune function, cell division, production of nitric oxide etc. In addition, many other claims have been made for its biological effects such as increasing muscle mass and reducing the size of fat depots in the body, etc. but these claims remain unproven.

L-Arginine is a component of several human injectable antibiotic products as an aid to solubilize the antibiotic. It can be found in:

- AZACTAM® (aztreonam) at a level of 780 mg per gram of aztreonam[3]
- MAXIPIME® (cefepime) at a level of 725 mg per gram of cefepime[4]
- VELOSEF® (cephradine) quantity not listed.

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[1] http://www.nutritiondata.com/foods-000089000000000000000.html
[2] http://www.supplementnews.org/wiki/arginine
[3] USFDA approved prescribing information for AZACTAM®
[4] USFDA approved prescribing information for MAXIPIME®

In a pilot clinical trial conducted in Poland, 792 patients with acute myocardial infarction (MI) were given either placebo or 3 grams of L-Arginine orally in capsules three times daily for a period of 30 days. The results of the study showed a beneficial trend in patients with an acute MI while also demonstrating that 9 grams of L-Arginine orally is safe and well tolerated.[5]

The level of L-Arginine in Matrix's atorvastatin calcium tablets 80 mg is identified as (b) (4) per tablet and which is given once daily to patients. This level is far below the level found in common foods and the amounts given parenterally to sick patients with bacterial infections and orally to patients with acute MI. It would therefore seem prudent for the US FDA to accept the inclusion of L-Arginine at (b) (4) per tablet in this drug product given what is known about this semi-essential amino acid and the recognition of a very low risk to safety of the drug-ingesting patient.

[5] Bednarz, B. et al, Efficacy and safety or oral l-arginine in acute myocardial infarction. Results of multicenter, randomized, double-blind, placebo-controlled ARAMI pilot trial, Kardiol. Pol., 2005, 62: 421-426.

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2	Soy protein isolate, potassium type, crude protein basis Arginine: 4156mg
3	Soy protein isolate, potassium type Arginine: 4093mg
4	Seeds, cottonseed flour, low fat (glandless) Arginine: 4056mg
5	Gelatins, dry powder, unsweetened Arginine: 3951mg
6	Soy protein isolate Arginine: 3947mg
7	Peanut flour, defatted Arginine: 3818mg
8	Crustaceans, crab, alaska king, raw Arginine: 3805mg
9	Crustaceans, shrimp, mixed species, cooked, moist heat Arginine: 3689mg
10	Crustaceans, lobster, northern, cooked, moist heat Arginine: 3655mg
11	Crustaceans, lobster, northern, raw Arginine: 3648mg
12	Crustaceans, crab, blue, raw Arginine: 3626mg
13	Crustaceans, crab, blue, canned Arginine: 3622mg
14	Crustaceans, crayfish, mixed species, wild, raw Arginine: 3619mg
15	Seeds, cottonseed meal, partially defatted (glandless) Arginine: 3615mg
16	Mollusks, whelk, unspecified, raw Arginine: 3603mg

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Arginine: 3597mg

18 Crustaceans, crab, queen, cooked, moist heat
Arginine: 3597mg

19 Crustaceans, crab, queen, raw
Arginine: 3591mg

20 Mollusks, whelk, unspecified, cooked, moist heat
Arginine: 3590mg

21 Crustaceans, crayfish, mixed species, wild, cooked, moist heat
Arginine: 3568mg

22 Crustaceans, crab, dungeness, cooked, moist heat
Arginine: 3538mg

23 Crustaceans, crab, dungeness, raw
Arginine: 3537mg

24 Crustaceans, crayfish, mixed species, farmed, cooked, moist heat
Arginine: 3512mg

25 Crustaceans, crab, alaska king, cooked, moist heat
Arginine: 3484mg

26 Crustaceans, crab, blue, cooked, moist heat
Arginine: 3461mg

27 Soy protein isolate, PROTEIN TECHNOLOGIES INTERNATIONAL, SUPRO
Arginine: 3454mg

28 Soy protein isolate, PROTEIN TECHNOLOGIES INTERNATIONAL, ProPlus
Arginine: 3421mg

29 Crustaceans, shrimp, mixed species, raw
Arginine: 3349mg

30 Spinach, frozen, chopped or leaf, unprepared
Arginine: 3317mg

31 Seaweed, spirulina, raw
Arginine: 3285mg

32 Crustaceans, shrimp, mixed species, canned
Arginine: 3262mg

33 Crustaceans, spiny lobster, mixed species, cooked, moist heat
Arginine: 3222mg

34 Crustaceans, spiny lobster, mixed species, raw
Arginine: 3212mg

35 Seeds, sesame flour, partially defatted
Arginine: 3131mg

36 Turkey, fryer-roasters, light meat, meat only, raw
Arginine: 3125mg

37 Seeds, sunflower seed flour, partially defatted
Arginine: 3111mg

38 Turkey, fryer-roasters, breast, meat only, cooked, roasted
Arginine: 3107mg

39 Turkey, fryer-roasters, breast, meat only, raw
Arginine: 3092mg

40 Seeds, cottonseed flour, partially defatted (glandless)
Arginine: 3082mg

41 Turkey, fryer-roasters, light meat, meat only, cooked, roasted
Arginine: 3009mg

42 Mollusks, cuttlefish, mixed species, raw
Arginine: 3000mg

43 Mollusks, cuttlefish, mixed species, cooked, moist heat
Arginine: 3000mg

44 Turkey, fryer-roasters, wing, meat only, raw
Arginine: 2961mg

45 Spinach, frozen, chopped or leaf, cooked, boiled, drained, with salt
Arginine: 2877mg

46 **Spinach, frozen, chopped or leaf, cooked, boiled, drained, without salt**
Arginine: 2877mg

47 **Lupins, mature seeds, cooked, boiled, with salt**
Arginine: 2877mg

48 **Turkey, young tom, light meat, meat only, raw**
Arginine: 2866mg

49 **Seaweed, spirulina, dried**
Arginine: 2861mg

50 **Turkey, all classes, light meat, raw**
Arginine: 2857mg

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Source:
http://www.supplementnews.org/wiki/arginine

Arginine Introduction

Arginine is classified as a semi, conditionally essential amino acid. It is nonessential in nature, but becomes essential in times of extreme stress. The body's ability to synthesize this amino acid is lost during these traumatic periods. Adequate dietary intake is therefore necessary to meet the increased physiological need.

Synthesized in the kidney, *arginine* is a vital amino acid, critical for numerous metabolic processes. Processes such as nitrogen catabolism, the Krebs-Henseleit urea cycle, and detoxification of ammonia are directly dependent upon arginine. It also serves as a precursor to a host of hormones, neurotransmitters, and proteins. Arginine may also be used for biological energy if glycogen is needed by the body.

Supplemental L-arginine is also acknowledged for its antioxidant properties, immunological benefit, and wound repair activity. It shows great promise in the prevention of cardio vascular disorders (e.g. atherosclerosis, angina pectoris), supporting male infertility, and aids in both kidney and liver functioning. Claims that L-arginine supplementation enhances the reduction of body fat and increases both lean muscle mass and exercise performance are, however, unsubstantiated.

Edit

Arginine Food Sources

The majority of **arginine** is derived from plant and animal proteins. The highest concentrations are found in plant and soy proteins, rather than animal protein (which is typically richer in other amino acids). The average *daily intake of arginine* ranges from 3 - 5 grams (g). Serving sizes below are based upon 100 grams of a given food source and are expressed in milligrams, representing the amount of arginine contained.

Vegetables and Vegetable Products	
mg/100g	Food Name
4246	Spinach, frozen, chopped or leaf, unprepared
3506	Spinach, frozen, chopped or leaf, cooked, boiled, drained, without salt
3506	Spinach, frozen, chopped or leaf, cooked, boiled, drained, with salt
3286	Seaweed, spirulina, raw
2861	Seaweed, spirulina, dried

Nut and Seed Products	
mg/100g	Food Name
4466	Seeds, sesame flour, low-fat
4057	Seeds, cottonseed flour, low fat (glandless)
3616	Seeds, cottonseed meal, partially defatted (glandless)
3131	Seeds, sesame flour, partially defatted
3111	Seeds, sunflower seed flour, partially defatted
3082	Seeds, cottonseed flour, partially defatted (glandless)

Legumes and Legume Products	
mg/100g	Food Name
4157	Soy protein isolate, potassium type, crude protein basis
4093	Soy protein isolate, potassium type
3947	Soy protein isolate
3819	Peanut flour, defatted
3455	Soy protein isolate, Protein Technologies International, Supro
3422	Soy protein isolate, Protein Technologies International, ProPlus

Finfish and Shellfish Products	
mg/100g	Food Name
3805	Crustaceans, crab, alaska king, raw
3690	Crustaceans, shrimp, mixed species, cooked, moist heat
3656	Crustaceans, lobster, northern, cooked, moist heat
3649	Crustaceans, lobster, northern, raw
3626	Crustaceans, crab, blue, raw
3623	Crustaceans, crab, blue, canned
3619	Crustaceans, crayfish, mixed species, wild, raw
3603	Mollusks, whelk, unspecified, raw
3597	Crustaceans, crab, queen, cooked, moist heat
3597	Crustaceans, crayfish, mixed species, farmed, raw
3592	Crustaceans, crab, queen, raw
3590	Mollusks, whelk, unspecified, cooked, moist heat
3569	Crustaceans, crayfish, mixed species, wild, cooked, moist heat
3539	Crustaceans, crab, dungeness, cooked, moist heat
3538	Crustaceans, crab, dungeness, raw

3513	Crustaceans, crayfish, mixed species, farmed, cooked, moist heat
3485	Crustaceans, crab, alaska king, cooked, moist heat
3461	Crustaceans, crab, blue, cooked, moist heat
3361	Crustaceans, shrimp, mixed species, canned
3350	Crustaceans, shrimp, mixed species, raw
3222	Crustaceans, spiny lobster, mixed species, cooked, moist heat
3213	Crustaceans, spiny lobster, mixed species, raw
3000	Mollusks, cuttlefish, mixed species, raw
3000	Mollusks, cuttlefish, mixed species, cooked, moist heat

Poultry Products	
mg/100g	Food Name
3125	Turkey, fryer-roasters, light meat, meat only, raw
3107	Turkey, fryer-roasters, breast, meat only, cooked, roasted
3092	Turkey, fryer-roasters, breast, meat only, raw
3009	Turkey, fryer-roasters, light meat, meat only, cooked, roasted
2961	Turkey, fryer-roasters, wing, meat only, raw
2867	Turkey, young tom, light meat, meat only, raw

Sausages and Luncheon Meats	
mg/100g	Food Name
3475	Turkey, white, rotisserie, deli cut
3020	Turkey breast meat

Sweets	
mg/100g	Food Name
3951	Gelatins, dry powder, unsweetened

[1]

Edit

Arginine Uses

Arginine has been a major contributor towards the research and understanding of various diseases. Clinical applications cite the effectiveness of supplemental arginine on both physical and cognitive functioning. The L-form of arginine is recommended for supplemental assistance with regard to varying physiological conditions. [2]

Among the most important uses of **supplemental arginine** is its function within the human metabolic processes. Arginine provides the means for the metabolism of muscle, protein, and

nitrogen. [3, 4] Arginine is responsible for maintaining a positive nitrogen balance within the body. It accomplishes this task by excreting excess nitrogen and acting as a mechanism for the storage and transportation of nitrogen. Arginine is equally critical for the reduction of nitrogen loss in severe trauma patients. Supplemental arginine in these individuals may enhance protein synthesis; resulting in elevated wound healing properties, and immune system functioning. [5, 6] These benefits may also be witnessed in healthy persons who supplement his/her diet with *L-arginine*.

Arginine may also be central in the overall health of the circulatory system. Arginine is a precursor to the neurotransmitter nitric oxide (NO). NO is responsible for the constriction and dilation of blood vessels located within the brain. Because of this, arginine (in the form of *arginine pyroglutamate*) may provide us with improved cognitive function. [7] Combined with its polyamine increasing properties, the ability for arginine to improve brain function may ultimately benefit Alzheimer's sufferers. [2] Researchers have also used arginine to enhance nitric oxide metabolism in patients suffering from angina, congestive heart failure, and interstitial cystitis. [8]

By increasing the activity of the thymus gland, **arginine** may enhance immune system function. [6] This may prove especially beneficial in the prevention of certain types of cancers. The thymus gland is responsible for the production of T lymphocytes (T-cells), which are important constituents of immunomodulatory activity. By increasing T-cells, and reducing polyamines via arginine supplementation, it may be possible to inhibit the development of tumors and other malignancies. [3] Nitric oxide, activated from arginine, is also used by the immune system in combating cancer.

Research also indicates that **arginine** may be effective in reducing Low-Density Lipoproteins (LDLs), or bad cholesterol levels. [9] Arginine may also yield extremely valuable antioxidant activities. It has been shown to diminish the oxidation of LDLs and inhibit lipid peroxidation. This is critical, as the oxidation of LDL is believed to be an important first step in the formation of atheromatous deposits, especially on the innermost layer of arterial walls (*atherogenesis*).

Arginine may also increase levels of glucose, prolactin, and most importantly, human growth hormone (HGH). The release of human growth hormone may be influenced by arginine's potential of blocking the secretion of somatostatin, a hormone which inhibits HGH production. [10] Treatment of injuries, strengthening of the immune system, lean muscle composition, and anti-aging properties; all are associated with prominent levels of HGH. Arginine may further enhance HGH release when combined (stacked) with the amino acids lysine and ornithine. [11]

Although it is unclear why, the elderly's response is often better than other age groups concerning *arginine supplementation* and growth hormone release. [2]

The **benefits of arginine** supplementation in males may be far superior in comparison to its use in women. Because arginine is found in high concentrations in seminal fluid, it may be advantageous in treating sterility in men. [12] As little as four grams of arginine has proven effective in clinical research for this purpose. Some 80% percent of subjects studied, who received this dosage, reported a dramatic improvement in libido, erection, and in some female cases, pregnancy. [13] The motility of sperm may also be positively impacted by the supplementation of arginine.

Although there are many claims regarding arginine's ability to enhance exercise performance and assist in the development of lean body mass, research remains unclear. Arginine does, however, play an important role in the transport, elimination, and storage of nitrogen; all of which are significant in the complex metabolic processes of muscle. The amino acid creatine, a popular nutritional supplement, is also a derivative of arginine. Clearly, the topic of arginine's supplementation in "bodybuilding" merits further research.

Edit

Arginine Dosages

Because arginine is considered a nonessential amino acid, the National Research Council's Food and Nutrition Board has not established a *Recommended Daily Allowance* (*RDA*).

The U.S. National Academy of Sciences recommends that healthy people achieve .36 grams of highly bioavailable protein for each pound of bodyweight; equaling 0.8 grams of protein per kilogram of bodyweight.

Edit

Arginine Toxicities and Deficiencies

Arginine Deficiencies

It is uncommon for individuals to develop a deficiency of any nonessential acid. Inadequacies of arginine are rare, but have occurred. Signs and symptoms of a deficiency include; rash, hair loss, hair breakage, poor wound healing, constipation, fatty liver, hepatic cirrhosis, and hepatic coma. [2] In cases of severe deficiency, symptoms may include muscle weakness, impairments in liver lipid metabolism, and complications in the production of insulin and glucose.

Arginine Toxicities

Massive dosages of arginine often are accompanied by a coarsening and thickening of skin tissue, nausea, weakness, and diarrhea. Excessive dosages may also activate and promote viral growth. For this reason, individuals suffering from herpes, or other viral infections, should not take arginine-containing supplements.[15]

Edit

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ORIGINAL ARTICLES
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Bronisław Bednarz, Tomasz Jaxa-Chamiec, Paweł Maciejewski, Michał Szpajer[1], Krzysztof Janik[2], Jacek Gniot[3]
Teresa Kawka-Urbanek[4], Dorota Drozdowska[5], Jacek Gessek[6], Henryk Laskowski[7]

Efficacy and safety of oral l-arginine in acute myocardial infarction. Results of multicenter, randomized, double-blind, placebo-controlled ARAMI pilot trial

Postgraduate Medical School, Department of Cardiology, Grochowski Hospital, Warsaw; [1] PCKMarine Hospital, Gdynia;
[2] T. Chałubiński Hospital, Częstochowa; [3] City Hospital, Puławy; [4] Voivodship Hospital, Skierniewice;
[5] City Hospital, Świecie; [6] City Hospital, Toruń; [7] Voivodship Hospital, Leszno, Poland

Aims. L-arginine is a substrate for nitric oxide (NO) synthesis in vascular endothelial cells. NO bioavailability is decreased during myocardial infarction (MI). It might be expected that administration of L-arginine may maintain NO production and alleviate the course of MI. The aim of the study was to assess safety and effects of treatment with L-arginine on the clinical course of MI.

Methods and Results. 792 patients (mean age 64 years, 551 men) with ST segment elevation MI admitted within 24h after the onset of symptoms were randomized to oral L-arginine (3.0 t.i.d p.o. for 30 days) or placebo on top of routine therapy. The end point which was the composite of 30 day cardiovascular death, reinfarction, successful resuscitation, shock/pulmonary edema or recurrent myocardial ischemia occurred in 24% patients treated with L-arginine and 27% with placebo (OR 0.63, 95% CI 0.39-1.02, p=0.06). The end point was observed less frequently in 226 patients with hyperlipidemia (19 vs 31, p<0.05). No serious adverse effects were observed during L-arginine supplementation.

Conclusions. This study, which is the first attempt to use L-arginine in MI, showed that oral L-arginine supplementation was well tolerated. Beneficial nonsignificant trend was observed towards reduction of major clinical events.

Key words: L-ARGININE – MYOCARDIAL INFARCTION

(Kardiol. Pol. 2005, 62, 421)

INTRODUCTION

It has been well established that endothelial dysfunction leading to depressed production of nitric oxide (NO), plays an essential role in the pathogenesis of coronary artery disease (1,2) and is causally involved in the development of an acute coronary syndrome promoting thrombus formation and coronary occlusion (3-7).

L-arginine which is the physiological precursor of nitric oxide, can ameliorate endothelial dysfunction in hypercholesterolemia (8-10), chronic ischemic heart disease (11-13), coronary transplant vasculopathy (14) and peripheral arterial occlusive disease (15).

The beneficial effects of L-arginine administration have been documented in patients with microvascular (11,13), stable (12,16,17) or intractable (18) angina pectoris. The benefits included augmentation of nitric oxide-dependent coronary arterial (12,13) and microvascular (11,13) dilation, improved exercise tolerance (16,19), relieved exercise-induced myocardial ischemia (17), alleviation of coronary pains (18).

The promising therapeutic potential of L-arginine demonstrated by the cited small studies has not yet been firmly established in a controlled trial. We still have no data on the effects of acceptable doses of L-arginine in patients with acute coronary events. Enhanced vasodilation, decreased platelet aggregation, reduced adhesion of blood elements to the vessel wall, all afforded by L-arginine-nitric oxide pathway (20), might be expected to improve myocardial ischemia in patients with acute coronary syndrome.

Therefore, the aim of this randomized, placebo-controlled pilot study was to test the tolerance and effectiveness of L-arginine supplementation in patients with acute myocardial infarction with ST segment elevation (MI).

The results of this study were partly presented at the scientific sessions of the European Society of Cardiology, Vienna, August 30 – September 3, 2003 and American College of Cardiology, New Orleans, March 7-10, 2004.
The study was supported by the Polish State Committee for Scientific Research (grant number 4P05B 041 18) and the Proclinica Foundation, a non-profit organisation, Warsaw, Poland

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METHODS

Study organization

This was a prospective, multicenter, randomized, placebo-controlled and double-blind trial. The study was organized and conducted by the steering committee of the coordinating center at the Postgraduate Medical School, Grochowski Hospital in Warsaw and 36 participating community hospitals in Poland (see Appendix) and supported by the Polish State Committee for Scientific Research (grant number 4P05B 041 18) and the Proclinica Foundation, a non-profit organisation, Warsaw, Poland.

Study population

Patients of either gender, age ≥21 years, were eligible if they presented with symptoms of acute MI within 24 hours prior to admission. The diagnosis of acute MI was confirmed by typical electrocardiographic pattern (ST-segment elevation of 2 mm or more in at least two contigous leads or new LBBB) and typical chest pain lasting more than 20 minutes and/or maximal value of biochemical markers of myocardial necrosis (CK-MB and CK) greater than 2 times the upper limit of normal. Patients were excluded if they presented with cardiogenic shock, hypotension (a systolic blood pressure of less than 100 mmHg for at least 30 minutes), pulmonary edema, lost of consciousness, kidney failure (creatinine >2 mg/dl) or major systemic illnesses that might influence the prognosis.

Randomization and treatment

Enrolment in the trial began on March 1, 2000 and ended on May 31, 2002. The 24 h randomization was performed by telephone in the coordinating center. Eligible patients were randomized to one of the three arms: L-arginine, antioxidant vitamins or placebo on top of routine therapy. A report concerning antioxidant vitamins will be presented separately. The intervention group was given L-arginine 3.0 g p.o. t.i.d. (1.0 g capsules) for a total period of 30 days. The placebo group received capsules of placebo t.i.d. identical to L-arginine for the same time of 30 day treatment. No community hospitals participating in the study had on-site angiographic facilities at the time of the study. Therefore, the patients who required interventional treatment were not eligible and were transferred to tertiary centers.

Ethics

The study was approved by the Ethic Committee of the National Postgraduate Medical School in Warsaw and, where necessary, by the ethics committee of participating centers. All patients were informed about the study and gave written consent before randomization.

Clinical outcomes

The end point was the composite of 30 day cardiovascular mortality, successful resuscitation, reinfarction, shock/pulmonary edema or recurrent myocardial ischemia. Prespecified subgroups to be analyzed were defined to be gender, age (<70 or ≥70 years), localization of MI, fibrinolytic therapy, lipid profile on admission,a history of MI, diabetes mellitus, hypertension, smoking.

Cardiovascular death was defined as death due to coronary artery disease (including sudden cardiac death), stroke, pulmonary embolism, acute heart failure or cardiac arrhythmia. New MI was diagnosed when ischemic pain lasting more than 20 minutes recurred and CK-MB or CK values increased by at least 50% of the previous value (21). Recurrent ischemia was diagnosed by new ischemic resting chest pain with new ST-segment depression of at least 0.1 mV and/or necessity of heparin administration.

Adjudication Committee

An independent, three member, blinded, end point committee was established to review and adjudicate all suspected end points.

Biochemical variables

Blood samples for lipid profile were taken within 24 hours of onset of MI. Lipid abnormalites were diagnosed when total cholesterol level was ≥240 mg/dl and/or LDL cholesterol level was ≥160 mg/dl – which indicates high levels according to ATP III classification (23).

Statistical analysis

All comparisons were performed on an intention-to-treat basis. The obtained result are presented as mean values with standard deviation or as frequency tables. Comparison between groups was performed using χ^2 tests for differences in the proportions of categorical variables and Students t test for continuous variables. All tests were two-sided and considered significant at $p \leq 0.05$. Multivariate logistic regression was carried out for binary response or proportional hazard's regression for time to failure adjusted for age, gender, infarct location, use of thrombolytic treatment, history of myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia and smoking habit. In order to investigate whether certain prognostic factors influenced the results, homogenity test of odds ratios based on the logit approach and the Mantel-Haenszel test were performed. Calculations were made using Stata Statistical Software: Release 7.0, College Station, TX, Stata Corporation.

RESULTS

Study group

The study group consisted of 792 patients. 2456 patients fulfilled the entry criteria, but 1664 patients were excluded. The reasons for exclusion are presented in Table I. Complete 30 day clinical data were available for 774 patients (98%).

Clinical characteristics of the study group are presented in Table II.

In-hospital medications are listed in Table III; there were no significant differences between the groups.

Study end-point

During 30 days of treatment the composite end point occurred in 104 (27%) patients allocated to placebo and in 93 (24%) allocated to L-arginine (p=0.06) (Table IV). Univariate analysis of the prespecified subgroups showed consistent tendency towards benefit among patients who received L-arginine (Figure 1). An excess of events in the

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Table I. Reasons of exclusion from randomization of 1664 patients with ST segment elevation and/or new LBBB. Data are presented as number of patients

Patients fulfilling the entry criteria	2456
Patients excluded from the trial	1664
Reason for exclusion	
transfered to other hospital for primary angioplasty	*160*
omitted in error	*22*
other major illnesses	*231*
lack of patient consent	*379*
shock	*168*
hypotension	*159*
cardiac arrest before randomization	*143*
patients randomized to receive antioxidant vitamins	*402*
Patients included in the ARAMI trial	792

patients with hyperlipidemia in the placebo group versus L-arginine group was observed ($p<0.046$). However, given small group of patients in each subgroup this may be a chance occurence.

Compliance with study treatment and adverse effects

The study medications were withdrawn because of adverse effects, considered to be related to the study treatment, in 9 patients in the L-arginine group and 10 patients in the placebo group (Table V).

DISCUSSION

This is the first controlled study evaluating the tolerance and effectiveness of L-arginine supplementation in a homogenous group of patients with acute MI.

As outlined above, it has been observed that L-arginine substance exerts strong trend ($p=0.06$) trend towards reduction of major clinical events during a 30 day treatment.

Until now clinical studies on possible application of oral L-arginine in the coronary artery disease were conducted in the setting of chronic angina and produced conflicting results. Marked improvement of exercise tolerance (16,17,19) and improvement of angina (19) there were reported, but other authors did not observe such positive effects (23,24).

The concept of clinical utilization of L-arginine in acute MI is derived from basic research. Acute ischemia and reperfusion result in endothelial dysfunction (3,5-7,25,26) which is reflected, among others, by reduced release of NO (3,25,26). Coronary vasodilator response is significantly impaired after acute MI up to 6 months, also in areas of the myocardium not directly supplied by the infarct-related artery (4).

Table II. Baseline patient characteristics

	Placebo n=398	L-arginine n=394
Male sex [n (%)]	276 (69%)	274 (70%)
Age [years, mean ± SD]	62±11.3	63±11.2
Age ≥70 years [n (%)]	109 (27%)	113 (29%)
Medical history [n (%)]		
Previous MI	54 (14%)	51 (13%)
CABG	4 (1%)	5 (1%)
PTCA	3 (1%)	4 (1%)
Hypertension	193 (48%)	187 (47%)
Diabetes mellitus	63 (16%)	54 (14%)
Current smoker	255 (64%)	270 (69%)
Time from onset of pain to beginning the study therapy [hours, mean ± SD]	9.4±7.11	10.1±7.6
Time from onset of pain to beginning the thrombolytic therapy [hours, mean ± SD]	2.7±1.8	2.9±1.7
Systolic blood pressure on admission [mmHg, mean ± SD]	135±22	134±21.8
Diastolic blood pressure on admission [mmHg, mean ± SD]	83±12.6	82±13.0
Heart rate on admission [bpm, mean ± SD]	78±15.3	78±16.6
Killip class on admission [n (%)] I II III IV	 324 (81%) 68 (17%) 6 (2%) 0	 340 (86%) 50 (13%) 3 (1%) 1 (0.3%)
Location of MI [n (%)]		
Anterior	173 (43%)	153 (39%)
Lateral	126 (32%)	96 (24%)
Inferior	207 (52%)	231 (59%)
Posterior	57 (14%)	47 (12%)
LBBB	11 (3%)	2 (0.5%)
Other	36 (9%)	39 (10%)
Echocardiographic examination at the 3rd day after admission	n = 173	n = 167
Wall motion score index [points, mean ± SD]	1.51±0.39	1.51±0.35
Left ventricular ejection fraction [%, mean ± SD]	49.1±9.9	48.2±10.5
Lipid profile on admision	n = 362	n = 363
Total cholesterol [mg/dl, mean ± SD]	206±62	204±66
LDL-cholesterol [mg/dl, mean ± SD]	127±50	126±53

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Table III. In-hospital medications. Data are presented as number (%) of patients

	Placebo n=398		L-arginine n=394		p
	n	%	n	%	
Aspirin	389	98	388	98	ns
Thrombolytic therapy	340	85	336	85	ns
Beta-blockers orally	321	81	322	82	ns
ACE-inhibitors	279	70	280	71	ns
Nitrates orally	273	69	264	67	ns
Low molecular weight heparin	245	62	252	64	ns
Nitrates i.v.	227	57	212	54	ns
Statins	211	53	207	53	ns
Diuretics	132	33	120	30	ns
Unfractioned heparin	94	24	92	23	ns
Beta-blockers i.v.	67	17	65	17	ns
Ticlopidine	48	12	46	12	ns
Oral anticoagulants	35	9	35	9	ns
Digitalis	30	8	28	7	ns
Platelet GP IIb/IIIa blockers	10	3	8	2	ns
Fibrates	10	3	8	2	ns
Angiotensin II receptor blockers	7	2	5	1	ns

Table IV. Major clinical events occurring at 30 days. Data presented as number (%) of patients. More than one complication occurred. in some patients

	Placebo n=398		L-arginine n=394		p
	n	%	n	%	
Cardiovascular death	35	9	30	8	ns
New non-fatal MI	11	3	15	4	ns
Recurrent ischemia	52	13	36	9	ns
Successful resuscitation due to VF/VT	10	3	8	2	ns
Acute heart failure	41	10	29	7	ns

MI – myocardial infarction, VF – ventricular fibrillation, VT – ventricular tachycardia

Table V. Adverse effects considered to be due to the study treatment. Data presented as number (%) of patients

	L-arginine n=394	Placebo n=398
Hypotension	2 (0.5%)	1 (0.3%)
Gastrointestinal disorders	7 (1.8%)	9 (2.3%)

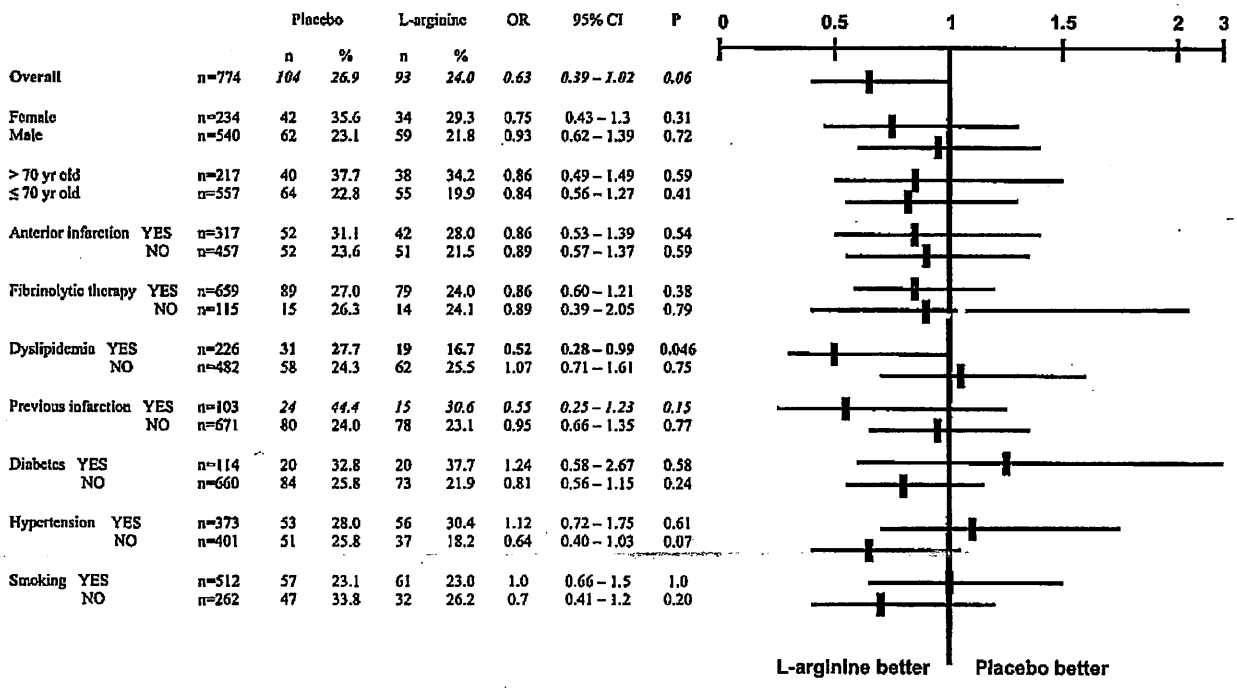


Fig. 1. End point during 30 days of supplementation with L-arginine

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Several authors revealed that L-arginine is effective in the animal model of acute myocardial ischemia/reperfusion. It has been found that L-arginine reduces necrotic injury (27,28), attenuates neutrophil migration to ischemic tissue (27,29), reduces adherence of neutrophils to coronary arterial endothelium (30), preserves vasorelaxation to acetylocholine (27,29, 31), decreases superoxide generation (32) and protects cardiomiocytes against hypercontracture (28).

The results of our study which showed beneficial trend of L-arginine in MI, are strongly supported by the above data. Hence it might be speculated that the results of L-arginine administration would have been more convincing had the study group been larger.

In the present study, L-arginine supplementation appears to have exerted beneficial effect in the subgroup of patients with elevated total cholesterol and/or LDL-cholesterol levels. Given the small number of patients these results may be a play of chance. But on the other hand, these findings might be considered authentic because they are also supported by an ample experimental and clinical data.

In hypercholesterolemic subjects, L-arginine increases flow-mediated vasodilatation, (10,33), augments forearm blood flow response to acetylocholine (9), restores acetylocholine-induced increase in coronary blood flow (8) and attenuates increased platelet reactivity (34). L-arginine also neutralizes the inhibitory effect of native and oxidized LDLs on NO generation (35).

One of the mechanisms leading to endothelial dysfunction in hypercholesterolemic humans is elevated plasma level of asymmetric dimethylarginine (ADMA) (36). ADMA is an endogenous, competitive inhibitor of NO synthase (37). An elevated level of ADMA, with normal level of L-arginine, decreases L-arginine/ADMA ratio and reduces NO synthesis. Exogenous L-arginine given to patients with hypercholesterolemia may compete with ADMA, endogenous NO synthase inhibitor to restore NO synthesis and reverse endothelial dysfunction (36).

Limitations of the study

The small group of patients enrolled in the trial is the main limitation of the study. However, its aim was to test the tolerance of this medication and obtained a preliminary data to consider a larger study powered enough to obtain conclusive results.

The dose of L-arginine and the mode of supplementation we adopted is open for discussion. Perhaps, we should have administrated i.v. loading dose of the substance to receive maximal effects in the shortest time possible. However, there was no data on the tolerance of L-arginine in acute MI and we have chosen an oral route for safety reasons.

Another limitation of the study is the delay of approximately 6-7 hours of L-arginine administration with respect to reperfusion therapy. Given also an oral route we adopted, this substance commenced its action rather late when a portion of the ischemic myocardium might have become irreversibly necrotic. In the future study, an effort should be made to administer L-arginine as soon as possible after admission in loading i.v. dose.

CONCLUSIONS

This controlled pilot study has shown that the supplementation with L-arginine is safe, well tolerated and seems to improve clinical course of acute MI. A larger study is warranted to confirm or refute this novel, inexpensive therapy.

Appendix: The ARAMI Study Group

Data and Safety Monitoring Committee:
Prof. Danuta Liszewska-Pfeifer, Prof. Andrzej Dyduszyński, Prof. Jerzy Kuch.

The names (and locations) of ARAMI co-investigators:
L. Ceremużyński, B. Bednarz, T. Jaxa-Chamiec – coordinators (Warszawa), Z. Binio (Grójec), P. Burduk (Bydgoszcz), H. Danielewicz (Grudziądz), D. Drozdowska (Świecie), D. Durajska (Pabianice), J. Gessek (Toruń), J. Gniot (Puławy), M. Godlewski (Garwolin), M. Goszczyńska (Żyrardów), A. Górniakowska (Zgierz), H. Halaczkiewicz (Starachowice), K. Janik (Częstochowa), M. Kaja (Ostrów Wielkopolski), A. Karski (Ryki), T. Kawka-Urbanek (Skierniewice), Z. Kiedrowicz (Słupsk), A. Kleinork (Zamość), W. Krasowski (Gdańsk), W. Krzyżanowski (Ostrów Mazowiecki), L. Kurianowicz (Biała-Podlaska), H. Laskowski (Leszno), W. Łada (Warszawa), J. Maciejewicz (Kraków), S. Malinowski (Nowy Sącz), J. Mormul (Jarosław), E. Nartowicz (Bydgoszcz), M. Ogórek (Piotrków Trybunalski), W. Supinski (Gorzów Wielkopolski), J. Surwilo (Kościerzyna), M. Szpajer (Gdynia), R. Szyda (Gniezno), M. Świdziński (Warszawa), R. Turkiewicz (Kalisz), J. Walewski (Maków Mazowiecki), Z. Wojtasik (Miechów), Z. Zieliński (Radomsko).

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Received: 28.12.2004

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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/

Theresa Liu

4/17/2009 08:27:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-226

Mylan Pharmaceuticals Inc.
U.S. Agent for: Matrix Laboratories Limited
Attention: Ronald T. Groman
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated March 18 and March 23, 2009 and your correspondence dated March 24 and March 25, 2009.

NAME OF DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

DATE OF APPLICATION: December 30, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 2008

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between

you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240)276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeanne Skanchy
Project Manager
(240) 276-8467

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
4/14/2009 07:09:39 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 91-226 **FIRM NAME**: MATRIX LABORATORIES INC.

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM

DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Random Queue: 12

Chem Team Leader: Iser, Robert Chem PM: Jeanne Skanchy Labeling Reviewer: Ann Vu
Bio PM: Nam Chuh

Letter Date: DECEMBER 30, 2008 **Received Date**: DECEMBER 31, 2008

Comments: EC- 4 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Saundra T. Middleton	**Recommendation:**
Date 3/18/2009	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date: ____**

ADDITIONAL COMMENTS REGARDING THE ANDA:

3/18/2009 – Requested the Pharm/Tox informationfor L-Arginine be submitted electronically in the interim. NOTE: The use of L-Arginine was used in the formulation. L-Arginine has never been used in an approved drug product before. Matrix has submitted Pharm/Tox information on L-Arginine and this will be sent for consult.

Ronald Groman was advised with regards to future submission that patent and exclusivity statement should be separated out.

3/18/2009 – electronic copy was requested from Mylan and received 3/24/2009

3/23/2009 – Mr. Groman was asked to address the newly issued patent RE40667. Addressed 3/25/2009

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 30, 2008	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PIII to '893 and '995 and PIV to '104, '156 and '971 3/25/2009 patent amendment – PIII to RE 40667 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 1-08-2017 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES - will not market until I-523 has expired	☒

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	Delist Requested
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 8, 2016	Y			
020702	004	5969156*PED	Jan 8, 2017				
020702	004	6126971	Jan 19, 2013		Y		
020702	004	6126971*PED	Jul 19, 2013				
020702	004	RE40667	Dec 28, 2010	Y	Y	U-162	
020702	004	RE40667*PED	Jun 28, 2011				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020702	004	I-471	Sep 21, 2008
020702	004	I-523	Mar 2, 2010

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-161	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT
U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA
U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA

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

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES # 21477 b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒
1.12.11	**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 or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use **YES** 2. Active ingredients **YES** 3. Inactive ingredients **YES** 4. Route of administration **YES** 5. Dosage Form **YES** 6. Strength **YES**	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒

1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES – 10 mg, 20 mg and 40 mg	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Electronic **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained **YES** **1.14.1.3** 1 package insert (content of labeling) submitted electronically **YES** ***Was a proprietary name request submitted? **NO** (If yes, send email to Labeling Reviewer indicating such.) The container labeling is presented for following configurations: **Sr. No.** / **Strength** / **Bottle Packs** / **Bulk Shipment Packs** 1 / 10 mg / 90's count, 500's count / (b) (4) 2 / 20 mg / 90's count, 500's count / (b) (4) 3 / 40 mg / 90's count, 500's count / (b) (4) 4 / 80 mg / 90's count, 500's count / (b) (4)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained **YES** **1.14.3.3** 1 RLD label and 1 RLD container label **YES**	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF YES** **Word Processed e.g., MS Word YES** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR) YES** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) YES** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product YES** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF YES** **Word Processed e.g., MS Word YES** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary **YES** Table 4. Bioanalytical Method Validation **YES** Table 6. Formulation Data **YES** **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **YES** **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies **YES** Table 3. Statistical Summary of the Comparative BA Data **YES** **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **YES** **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies **YES**	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) **YES** 2. Function or Responsibility **YES** 3. Type II DMF number for API **YES # 21477** 4. CFN or FEI numbers **YES**	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) **YES** **3.2.S.4.2 Analytical Procedures YES** **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples **YES** 2. Samples-Statement of Availability and Identification of: a. Drug Substance **YES** b. Same lot number(s) **YES** **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) **YES** 2. Applicant certificate of analysis **YES** **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems – IN DMF**	☒
3.2.S.7	**Stability – IN DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition **YES** 2. Inactive ingredients and amounts are appropriate per IIG **YES – except for the use of L-Arginine which has never been used before in an approved drug product. Pharm/Tox data was submitted by Matrix and will be sent for consult.**	☐
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report **YES**	☒

3.2.P.3

☒

Manufacture

3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)

1. Name and Full Address(es)of the Facility(ies) **YES**
2. CGMP Certification: YES
3. Function or Responsibility **YES**
4. CFN or FEI numbers **YES**

3.2.P.3.2 Batch Formula YES

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process **YES**
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4)

Batch Size

A comparison of the exhibit and intended commercial batch sizes is shown below. The commercial batch size is within 10 times of the exhibit batch size.

Strength	Exhibit Batch size*		Intended Commercial Batch size			
	kg	units	kg	units		
(b) (4)					(b) (4)	
10 mg						
20 mg						
40 mg						
80 mg						

* For exhibit batches, one batch of (b) (4) was prepared and subdivided for (b) (4) of 10 mg (b) (4) 20 mg (b) (4) 40 mg (b) (4) and 80 mg (b) (4) strengths.

3. If sterile product: Aseptic fill / Terminal sterilization NA
4. Reprocessing Statement **YES**

3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

1. Microbiological sterilization validation NA
2. Filter validation (if aseptic fill) NA

3.2.P.4

☒

Controls of Excipients (Inactive Ingredients)

Source of inactive ingredients identified **YES**

3.2.P.4.1 Specifications

1. Testing specifications (including identification and characterization) **YES**
2. Suppliers' COA (specifications and test results) **YES**

3.2.P.4.2 Analytical Procedures

3.2.P.4.3 Validation of Analytical Procedures

3.2.P.4.4 Justification of Specifications

Applicant COA

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s) YES** **3.2.P.5.2 Analytical Procedures YES** **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form **YES** 2. Same lot numbers **YES** **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form **YES** **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) **YES** 2. Components Specification and Test Data **YES** 3. Packaging Configuration and Sizes **YES** 4. Container/Closure Testing **YES** 5. Source of supply and suppliers address **YES**	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted **YES** 2. Expiration Dating Period **YES – (b)(4) MONTHS** **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments **YES** **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data **YES** 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation **YES – SEE BELOW** **3.2.R.1.P.2 Information on Components YES** **3.2.R.2.P Comparability Protocols NO** **3.2.R.3.P Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

· **What is the reconciliation of the exhibit batch?**

Please see tabulated below the reconciliation of the exhibit batch.

SUMMARY OF YIELD RECONCILIATION

Product Name: (b) (4) for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Batch #: 1004885

Batch Size: (b) (4)

#	**Particulars**	(b) (4)
1	Theoretical Qty (Kg)	(b) (4)
2	Actual Qty (Kg)	
3	Samples @ (kg)	
4	Actual Yield (%) = (2) x 100 / (1)	

Division of (b) (4)

The (b) (4) of Batch # 1004885 wa (b) (4) strengths details of which are presented belo

Strength & Batch #	(b) (4) Actual quantity	Theoretical quantity
10 mg (Batch # 1004888)	(b) (4)	
20 mg (Batch # 1004889)		
40 mg (Batch # 1004890)		
80 mg (Batch # 1004891)		

@ Samples drawn for testing / evaluation purposes.

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 10 mg
Batch #: 1004888
Batch size: (b) (4)

MANUFACTURING		
#	Particulars	(b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	
4	Rejections Non-recoverable @@	
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING	(b) (4)
Particulars	
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes
@@ In-process checks or known losses accounted during processing

(b) (4)

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 20 mg
Batch #: 1004889
Batch size: (b) (4)

MANUFACTURING

#	Particulars	(b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	
4	Rejections Non-recoverable @@	
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING

Particulars	(b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes
@@ In-process checks or known losses accounted during processing

(b) (4)

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 40 mg
Batch #: 1004890
Batch size: (b) (4)

MANUFACTURING		
#	Particulars	[redacted] (b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	
4	Rejections Non-recoverable @@	
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING	
Particulars	[redacted] (b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

[redacted] (b) (4)

@ Samples drawn for testing / evaluation purposes
@@ In-process checks or known losses accounted during processing

[redacted] (b) (4)

SUMMARY OF YIELD RECONCILIATION

Product Name: Atorvastatin Calcium Tablets, 80 mg
Batch #: 1004891
Batch size: [redacted] (b) (4)

MANUFACTURING		
#	Particulars	[redacted] (b) (4)
1	Theoretical Qty	
2	Actual Qty	
3	Samples @	

4	Rejections Non-recoverable @@	(b) (4)
5	Actual Yield (%) = (2) x 100 /(1)	
6	Rejections Non-recoverable (%) = (4) x 100/ (1)	

PACKAGING

Particulars	(b) (4)
Total packaged #	
Total units (# packaged x count)	
Total	
Rejections (Non-recoverable)@@	

(b) (4)

@ Samples drawn for testing / evaluation purposes

@@ In-process checks or known losses accounted during processing

(b) (4)

MODULE 5

CLINICAL STUDY REPORTS ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) **YES** b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **NA** **2. Lot Numbers of Products used in BE Study(ies):** Study # 022-08 and 162-08 Lot number **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **YES** 2. Summary Bioequivalence tables: Table 10. Study Information **YES** Table 12. Dropout Information **YES** Table 13. Protocol Deviations **YES** **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information **YES** Table 16. Composition of Meal Used in Fed Bioequivalence Study **YES** **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples **YES** Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses **YES** Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **YES** **5.3.7** **Case Report Forms and Individual Patient Listing YES**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) Fed and Fasting on the 80 mg 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **YES – see below** 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: **YES**	☒

Table 3A Statistical Summary of the Comparative Bioavailability Data

a) Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (Study No. 022-08)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max} (ng/mL)	78.6529	73.2673	107.35	94.47 – 121.99
AUC_{0-t}	325.1762	308.0635	105.55	99.01 – 112.53
AUC_{0-INF}	329.3475	312.2741	105.47	98.97 – 112.39

Table 3B Statistical Summary of the Comparative Bioavailability Data

a) Atorvastatin

Atorvastatin Calcium Tablets 80 mg Dose (80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 162-08)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
C_{max} (ng/mL)	47.3025	49.3465	95.86	86.49 - 106.23
AUC_{0-t} (ng*h/mL)	249.3969	262.2604	95.10	88.88 – 101.74
AUC_{0-INF} (ng*hr/mL)	254.7854	268.3049	94.96	88.84 – 101.50

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008

Table 6 Formulation Data

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet
(b) (4)	10 mg	20 mg	40 mg	80 mg	
Atorvastatin Calcium					(b) (4)
Microcrystalline cellulose (b) (4)					
Colloidal silicon dioxide (b) (4)					
Sodium carbonate anhydrous					
L-Arginine					
Anhydrous lactose (b) (4)					
Croscarmellose sodium (b) (4)					
Hydroxypropyl cellulose (b) (4)					
Magnesium stearate (b) (4)					
(b) (4)					
(b) (4)					
(b) (4)					

Inactive ingredient confirmation per unit for 91-226:

CELLULOSE, MICROCRYSTALLINE (b) (4)

SILICON DIOXIDE, COLLOIDAL (b) (4)

(b) (4) (b) (4)

L-ARGININE – NOT FOUND – PHARM/TOX DATA SUBMITTED BY MATRIX – WILL BE SENT FOR CONSULT

LACTOSE, ANHYDROUS (b) (4)

CROSCARMELLOSE SODIUM (b) (4)

HYDROXYPROPYL CELLULOSE (b) (4)

MAGNESIUM STEARATE (b) (4)

(b) (4) (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/

Martin Shimer

4/7/2009 11:26:18 AM

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722. Fax : 27700343
E-mail:matrix@matrixlabsindia.com

PIII to '667 and ack that I-471 has expired. S. Middleton 4/1/09

March 25, 2009

To:
Office of Generic Drugs, CDER, FDA
Gary J Buehler, Director
Document Control Room
Metro Park North II
7500, Standish Place, Room 150
Rockville MD 20855-2773

Patent Amendment
(Prior to ANDA acceptance for newly listed patent)

NEW CORRESP
N/XP

Subject: ANDA # 91-226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Buehler:

Reference is made to a telephonic call from the Agency (Ms Middleton) dated March 18, 2009 requesting a patent amendment addressing a new patent listing (U.S.patent # RE 40667) in FDA's Electronic Orange Book for **LIPITOR®**, which forms the basis of submission for the subject ANDA.

A patent amendment that addresses said newly listed patent is enclosed. Matrix is providing a Paragraph III certification for the said patent. The amendment also updates that the I-471 exclusivity has expired on September 21, 2008.

This patent amendment includes information in addition to what has been mentioned in earlier patent and exclusivity certifications and is merely an update to reflect the updated information in FDA's Electronic Orange Book.

Should you require any additional information, please contact Ronald T. Groman at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

March 25, 2009.

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

RECEIVED
MAR 27 2009
OGD

Cc: Ms. Saundra Middleton, OGD, CDER, FDA.

MATRIX

MAR 2 5 2009

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ATORVASTATIN CALCIUM TABLETS,
10 mg, 20 mg, 40 mg and 80 mg

ANDA # 91-226

U.S. PATENT NO. RE40667
PARAGRAPH III CERTIFICATION

Dear Mr. Buehler:

Matrix Laboratories Limited. ("Matrix") previously filed its patent certifications and exclusivity information for the above-referenced product. At the time of these filings, Matrix's certifications were correct. This current amendment is submitted to address a new patent filing (U.S. Patent No. RE40667) by the holder of the referenced drug, which was filed subsequent to Matrix's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Matrix certifies that in its opinion and to the best of its knowledge according to the patent information published by FDA in the document entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," 29th Edition as found in the "Electronic Orange Book" published at the FDA web site, U.S. Patent No. RE40667 claims the referenced product, (Lipitor®). U.S. Patent No. RE40667 expires on December 28, 2010, with an associated pediatric exclusivity that expires on June 28, 2011. Use Code, U-162 ("Method of Use to Inhibit Cholesterol Synthesis in a Human Suffering from Hypercholesterolemia") is associated with this patent.

Pursuant to 21 C.F.R. § 314.94(a)(3)(ii), Matrix certifies that according to the exclusivity information published by FDA in the "Approved Drug Products with Therapeutic Equivalence Evaluations," 29th Edition as set forth in the "Electronic Orange Book" published at FDA's web site, the following unexpired period of market exclusivity is associated with the referenced product:

- I-523 Exclusivity ("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"), which expires on March 2, 2010.

The referenced product was previously covered by the following exclusivity:

- I-471 Exclusivity, ("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"), which expired on September 21, 2008.

The patent information identified above is in addition to the patent and exclusivity information set forth in Matrix's previous submissions. This amendment is merely an update to reflect the newly filed patent information. Accordingly, Matrix seeks approval to market its Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 4,681,893; 5,273,995; and RE40667 and their associated pediatric exclusivities; following the expiration of the I-523 exclusivity; and prior to the expiration of U.S. Patent Nos. 5,686,104; 5,969,156 and 6,126,971 and their associated pediatric exclusivities.

Sincerely,
On behalf of Matrix Laboratories Limited

Indu Bhushan
FDF-Technical Operations

Sandeep K. Rathod
Intellectual Property

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

Sent for Consult 4/1/09

March 24, 2009

N - 000 - MC

To:
Office of Generic Drugs, CDER, FDA
Gary J Buehler, Director
Document Control Room
Metro Park North II
7500, Standish Place, Room 150
Rockville MD 20855-2773

New Correspondence

Subject: ANDA # 91-226, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Mr. Buehler:

Reference is made to a telephonic conversation dated March 18, 2009 with our US-agent (Mylan) requesting an electronic copy of the pharmacology and toxicology report of L-Arginine submitted in the subject ANDA.

As requested, the report has been sent to Ms. Saundra Middleton via email. Additionally, Matrix through this amendment is submitting a hard copy of the same report to the document control room.

Should you require any additional information, please contact Ronald T. Groman at (304) 554-5899, or by facsimile at (304) 285-6407.

Sincerely,
For Matrix Laboratories Limited, India

March 24, 2009.

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Ronald T. Groman
March 24, 2009

Ronald T Groman
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited India

Cc: Ms. Saundra Middleton, OGD, CDER, FDA.

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OGD

MATRIX

Matrix Laboratories Limited
1-1-151/1, IV Floor, Sairam Towers, Alexander Road
Secunderabad - 500 003, India
Tel : 91-40-27700363, 66327722, Fax : 27700343
E-mail:matrix@matrixlabsindia.com

December 30, 2008

To:

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Original ANDA Submission

Subject: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Dear Mr. Buehler:

Matrix Laboratories Limited, India (Matrix) hereby submits an Abbreviated New Drug Application (ANDA) for Atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg pursuant to section 505 (j) of the Food, Drug and Cosmetic Act (Act).

This ANDA refers to the listed drug; **LIPITOR®** (Atorvastatin calcium) 10 mg, 20 mg, 40 mg and 80 mg of Pfizer Pharmaceuticals Inc. approved under **NDA # 20-702.**

A patent and exclusivity certification is enclosed in module # 1 of this ANDA. Matrix is providing a **Paragraph-IV** certification for this ANDA.

Drug substance (Atorvastatin calcium) used for exhibit batches in this ANDA is manufactured by Matrix at its USFDA approved Jeedimetla (Unit-3) facility in Hyderabad, Andhra Pradesh, India. A copy of the DMF (# 21477) letter of authorization is included in this ANDA.

The proposed commercial manufacturing, packaging and control testing site for the drug product (Matrix Laboratories Limited, Sinnar, Nashik, Maharashtra State, India) is the same as used for exhibit batches that are part of this ANDA.

Matrix is providing 1, 2 and 3-months accelerated (b) (4) and 6 months long-term (25 ± 2°C/60 ± 5 %RH) stability data in the proposed market packs. Matrix is also providing (b) (4) months holding time data (b) (4) in the bulk-shipment packs. The stability results comply with the proposed shelf-life specifications.

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E-mail:matrix@matrixlabsindia.com

The drug substance and the drug product are not compendia articles. Matrix has followed DMF holder's methods for testing of drug substance (Atorvastatin calcium). These methods have been fully validated by Matrix and are supported by appropriate validation. A copy of the validation reports (which are also part of the DMF) has been included in ANDA for ease of Agency's review.

Matrix has developed in-house specifications and test methods for drug product. All test methods are supported by appropriate validation. A copy of the validation reports has been included in this ANDA.

Method validation package (3 copies) consisting of drug substance and drug product methods, specifications, testing data, method validation reports and sample availability statements is being submitted with this ANDA. Matrix is committed to resolve any analytical validation related issues that may arise during Agency review or after approval of this ANDA.

Matrix has conducted fasting and fed bioequivalence studies for 80 mg strength in support of this ANDA. The bioequivalence study reports included in this ANDA demonstrate that Matrix's Atorvastatin calcium tablets, 80 mg are bioequivalent to Pfizer's LIPITOR® (Atorvastatin calcium) tablets, 80 mg under fasting and fed conditions. A CD containing SAS data and DBE summary tables is attached to the inner cover of the review (Bio) copy of this ANDA.

A request for BE waiver for the lower strengths, supported by formulation proportionality and similar dissolution data is enclosed in module 1.

The clinical phase of bioequivalence studies was conducted at (b) (4) Ltd., India and bio-analytical phase was conducted at (b) (4) (b) (4) The facility of (b) (4) has successfully undergone USFDA inspection during (b) (4) Matrix's Clinical Research Center has also successfully undergone USFDA inspection during 4 to 5 June 2008. Financial disclosures/certifications for the subject study have been provided in module #1.

The conditions of use, active ingredient, strengths, dosage form and route of administration of Matrix's Atorvastatin calcium tablets are the same as that of the listed drug, LIPITOR® (Atorvastatin calcium) tablets. Electronic labeling (PDF and word format) consisting of *side-by-side* comparison of labeling and proposed *draft* labeling are provided on a CD attached to the inner cover of the archival copy of this ANDA. A Structured Product Labeling (SPL) version of the generic product labeling is also submitted in this CD. This CD also contains Quality Overall Summary (QOS) in the QbR format and the ANDA table of contents.

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Secunderabad - 500 003, India
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E-mail:matrix@matrixlabsindia.com

Atorvastatin calcium tablets that are the subject of this ANDA are planned for distribution in the United States through Mylan Pharmaceuticals Inc. USA (Mylan). Please note that Mylan holds a majority stake in Matrix and acts as distributor for many of Matrix manufactured products.

Details of US-regulatory agent for Matrix Laboratories Limited, India are provided below. A letter of authorization is included in module # 1 of this ANDA.

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road, P. O. Box 4310
Morgantown, WV 26504-4310, USA

Primary Contact:
Ronald T. Groman, Director
Phone : (304) 554-5899
(800) 848-0461, Ext. 5899
Fax : (304).285.6407

Secondary Contact:
S. Wayne Talton, Vice President
Phone : (304) 554-6551
(800) 848-0461, Ext. 6551
Fax : (304).285.6407

A field copy consisting of CMC sections included in this ANDA is being submitted to the Office of Generic Drugs. In accordance with the recently enacted Food and Drug Administration Amendments Act of 2007, a certification in the Form FDA 3674 is included in Module 1.1.2 of this ANDA.

This submission is organized as detailed in the table below.

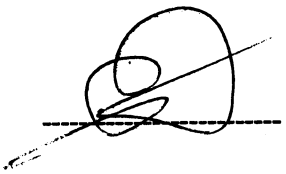
Details	**Module #**				
	1	**2**	**3**	**5**	**Total**
	# of volumes				
Archival Copy (With CD containing QOS-QbR, e-labeling and ANDA Table of contents)	1	1	9	37	**48**
Review Copy (Copy of CMC sections)	1	1	9	NA	**11**
Review Copy (Bioavailability and Bioequivalence) (With CD containing raw data in SAS transport file, DBE summary tables and ANDA Table of contents)	1	1	NA	37	**39**
Field Copy (A true third copy of CMC sections)	NA	NA	9	NA	**9**
Method validation package (3 volume x 3 copies)	NA	NA	NA	NA	**9**

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E-mail:matrix@matrixlabsindia.com

Please forward any written communications regarding this submission to Ronald T Groman. If you need any additional information, please feel free to contact Ronald T Groman at (304).554.5899.

Sincerely,
For Matrix Laboratories Limited, India



Dec 30, 2008.

Nitin Bhattad
Regulatory Affairs
Matrix Laboratories Limited, India

Date

Ronald T. Groman

December 30, 2008

Ronald T Groman
Mylan Pharmaceuticals Inc.
US-Agent, Matrix Laboratories Limited, India

Date