CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 091624

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

Sponsor: Kudco Ireland Limited

Approval Date: April 5, 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091624

Kremers Urban Pharmaceuticals Inc.
U.S. Agent for: Kudco Ireland Limited
Attention: Kurt Zimmer
RA Manager
1101 C Avenue West
Seymour, IN 47274

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 15, 2009, 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 complete response letter issued by this office on November 9, 2012, and to your amendment dated November 21, 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 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 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 Kudco Ireland Limited (Kudco) 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 Kudco 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. Kremers Urban, LLC, Kudco Ireland, Ltd., and Kremers Urban Pharmaceuticals, Inc., Civil Action No. 09-924-LPS]. You notified the agency that the case has been dismissed by the court.

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.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those

responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

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}

Kathleen Uhl, M.D.
Acting Director
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 WEST

04/05/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

COMPLETE RESPONSE LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 091624

COMPLETE RESPONSE

Kremers Urban Pharmaceuticals Inc.
U.S. Agent for: Kudco Ireland Limited
Attention: Elaine Siefert
Director, Regulatory Affairs
1101 C Avenue West
Seymour, IN 47274

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated July 15, 2009, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

We acknowledge receipt of your amendments dated February 26, and March 4, 2010; January 12, June 27, August 18, and October 31, 2011; and April 24, May 9, June 4, and September 7, 2012.

We have completed our review of this application and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

A. The deficiencies presented below represent MINOR deficiencies:

(b) (4) ne

2. Please provide the updated information of the reference standards used in the quantitation of the impurities in your drug product.

3. You have stated in your recent amendment dated 9/7/2012, a specification of (b) (4) will be applied to the assay for stability samples. This range is not

acceptable. The Agency recommends you to [redacted] (b) (4) or assay in stability.

4. Please provide most updated drug product release and stability specifications.

5. Your amendment dated Sept 7, 2012 reports no significant changes in assay values for the samples analyzed using the old sample prep and the new. Therefore, please provide a root cause investigation report for [redacted] (b) (4)

BIOEQUIVALENCE

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

We acknowledge that you will conduct dissolution testing using the current FDA-recommended method for your test product, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The dissolution method is as follows:

Medium:	0.3% Tween 80 in 0.05 M Phosphate buffer, pH 6.8
Volume:	900 mL
Temperature:	37ºC ± 0.5□C
USP Apparatus:	Type II (Paddle)
Rotation (rpm):	75 rpm

The test product should meet the following specification:

NLT [redacted] (b) (4)% (Q) of the labeled amount of Atorvastatin is dissolved in 30 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.

LABELING

The Division of Labeling has no further questions at this time. Please check the DRUGS@FDA website before your next submission and submit any revised labeling, as necessary.

FACILITY INSPECTIONS

The Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a Minor AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION- *MINOR AMENDMENT*** should appear prominently in your cover letter. **COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

If you have any questions, call Robert Gaines, Regulatory Project Manager, at (240) 276-8495.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
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 on behalf of ROBERT T GAINES
11/09/2012

ROBERT L WEST
11/09/2012
Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

LABELING

Atorvastatin Calcium Tablets

CIA75883C

℞ only

Rev. 3E 11/2012

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

Dosage and Administration (2.6)	10/2012
Warnings and Precautions (5.1)	10/2012
Drug Interactions (7)	02/2012

INDICATIONS AND USAGE

Atorvastatin Calcium Tablets is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:
- Reduce the risk of MI, stroke, evascularization p ocedures, and angina in patients w thout CHD, but w th multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients w th type 2 diabetes w thout CHD, but w th multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, evascularization procedures, hospitalization for CHF, and angina in patients w th 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 w th hypertriglyceridemia and prima y dysbetalipop oteinemia (1 2).
- Reduce total-C and LDL-C in patients w th homozygous familia hype cholesterolemia (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 familia hype choleste olemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
Atorvastatin Calcium Tablets has not been studied in *Fredrickson* Types I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring la ge LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum ecommended dose: 20 mg once daily (2 2).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who a e 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 habdomyolysis): Risks inc ease when higher doses are used concomitantly with cyclosporine and st ong CYP3A4 inhibitors (e g., clar th omycin, itraconazole, HIV protease inhibitors). P edisposing factors include advanced age (> 65), uncont olled hypothy oidism, and renal impairment Rare cases of rhabdomyolysis w th acute enal failu e seconda y to myoglobinuria have been eported. Advise patients to p omptly eport to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. Atorvastatin Calcium Tablets therapy should be discontinued if myopathy is diagnosed or suspected (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 hemor hagic st oke was seen in patients without CHD but w th st oke or TIA within the p evious 6 months in the Atorvastatin Calcium Tablets 80 mg group vs. placebo (5.5).

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated w th Atorvastatin Calcium Tablets in placebo-controlled trials rega dless of causality were: nasopha yngitis, arthralgia, diar hea, pain in ext emity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at (1-866-822-0068) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drug Interactions Associated w th Inc eased Risk of Myopathy/Rhabdomyolysis (2 6, 5.1, 7, 12 3)

Interacting Agents	P escribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C p otease inhibitor (telaprevir)	Avoid atorvastatin
HIV p otease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV p otease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamp enavir, fosamp enavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV p otease inhibitor (nelfinavir) Hepatitis C protease inhibitor (bocep evir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Use w th fibrate products or lipid-modifying doses (≥1 g/day) of niacin inc eases the risk of adverse skeletal muscle effects. Caution should be used when prescribing w th Atorvastatin Calcium Tablets (7).
- Digoxin: Patients should be monit ored app opriately (7 8).
- Oral Contraceptives: Values for norethind one and ethinyl estradiol may be increased (7 9).
- Rifampin should be simultaneously co-administe ed with Atorvastatin Calcium Tablets (7.7).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients with ch onic alcoholic liver disease (12 3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy w th lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for athe osclerotic vascular disease due to hype choleste olemia. Drug therapy is ecommended as an adjunct to diet when the response to a diet restricted in saturated fat and choleste ol and other nonpharmacologic measu es alone has been inadequate. In patients w th CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously w th diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but w th multiple risk factors for co ona y heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Atorvastatin Calcium Tablets is indicated to:
- Reduce the risk of myoca dial infa ction
- Reduce the risk of st oke
- Reduce the risk for revascularization p ocedures and angina

In patients w th type 2 diabetes, and without clinically evident coronary heart disease, but w th multiple risk factors for co ona y heart disease such as etinopathy, albuminuria, smoking, or hypertension, Atorvastatin Calcium Tablets is indicated to:
- Reduce the risk of myoca dial infa ction
- Reduce the risk of st oke

In patients with clinically evident coronary heart disease, Atorvastatin Calcium Tablets 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 p ocedures
- Reduce the risk o hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin Calcium Tablets is indicated:
- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to inc ease HDL-C in patients with primary hype cholesterolemia (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 prima y dysbetalipoproteinemia *(Fredrickson* Type III) who do not espond adequately to diet;
- To reduce total-C and LDL-C in patients w th homozygous familial hype choleste olemia as an adjunct to other lipid-lowering treatments (e g., LDL aphe esis) or if such t eatments 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 hypercholeste olemia if after an adequate trial of diet therapy the following findings are p esent:
  1. LDL-C emains ≥ 190 mg/dL or
  2. LDL-C emains ≥ 160 mg/dL and:
     - the e is a positive family history of p emature ca diovascular disease or
     - two or mo e other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin Calcium Tablets has not been studied in conditions where the major lipop otein abnormality is elevation of chylomic ons *(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 ecommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who equi e a la ge eduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, w th 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 acco dingly.

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

The ecommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses g eater than 20 mg have not been studied in this patient population). Doses should be individualized acco ding to the recommended goal of therapy [see cur ent *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 w th homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e g., LDL apheresis) in these patients or if such treatments a e unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used w th bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used w th 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 w th renal dysfunction is not necessa y [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 p otease 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 p escribing atorvastatin calcium tablets and the lowest dose necessa y employed. In patients taking clar thromycin, 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 taking the HIV inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and app opriate clinical assessment is recommended to ensure that the lowest dose necessa y of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who a e pregnant or may become pregnant. Atorvastatin calcium tablets may cause fetal harm when administered to a p egnant woman. Serum cholesterol and triglycerides inc ease 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 prima y hype choleste olemia. The e a e no adequate and well-cont olled studies of atorvastatin calcium tablets use during pregnancy; however in rare reports, congenital anomalies we e observed following intrauterine exposure to statins. In rat and rabbit animal ep oduction studies, atorvastatin evealed no evidence of teratogenicity. ATORVASTATIN CALCIUM TABLETS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin calcium tablets should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing Mothers

It is not known whether atorvastatin is exc eted 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 eactions in nursing infants, women who equi e atorvastatin calcium tablets treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium tablets and with other drugs in this class. A histo y of enal impairment may be a risk factor for the development of habdomyolysis. 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 w th inc eases in c eatine phosphokinase (CPK) values >10 times ULN. The concomitant use o higher doses of atorvastatin w th certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e g., clar th omycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/ habdomyolysis.

The e have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: p oximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin t eatment; muscle biopsy showing nec otizing myopathy without significant inflammation; improvement w th immunosupp essive agents.

Myopathy should be conside ed in any patient w th diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report p omptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing atorvastatin calcium tablets. Atorvastatin calcium tablets therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment w th drugs in this class is inc eased with concurrent administration of cyclosporine, fibric acid derivatives, eryth omycin, clar thromycin, the hepatitis C p otease inhibitor telap evir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamp enavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin calcium tablets and fibric acid derivatives, e ythromycin, clar thromycin, 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 ca efully 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 c eatine phosphokinase (CPK) determinations may be conside ed in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing ecommendations for interacting agents a e 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 p otease inhibitor (telap evir)	Avoid atorvastatin
HIV p otease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV p otease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamp enavir, fosamp enavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV p otease inhibitor (nelfinavir) Hepatitis C protease inhibitor (bocep evir)	Do not exceed 40 mg atorvastatin daily
* Use with caution and with the lowest dose necessary (12.3)	

Cases of myopathy, including habdomyolysis, have been eported w th atorvastatin co-administe ed w th colchicine, and caution should be exe cised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.11)*].

Atorvastatin calcium tablets 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 w th biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium tablets in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Inc eases in liver function tests (LFT) in other patients we e not associated w th jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels eturned to or near p etreatment levels w thout sequelae. Eighteen of 30 patients with persistent LFT elevations continued t eatment with a educed dose of atorvastatin calcium tablets.

It is recommended that liver enzyme tests be obtained prior to initiating therapy w th atorvastatin calcium tablets and epeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failu e in patients taking statins, including atorvastatin. If serious liver inju y with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during t eatment w th atorvastatin calcium tablets, p omptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium tablets.

Atorvastatin calcium tablets should be used w th caution in patients who consume substantial quantities of alcohol and/or have a histo y of liver disease. Active liver disease or unexplained persistent transaminase elevations a e contraindications to the use of atorvastatin calcium tablets [see *Contraindications (4.1)*].

5.3 Endocrine Function

Inc eases in HbA_{1c} and fasting serum glucose levels have been reported w th HMG-CoA eductase inhibitors, including atorvastatin calcium tablets.

Statins interfere w th cholesterol synthesis and theo etically might blunt adrenal and/or gonadal steroid p oduction. Clinical studies have shown that atorvastatin calcium tablets does not reduce basal plasma cortisol concentration or impair ad enal 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 administe ed concomitantly w th drugs that may dec ease the levels or activity of endogenous ste oid 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 hemor hage and optic nerve vacuolation we e 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 esulted in a systemic exposure app oximately 16 times the human plasma a ea-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one t eated 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 hemor hages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs t eated w th other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of etinogeniculate 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 P evention by Agg essive Reduction in Choleste ol Levels (SPARCL) study whe e atorvastatin calcium tablets 80 mg vs. placebo was administe ed in 4,731 subjects w thout CHD who had a st oke or TIA w thin the preceding 6 months, a higher incidence o hemorrhagic st oke was seen in the atorvastatin calcium tablets 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 hemor hagic stroke was similar across treatment g oups (17 vs. 18 for the atorvastatin and placebo g oups, respectively). The incidence of nonfatal hemorrhagic st oke was significantly higher in the atorvastatin g oup (38, 1 6%) as compa ed to the placebo g oup (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, we e associated w th a higher incidence o hemorrhagic st oke in the atorvastatin g oup [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse eactions a e 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 eaction rates observed in the clinical studies of a drug cannot be di ectly compa ed to rates in the clinical trials of another drug and may not eflect the rates observed in clinical practice.

In the atorvastatin calcium tablets placebo-cont olled clinical trial database of 16,066 patients (8755 atorvastatin calcium tablets vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) w th a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium tablets and 9 5% of the patients on placebo discontinued due to adverse reactions egardless of causality. The five most common adverse eactions in patients treated w th atorvastatin calcium tablets that led to treatment discontinuation and occurred at a rate g eater than placebo we e: myalgia (0.7%), diar hea (0 5%), nausea (0 4%), alanine aminotransferase increase (0 4%), and hepatic enzyme increase (0 4%).

The most commonly eported adverse reactions (incidence ≥ 2% and g eater than placebo) regardless of causality, in patients t eated w th atorvastatin calcium tablets in placebo controlled trials (n=8755) were: nasopharyngitis (8 3%), arthralgia (6 9%), diar hea (6 8%), pain in extremity (6 0%), and urina y tract infection (5.7%).

Table 2 summarizes the f equency of clinical adverse reactions, ega dless of causality, eported in ≥ 2% and at a rate g eater than placebo in patients treated w th atorvastatin calcium tablets (n=8755), f om seventeen placebo-controlled trials.

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

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8 3	12 9	5.3	7 0	4.2	8.2
Arthralgia	6 9	8 9	11.7	10.6	4.3	6.5
Diarrhea	6 8	7 3	6.4	14.1	5.2	6.3
Pain in extremity	6 0	8 5	3.7	9 3	3.1	5 9
Urinary tract infection	5.7	6 9	6.4	8 0	4.1	5.6
Dyspepsia	4.7	5 9	3.2	6 0	3.3	4.3
Nausea	4 0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3 8	5 2	3.2	5.1	2.3	3.6
Muscle Spasms	3 6	4 6	4.8	5.1	2.4	3.0
Myalgia	3 5	3 6	5 9	8 4	2.7	3.1
Insomnia	3 0	2 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 eactions eported in placebo-controlled studies include:

Body as a whole: malaise, py exia; *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 inc ease, 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 40–80 years, 19% women; 94 6% Caucasians, 2 6% Africans, 1 5% South Asians, 1 3% mixed/other) t eated with atorvastatin calcium tablets 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability p ofile of the g oup treated w th atorvastatin calcium tablets was comparable to that of the g oup treated w th 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 39–77 years, 32% women; 94 3% Caucasians, 2 4% South Asians, 2 3% Af o-Caribbean, 1 0% other) w th type 2 diabetes treated with atorvastatin calcium tablets 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse eactions or serious adverse eactions 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 29–78 years, 19% women; 94.1% Caucasians, 2 9% Blacks, 1.0% Asians, 2 0% other) with clinically evident CHD treated w th atorvastatin calcium tablets 10 mg daily (n=5006) or atorvastatin calcium tablets 80 mg daily (n=4995), there were mo e serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1 8%; 497, 9 9%, espectively) as compared to the low-dose g oup (69, 1 4%; 404, 8.1%, respectively) during a median follow-up of 4 9 years. Persistent transaminase elevations (≥3 x ULN twice w thin 4–10 days) occur ed in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0 2%) individuals w th atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but we e higher in the high-dose atorvastatin t eatment 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 26–80 years, 19% women; 99 3% Caucasians, 0.4% Asians, 0.3% Blacks, 0 04% other) t eated with atorvastatin calcium tablets 80 mg/day (n=4439) or simvastatin 20–40 mg daily (n=4449), the e was no difference in the overall f equency of adverse eactions or serious adverse eactions between the treatment groups during a median follow-up of 4 8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21–92 years, 40% women; 93 3% Caucasians, 3 0% Blacks, 0.6% Asians, 3.1% other) w thout clinically evident CHD but w th a stroke or transient ischemic attack (TIA) within the previous 6 months t eated w th atorvastatin calcium tablets 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4 9 years, the e was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice w thin 4–10 days) in the atorvastatin group (0 9%) compa ed to placebo (0.1%). Elevations of CK (>10 x ULN) were ra e, but were higher in the atorvastatin group (0.1%) compa ed to placebo (0 0%). Diabetes was eported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium tablets 80 mg educed the incidence of ischemic st oke (218/2365, 9.2% vs. 274/2366, 11 6%) and increased the incidence of hemor hagic st oke (55/2365, 2 3% vs. 33/2366, 1 4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin calcium tablets vs. 18 placebo). The incidence of non-fata hemorrhagic st okes was significantly greater in the atorvastatin g oup (38 non-fata hemorrhagic st okes) as compa ed to the placebo g oup (16 non-fatal hemor hagic st okes). Subjects who ente ed the study w th a hemor hagic st oke appeared to be at inc eased risk for hemor hagic st oke [7 (16%) atorvastatin calcium tablets vs. 2 (4%) placebo].

The e we e no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium tablets 80 mg/day g oup vs. 211 (8 9%) in the placebo g oup. The proportions of subjects who experienced ca diovascular death were numerically smaller in the atorvastatin calcium tablets 80 mg group (3 3%) than in the placebo g oup (4.1%). The proportions of subjects who experienced non-ca diovascular death were numerically larger in the atorvastatin calcium tablets 80 mg g oup (5 0%) than in the placebo group (4 0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapp oval use of atorvastatin calcium tablets Because these eactions are eported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their f equency or establish a causal elationship to drug exposu e.

Adverse eactions associated with atorvastatin calcium tablets therapy reported since market introduction, that are not listed above, rega dless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including e ythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), habdomyolysis, fatigue, tendon rupture, fatal and non-fata hepatic failu e, dizziness, dep ession, peripheral neu opathy, and panc eatitis.

There have been ra e reports of immune-mediated necrotizing myopathy associated w th statin use [see *Warnings and Precautions (5.1)*].

The e have been ra e postmarketing reports of cognitive impairment (e g., memo y loss, fo getfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports a e generally nonserious, and eversible upon statin discontinuation, w th variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10-17 years)

In a 26-week cont olled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1 6% Asians, 4 8% other), the safety and tolerability profile of atorvastatin calcium tablets 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during t eatment w th statins is increased w th concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or st ong CYP 3A4 inhibitors (e g., clarithromycin, HIV p otease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4

Atorvastatin calcium tablets is metabolized by cytoch ome P450 3A4. Concomitant administration of atorvastatin calcium tablets with strong inhibitors of CYP 3A4 can lead to inc eases 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 inc eased with concomitant administration of atorvastatin calcium tablets 80 mg w th clarithromycin (500 mg twice daily) compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin calcium tablets 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 inc eased w th concomitant administration of atorvastatin calcium tablets w th several combinations of HIV protease inhibitors, as well as with hepatitis C p otease inhibitor telap evir, compa ed to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking HIV p otease inhibitor tipranavir plus ritonavir, or the hepatitis C p otease inhibitor telaprevir, concomitant use of atorvastatin calcium tablets should be avoided. In patients taking the HIV p otease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary should be used. In patients taking the HIV p otease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamp enavir, or fosamprenavir plus ritonavir, the dose of atorvastatin calcium tablets should not exceed 20 mg and should be used w th caution [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*]. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor bocep evir, the dose of atorvastatin calcium tablets should not exceed 40 mg and close clinical monitoring is ecommended.

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

7.2 Grapefruit Juice

Contains one or more components that inhibit CYP 3A4 and can inc ease plasma concentrations of atorvastatin, especially w th excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolites a e substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e g., cyclosporine) can inc ease the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased w th concomitant administration of atorvastatin calcium tablets 10 mg and cyclosporine 5 2 mg/kg/day compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. The co-administration of atorvastatin calcium tablets with cyclosporine should be avoided [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Gemfibrozil

Due to an inc eased risk of myopathy/ habdomyolysis when HMG-CoA reductase inhibitors a e co-administe ed with gemfibrozil, concomitant administration of atorvastatin calcium tablets with gemfib ozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 Other Fibrates

Because it is known that the risk of myopathy during treatment w th HMG-CoA eductase inhibitors is increased w th concurrent administration of other fibrates, atorvastatin calcium tablets should be administe ed w th caution when used concomitantly w th other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when atorvastatin calcium tablets is used in combination w th niacin; a eduction in atorvastatin calcium tablets dosage should be conside ed in this setting [see *Warnings and Precautions (5.1)*].

7.7 Rifampin or other Inducers of Cytochrome P450 3A4

Concomitant administration of atorvastatin calcium tablets w th inducers of cytochrome P450 3A4 (e g., efavi enz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium tablets w th rifampin is ecommended, as delayed administration of atorvastatin calcium tablets after administration of rifampin has been associated w th a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

When multiple doses of atorvastatin calcium tablets and digoxin were coadministered, steady state plasma digoxin concentrations inc eased by approximately 20%. Patients taking digoxin should be monito ed appropriately.

7.9 Oral Contraceptives

Co-administration of atorvastatin calcium tablets and an oral contraceptive increased AUC values for norethind one and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These inc eases should be conside ed when selecting an oral contraceptive for a woman taking atorvastatin calcium tablets.

7.10 Warfarin

Atorvastatin calcium tablets had no clinically significant effect on p oth ombin time when administered to patients receiving chronic warfarin t eatment.

7.11 Colchicine

Cases of myopathy, including habdomyolysis, have been eported w th atorvastatin co-administe ed w th colchicine, and caution should be exe cised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Catego y X

Atorvastatin calcium tablets is contraindicated in women who are or may become p egnant. Serum cholesterol and triglycerides increase during normal p egnancy. Lipid lowering drugs offer no benefit during p egnancy because choleste ol and cholesterol derivatives are needed for normal fetal development. Athe osclerosis is a chronic p ocess, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholeste olemia therapy.

The e a e no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare eports of congenital anomalies following intrauterine exposu e to statins. In a review of about 100 p ospectively followed p egnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a th ee-to-four-fold inc eased risk of congenital anomalies over backg ound incidence. In 89% of these cases, drug treatment started befo e pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and eaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses esulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposu e based on surface a ea (mg/m²) [see *Contraindications, Pregnancy (4.3)*].

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

Statins may cause fetal harm when administe ed to a pregnant woman. Atorvastatin calcium tablets should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential haza ds. If the woman becomes pregnant while taking atorvastatin calcium tablets, it should be discontinued immediately and the patient advised again as to the potentia hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in patients 10-17 years of age with hete ozygous familia hype choleste olemia have been evaluated in a cont olled clinical trial of 6 months' duration in adolescent boys and postmena chal girls. Patients t eated w th atorvastatin calcium tablets had an adverse experience profile generally similar to that of patients treated w th placebo. The most common adverse experiences observed in both groups, egardless of causality assessment, we e infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited cont olled study, the e was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10-17 years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age) (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin calcium tablets therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium tablets has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

10 OVERDOSAGE

The e is no specific treatment for atorvastatin calcium tablets overdosage. In the event of an overdose, the patient should be t eated symptomatically, and supportive measures instituted as equi ed. Due to extensive drug binding to plasma p oteins, hemodialysis is not expected to significantly enhance atorvastatin calcium tablets clearance.

11 DESCRIPTION

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

PATIENT INFORMATION

Atorvastatin Calcium Tablets

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

If you have any questions about Atorvastatin Calcium Tablets, ask your doctor or pharmacist.

What is Atorvastatin Calcium Tablets?

Atorvastatin Calcium Tablets 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 is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

Atorvastatin Calcium Tablets can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:
- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin Calcium Tablets can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:
- eye problems, kidney problems, smoking, or high blood pressure.

Atorvastatin Calcium Tablets start to work in about 2 weeks.

What is Cholesterol?

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

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take Atorvastatin Calcium Tablets if you:
- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin Calcium Tablets may harm your unborn baby. If you get pregnant, stop taking Atorvastatin Calcium Tablets and call your doctor right away.
- are breast feeding. Atorvastatin Calcium Tablets can pass into your breast milk and may harm your baby.
- 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 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with Atorvastatin Calcium Tablets. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin Calcium Tablets and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:
- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

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

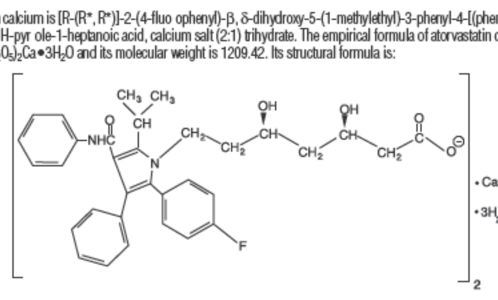
How Should I Take Atorvastatin Calcium Tablets?

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

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

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

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



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7 4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, c oscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium tablets is a selective, competitive inhibitor of HMG-CoA eductase, the rate-limiting enzyme that converts 3-hyd oxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of ste ols, including choleste ol. Cholesterol and triglycerides circulate in the bloodst eam as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (ve y-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and eleased into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human athe osclerosis and a e risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated w th a decreased cardiovascular risk.

In animal models, atorvastatin calcium tablets lower plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA eductase and choleste ol synthesis in the liver and by inc easing the number of hepatic LDL eceptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium tablets also educes LDL production and the number of LDL particles. Atorvastatin calcium tablets educes LDL-C in some patients w th homozygous familial hype cholesterolemia (FH), a population that ra ely responds to other lipid-lowering medication(s).

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

Atorvastatin calcium tablets educes total-C, LDL-C, and apo B in patients with homozygous and hete ozygous FH, nonfamilial forms of hype cholesterolemia, and mixed dyslipidemia. Atorvastatin calcium tablets also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium tablets reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and inc eases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium tablets reduces intermediate density lipoprotein choleste ol (IDL-C) in patients w th dysbetalipop oteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also p omote 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 co ona y heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermo e, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption: Atorvastatin calcium tablets is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium tablets dose. The absolute bioavailability of atorvastatin (pa ent drug) is approximately 14% and the systemic availability of HMG-CoA eductase inhibito y activity is approximately 30%. The low systemic availability is attributed to p esystemic clearance in gast ointestinal mucosa and/or hepatic first-pass metabolism. A though food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C eduction is similar whether atorvastatin calcium tablets is given w th or without food. Plasma atorvastatin calcium tablets concentrations a e lower (app oximately 30% for C and AUC) following evening drug administration compared w th morning. However, LDL-C eduction is the same rega dless of the time of day of drug administration [see *Dosage and Administration (2)*].

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

Metabolism: Atorvastatin calcium tablets is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation p oducts. *In vitro* inhibition of HMG-CoA eductase by ortho- and parahyd oxylated metabolites is equivalent to that of atorvastatin calcium tablets. App oximately 70% of circulating inhibitory activity for HMG-CoA eductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin calcium tablets metabolism by cytoch ome P450 3A4, consistent with inc eased plasma concentrations of atorvastatin calcium tablets in humans following co-administration w th eryth omycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucu onidation.

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

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium tablets are higher (approximately 40% for Cmax and 30% for AUC) in hea thy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a g eater deg ee of LDL-lowering at any dose of drug in the elderly patient population compa ed to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

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

Gender: Plasma concentrations of atorvastatin calcium tablets in women differ from those in men (app oximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C eduction w th atorvastatin calcium tablets between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C eduction of atorvastatin calcium tablets; thus, dose adjustment in patients w th renal dysfunction is not necessa y [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 w th end-stage enal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin calcium tablets since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with ch onic alcoholic liver disease, plasma concentrations of atorvastatin calcium tablets a e markedly increased. Cmax and AUC are each 4-fold g eater in patients with Childs-Pugh A disease. Cmax and AUC a e app oximately 16-fold and 11-fold increased, respectively, in patients w th Childs-Pugh B disease [see *Contraindications (4.1)*].

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

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC*	Change in Cmax*
†Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
†Tipranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
†Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10 6 fold
†,‡ Saquinavir 400 mg BID/ ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3 9 fold	↑ 4.3 fold
† Clar thromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
† Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
† Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
† Fosamp enavir 700 mg BID/ ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
† Fosamp enavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
† Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
† Grapefruit Juice, 240 mL QD §	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
E yth omycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%¶
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
† Rifampin 600 mg QD, 7 days (co-administe ed) #	40 mg SD	↑ 30%	↑ 2.7 fold
† Rifampin 600 mg QD, 5 days (doses separated) #	40 mg SD	↓ 80%	↓ 40%
† Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less than 1%
† Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%
Boceprevir 800 mg TID, 7 days	40mg SD	↑ 2 30 fold	↑ 2.66 fold

* Data given as x-fold change rep esent a simple ratio between co-administration and atorvastatin alone (i e., 1-fold = no change). Data given as % change ep esent % difference relative to atorvastatin alone (i e., 0% = no change).
† See Sections 5.1 and 7 for clinical significance.
‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposu e 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.
§ Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported w th excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).
¶ Single sample taken 8-16 h post dose.
# Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant eduction in atorvastatin plasma concentrations.

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

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

* See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 ra e tumors were found in muscle in high-dose females: in one, the e was a habdomyosarcoma and, in another, there was a fib osarcoma. This dose epresents a plasma AUC (0-24) value of app oximately 16 times the mean human plasma drug exposu e after an 80 mg oral dose.

A 2-year ca cinogenicity study in mice given 100, 200, or 400 mg/kg/day esulted in a significant increase in liver adenomas in high-dose males and liver ca cinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of app oximately 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 w thout metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT fo ward mutation assay in Chinese hamster lung cells, and the ch omosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse mic onucleus test.

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

14 CLINICAL STUDIES

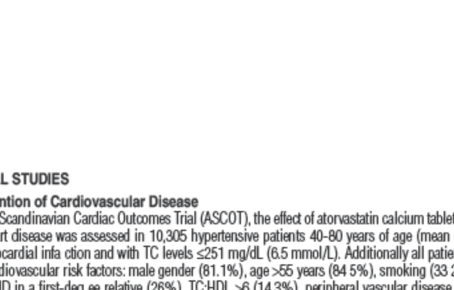
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium tablets on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infa ction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally all patients had at least 3 of the following ca diovascular risk factors: male gender (81.1%), age >55 years (84 5%), smoking (33 2%), diabetes (24 3%), history of CHD in a first-deg ee 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%), p oteinuria/albuminuria (62.4%). In this double-blind, placebo-cont olled study, patients we e t eated w th anti-hypertensive therapy (Goa BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to e ther atorvastatin calcium tablets 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients al eady en olled and minimized the imbalance of those characteristics ac oss the groups. Patients we e followed for a median duration of 3 3 years.

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

Atorvastatin calcium tablets significantly reduced the rate of co onary events [e ther fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium tablets group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium tablets g oup)] w th a relative risk eduction of 36% [(based on incidences of 1 9% for atorvastatin calcium tablets vs. 3 0% for placebo), p=0.0005 (see Figure 1)]. The risk eduction was consistent ega dless of age, smoking status, obesity or presence of enal dysfunction. The effect of atorvastatin calcium tablets was seen regardless of baseline LDL levels. Due to the small number of events, esults for women were inconclusive.

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



Atorvastatin calcium tablets also significantly decreased the elative risk for evascularization p ocedures by 42%. Although the reduction of fatal and non-fatal st okes did not reach a pre-defined significance level (p=0 01), a favorable t end was observed w th a 26% elative risk reduction (incidences of 1.7% for atorvastatin calcium tablets and 2 3% for placebo). The e was no significant diffe ence between the t eatment g oups for death due to cardiovascular causes (p=0 51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium tablets on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40-75 w th type 2 diabetes based on WHO criteria, without prior history of ca diovascular disease and with LDL ≤160 mg/dL and TG ≤600 mg/dL. In addition to diabetes, subjects had 1 or mo e of the following risk factors: cur ent smoking (23%), hypertension (80%), etinopathy (30%), or mic oalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-cont olled, double-blind clinical trial, subjects we e randomly allocated to either atorvastatin calcium tablets 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3 9 years. The primary endpoint was the occurrence of any of the major ca diovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or st oke. The primary analysis was the time to first occur ence 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 52mg/dL.

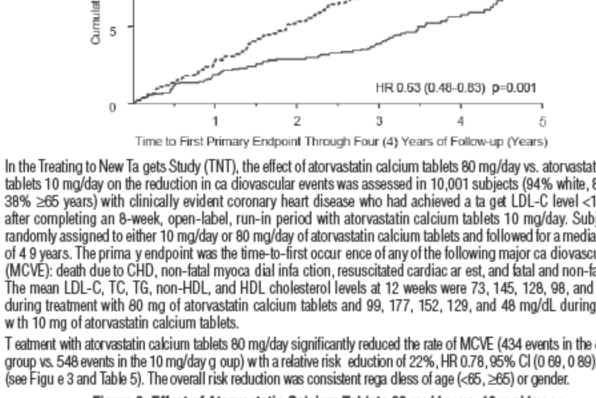
The effect of atorvastatin calcium tablets 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium tablets significantly reduced the rate of major ca diovascular events (prima y endpoint events) (83 events in the atorvastatin calcium tablets g oup vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0 63, 95% CI (0.48, 0 83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium tablets was seen egardless of age, sex, or baseline lipid levels.

Atorvastatin calcium tablets significantly educed the risk of stroke by 48% (21 events in the atorvastatin calcium tablets group vs. 39 events in the placebo group), HR 0 52, 95% CI (0.31, 0 89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium tablets group vs. 64 events in the placebo g oup), HR 0 58, 95.1% CI (0.39, 0.86) (p=0 007). There was no significant diffe ence between the treatment groups for angina, evascularization procedures, and acute CHD death.

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

Figure 2. Effect of Atorvastatin Calcium Tablets 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 Ta gets Study (TNT), the effect of atorvastatin calcium tablets 80 mg/day vs. atorvastatin calcium tablets 10 mg/day on the reduction in ca diovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a ta get LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium tablets 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium tablets and followed for a median duration of 4 9 years. The prima y endpoint was the time-to-first occur ence of any of the following major ca diovascular events (MCVE): death due to CHD, non-fatal myoca dial infa ction, resuscitated cardiac ar est, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium tablets and 99, 177, 152, 129, and 48 mg/dL during t eatment w th 10 mg of atorvastatin calcium tablets.

T eatment with atorvastatin calcium tablets 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 g oup) w th a relative risk eduction of 22%, HR 0.78, 95% CI (0 69, 0 89), p=0 0002 (see Figu e 3 and Table 5). The overall risk reduction was consistent rega dless of age (<65, ≥65) or gender.

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

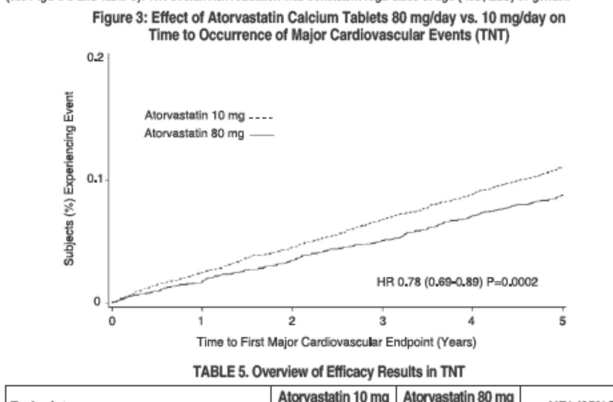


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR* (95%CI)
	n	(%)	n	(%)	
PRIMARY ENDPOINT					
First major cardiovascular endpoint	548	(10 9)	434	(8.7)	0.78 (0 69, 0 89)
Components of the Primary Endpoint					
CHD death	127	(2 5)	101	(2 0)	0 80 (0 61, 1 03)
Non-fatal, non-procedu e related MI	308	(6 2)	243	(4 9)	0.78 (0 66, 0 93)
Resuscitated cardiac ar est	26	(0 5)	25	(0 5)	0 96 (0 56, 1 67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2 3)	0.75 (0 59, 0 96)
SECONDARY ENDPOINTS†					
First CHF with hospitalization	164	(3 3)	122	(2 4)	0.74 (0 59, 0 94)
First PVD endpoint	282	(5 6)	275	(5 5)	0 97 (0 83, 1.15)
First CABG or other coronary evascularization p ocedure‡	904	(18.1)	667	(13 4)	0.72 (0 65, 0 80)
First documented angina endpoint‡	615	(12 3)	545	(10 9)	0 88 (0.79, 0 99)
All-cause mortality	282	(5 6)	284	(5.7)	1 01 (0 85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2 5)	0 81 (0 64, 1 03)
Noncardiovascular death	127	(2 5)	158	(3 2)	1 25 (0 99, 1 57)
Cancer death	75	(1 5)	85	(1.7)	1.13 (0 83, 1 55)
Other non-CV death	43	(0 9)	58	(1 2)	1 35 (0 91, 2 00)
Suicide, homicide, and other traumatic non-CV death	9	(0 2)	15	(0 3)	1 67 (0.73, 3 82)

HR=haza d ratio; CHD=coronary heart disease; CI=confidence interval; MI=myoca dial infa ction; CHF=congestive heart failu e; CV=cardiovascular; PVD=peripheral vascular disease; CABG=co ona y artery bypass graft
Confidence intervals for the Secondary Endpoints we e not adjusted for multiple comparisons
* Atorvastatin 80 mg: atorvastatin 10 mg
† Seconda y endpoints not included in prima y endpoint
‡ Component of other seconda y endpoints

Of the events that comprised the primary efficacy endpoint, t eatment w th atorvastatin calcium tablets 80 mg/day significantly educed the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated ca diac arrest (Table 5). Of the p edefined secondary endpoints, t eatment with atorvastatin calcium tablets 80 mg/day significantly educed the rate of corona y evascularization, angina, and hospitalization for heart failu e, but not peripheral vascular disease. The eduction in the rate of CHF with hospitalization was only observed in the 8% of patients w th a prior history of CHF.

The e was no significant difference between the treatment g oups for all-cause mortality (Table 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal st oke, were numerically smaller in the atorvastatin calcium tablets 80 mg g oup than in the atorvastatin calcium tablets 10 mg t eatment group. The proportions of subjects who experienced nonca diovascular death were numerically la ger in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg t eatment group.

In the Inc emental Dec ease in Endpoints Th ough Aggressive Lipid Lowering Study (IDEAL), t eatment w th atorvastatin calcium tablets 80 mg/day was compared to treatment with simvastatin 20-40 mg/day in 8,888 subjects up to 80 years of age w th a history of CHD to assess whether reduction in CV risk could be achieved. Patients we e mainly male (81%), white (99%) w th 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 w th no run-in period, subjects we e 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 t eatment w th 80 mg of atorvastatin calcium tablets and 105, 179, 142, 47, and 132 mg/dL during t eatment w th 20-40 mg of simvastatin.

The e was no significant difference between the treatment groups for the primary endpoint, the rate of first major co onary event (fatal CHD, non-fatal MI, and resuscitated ca diac ar est): 411 (9.3%) in the atorvastatin calcium tablets 80 mg/day g oup vs. 463 (10 4%) in the simvastatin 20-40 mg/day g oup, HR 0 89, 95% CI (0.78, 1 01), p=0 07.

The e we e no significant diffe ences between the treatment groups for all-cause mortality: 366 (8 2%) in the atorvastatin calcium tablets 80 mg/day g oup vs. 374 (8 4%) in the simvastatin 20-40 mg/day group. The p oportions of subjects who experienced CV or non-CV death were similar for the atorvastatin calcium tablets 80 mg g oup and the simvastatin 20-40 mg group.

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

Atorvastatin calcium tablets educes total-C, LDL-C, VLDL-C, apo B, and TG, and inc eases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic esponse is seen within 2 weeks, and maximum esponse is usually achieved within 4 weeks and maintained during ch onic therapy.

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

In two multicenter, placebo-cont olled, dose- esponse studies in patients with hyperlipidemia, atorvastatin calcium tablets given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG (Pooled esults a e provided in Table 6).

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

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

* Results a e pooled f om 2 dose-response studies.

In patients w th *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled f om 24 cont olled trials, the median (25th and 75th percentile) percent changes f om baseline in HDL-C for atorvastatin calcium tablets 10, 20, 40, and 80 mg were 6 4 (-1.4, 14), 8.7 (0, 17), 7 8 (0, 16), and 5.1 (-2.7, 15), espectively. Additionally, analysis of the pooled data demonstrated consistent and significant dec eases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients w th hyperlipidemia, atorvastatin calcium tablets was compared to other statins. After randomization, patients we e treated for 16 weeks with e ther atorvastatin calcium tablets 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 Calcium Tablets 10 mg	707	-27*	-36*	-28*	-17*	+7	-37*
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff †		-9.2, -6 5	-10.7, -7.1	-10 0, -6.5	-15.2, -7.1	-1.7, 2 0	-11.1, -7.1
Study 2							
Atorvastatin Calcium Tablets 10 mg	222	-25‡	-35‡	-27‡	-17‡	+6	-36‡
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff †		-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 Calcium Tablets 10 mg	132	-29§	-37§	-34§	-23§	+7	-39§
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff †		-8.7, -2.7	-10.1, -2.6	-8 0, -1.1	-15.1, -0.7	-4.3, 3 9	-9 6, -1 9

* Significantly different from lovastatin, ANCOVA, p ≤0 05
† A negative value for the 95% CI for the difference between treatments favors atorvastatin calcium tablets for all except HDL-C, for which a positive value favors atorvastatin calcium tablets. If the range does not include 0, this indicates a statistically significant difference.
‡ Significantly different from pravastatin, ANCOVA, p ≤0.05
§ Significantly different from simvastatin, ANCOVA, p ≤0.05

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

14.3 Hypertriglyceridemia (*Fredrickson* Type IV)

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

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

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

14.4 Dysbetalipoproteinemia (*Fredrickson* Type III)

The esults of an open-label c ossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipop oteinemia (*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 Calcium Tablets 10 mg	Atorvastatin Calcium Tablets 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 concur ent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium tablets. The mean LDL-C reduction in this study was 18%. Twenty-five patients w th a reduction in LDL-C had a mean esponse of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The emaining 3 eceptor-negative patients had a mean LDL-C eduction 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 10-17 years of age (mean age 14.1 years) with hete ozygous familial hypercholesterolemia (FH) or seve e hypercholeste olemia, we e randomized to atorvastatin calcium tablets (n=140) or placebo (n=47) for 26 weeks and then all eceived atorvastatin calcium tablets for 26 weeks. Inclusion in the study requi ed 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 p ematu e cardiovascular disease in a first or second-deg ee relative. The mean baseline LDL-C value was 218 6 mg/dL (range: 138 5–385.0 mg/dL) in the atorvastatin calcium tablets g oup compared to 230 0 mg/dL (range: 160.0–324 5 mg/dL) in the placebo group. The dosage of atorvastatin calcium tablets (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium tablets-t eated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

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

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

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

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 0–242 0 mg/dL) in the atorvastatin calcium tablets group compa ed to 228 5 mg/dL (range: 152 0–385 0 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in child en. The long-term efficacy of atorvastatin calcium tablets therapy in childhood to educe morbidity and mortality in adu thood has not been established.

15 REFERENCES

[1] National Choleste ol 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 supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40, and 80 mg atorvastatin.

10 mg tablets: debossed w th "1" on one side and plain on the other.

NDC 62175-890-46	bottles of 90
NDC 62175-890-43	bottles of 1000
NDC 62175-890-45	bottles of 5000

20 mg tablets: debossed w th "2" on one side and plain on the other.

NDC 62175-891-46	bottles of 90
NDC 62175-891-43	bottles of 1000
NDC 62175-891-45	bottles of 5000

40 mg tablets: debossed w th "40" on one side and plain on the other.

NDC 62175-892-46	bottles of 90
NDC 62175-892-41	bottles of 500
NDC 62175-892-44	bottles of 2500

80 mg tablets: debossed w th "80" on one side and plain on the other.

NDC 62175-897-46	bottles of 90
NDC 62175-897-41	bottles of 500
NDC 62175-897-44	bottles of 2500

Storage

Store at controlled oom temperature 20 - 25°C (68 - 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients taking Atorvastatin Calcium Tablets should be advised that cholesterol is a chronic condition and they should adhe e to their medication along w th their National Cholesterol Education P ogram (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 eport promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing Atorvastatin Calcium Tablets. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, w th their hea thcare professional.

17.2 Liver Enzymes

It is ecommended that liver enzyme tests be performed before the initiation Atorvastatin Calcium Tablets and if signs or symptoms of liver inju y occur. All patients treated with Atorvastatin Calcium Tablets should be advised to report promptly any symptoms that may indicate liver inju y, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using Atorvastatin Calcium Tablets. Discuss future pregnancy plans w th your patients, and discuss when to stop Atorvastatin Calcium Tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking Atorvastatin Calcium Tablets and call their healthca e professional.

17.4 Breastfeeding

Women who a e breastfeeding should be advised to not use Atorvastatin Calcium Tablets. Patients who have a lipid diso der and are b eastfeeding, should be advised to discuss the options w th their hea thcare professional.

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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 is 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. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking Atorvastatin Calcium Tablets. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual.
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

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

The following additional side effects have been reported with Atorvastatin Calcium Tablets: tiredness, tendon problems, memory loss, and confusion.

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

These are not all the side effects of Atorvastatin Calcium Tablets. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets?

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

General Information About Atorvastatin Calcium Tablets

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

This leaflet summarizes the most important information about Atorvastatin Calcium Tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Atorvastatin Calcium Tablets that is written for health professionals. Or you can go to www.kremersurban.com.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

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PATIENT INFORMATION
Atorvastatin Calcium Tablets

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

If you have any questions about Atorvastatin Calcium Tablets, ask your doctor or pharmacist.

What is Atorvastatin Calcium Tablets?

Atorvastatin Calcium Tablets 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 is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

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

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

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

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

Atorvastatin Calcium Tablets start to work in about 2 weeks.

What is Cholesterol?

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

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take Atorvastatin Calcium Tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin Calcium Tablets may harm your unborn baby. If you get pregnant, stop taking Atorvastatin Calcium Tablets and call your doctor right away.
- are breast feeding. Atorvastatin Calcium Tablets can pass into your breast milk and may harm your baby.
- 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 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

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

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

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

How Should I Take Atorvastatin Calcium Tablets?

- Take Atorvastatin Calcium Tablets exactly as prescribed by your doctor. Do not change your dose or stop Atorvastatin Calcium Tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with Atorvastatin Calcium Tablets. Your dose of Atorvastatin Calcium Tablets may be changed based on these blood test results.
- Take Atorvastatin Calcium Tablets each day at any time of day at about the same time each day. Atorvastatin Calcium Tablets can be taken with or without food.
  Don't break Atorvastatin Calcium Tablets before taking.
- Your doctor should start you on a low-fat diet before giving you Atorvastatin Calcium Tablets. Stay on this low-fat diet when you take Atorvastatin Calcium Tablets.
- If you miss a dose of Atorvastatin Calcium Tablets, take it as soon as you remember. Do not take Atorvastatin Calcium Tablets if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of Atorvastatin Calcium Tablets at the same time.
- If you take too much Atorvastatin Calcium Tablets or overdose, call your doctor or

Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

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

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  - dark amber colored urine
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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. Or you can go to www.kremersurban.com.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

LABELING REVIEWS

*****This AP summary supersedes the AP review dated 5/14/2012 in DARRTS*****

APPROVAL SUMMARY #3
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091624

Date of Submission: March 4, 2010, April 24, 2012 and November 21, 2012

Applicant's Name: KUDCO Ireland Limited

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

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Labeling Comments below are considered:

☒ No Comments (Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submissions dated 3/4/2010, 4/24/2012 and 11/21/2012.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

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

Note RPM - Labeling comments end here

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

	Date submitted	Final or Draft	Recommendation
CONTAINER **10 mg and 20 mg** = bottles of 90s, 5000s **40 mg and 80 mg** = bottles of 90s, 500s & 2500s	4/24/2012	Final	Acceptable for approval
CONTAINER **10 mg and 20 mg** = bottles of 1000's	3/4/2010	Final	Acceptable for approval
INSERT	11/21/2012	Final	Acceptable for approval
PATIENT INFORMATION	11/21/2012	Final	Acceptable for approval
SPL	11/21/2012		Acceptable for approval

REVISIONS NEEDED POST APPROVAL? Yes

1. CONTAINER: 10 mg and 20 mg, (1000's)
As agreed upon in the email correspondence from Mr. Kurt Zimmer to Betty Turner, dated 11/30/12 (Refer to FTR #8 PRODUCT LINE for email) please make the following revisions;

- (b) (4)
- Revise the "Distributed by" statement to read:
  Distributed by:
  Kremers Urban
  Pharmaceuticals Inc.
  Princeton, NJ 08540, USA

In addition, please make the following revisions.

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

contains…"

2. INSERT

FULL PRESCRIBING INFORMTION

A. 2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors-
   - Revise the fourth sentence to read "In patients taking the HIV protease inhibitor nelfinavir…"

B. 7.1 Strong Inhibitors of CYP 3A4
   Combination of Protease Inhibitors
   - Revise the first sentence to read "Atorvastatin AUC was significantly…..protease inhibitors, as well as with the hepatitis C protease …"

   - Revise the second sentence to read "Therefore, in patients taking the "HIV protease inhibitor tipranavir plus…"

Submit your revised labeling in the next annual report with all changes described in full.

The above post approval comments will be communicated to the firm to Kurt Zimmer at Kurt.Zimmer@ucb.com ((812) 523-5539) once the review has been signed off.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

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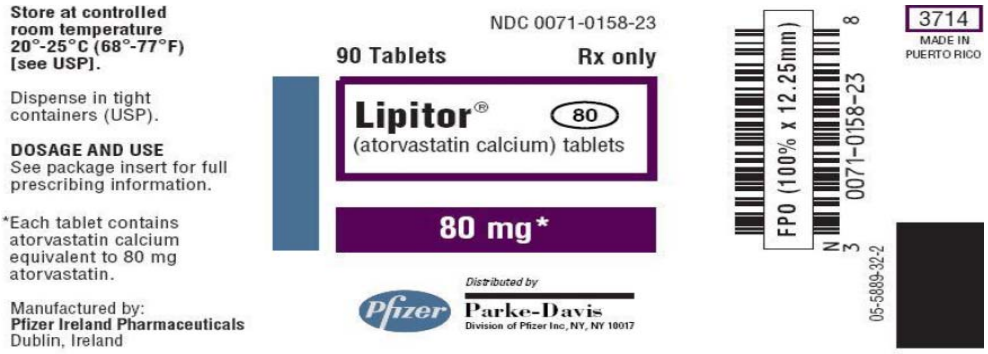
FOR THE RECORD: Please note that the first 2 review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 5/14/12 in DARRTS.

1. **MODEL LABELING**
   This review was based on the labeling of the RLD, Lipitor® (NDA 020702/S-062 and S-063) approved October 31, 2012.

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

   CONTAINER



2. **USP-35 (checked 11/30/2012)**
The DS is compendial.
ADDITIONAL REQUIREMENTS
• **Packaging and Storage:** Preserve in well-closed containers, and store at room temperature.

PF:
37(5) In-Process Revision: Atorvastatin Calcium Tablets

3. **PATENT AND EXCLUSIVITY**
Patent Data – NDA 020702

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**
5686104	Nov 11, 2014 PED May 11, 2015	U-213	Method of inhibiting cholesterol biosynthesis and treating hypercholesterolemia and method for treating hyperlipidemia	IV	None
5969156	Jul 8, 2016 PED Jan 8, 2017	-		IV	None
6126971	Jan 19, 2013 PED July 19, 2013			IV	None

Pfizer Inc. sued Kudco and Kremers Urban for the ‘156 patent. Case 1:09-cv-00924-UNA

Patent Amendment update 0009 submitted November 22, 2011
In the amendment dated 11/22/11, the firm notified the Agency of a Settlement Agreement that was reached between Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner-Lambert Company LLC, and the common parties of Kremers Urban LLC., Kudco Ireland LTD., and Kremers Urban Pharmaceuticals Inc.

WHEREAS, the Parties seek to resolve the Action without further litigation with respect to U.S. Patent No. 5,969,156 and its Re-examination Certificate (together, "the '156 Patent");

Additionally, a copy of the Order of Dismissal is included in this amendment dated 11/22/2011.

Exclusivity Data– NDA

Code	Reference	Expiration	**Labeling impact**
None	There is no unexpired exclusivity for this product		**None**

4. **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: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

5. **MANUFACTURING FACILITY**

Schwarz Pharma Manufacturing, Inc.
1101 C Avenue West
Seymour, Indiana 74274

6. **FINISHED PRODUCT DESCRIPTION**

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, round, film-coated tablets, debossed with “1” on one side and plain on the other.
20 mg: white, round, film-coated tablets, debossed with “2” on one side and plain on the other.
40 mg: white, round, film-coated tablets, debossed with “40” on one side and plain on the other.
80 mg: white, round, film-coated tablets, debossed with “80” on one side and plain on the other.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD:
Store at CRT 20-25°C (68-77°F) [see USP]. Dispense in tight containers (USP).

ANDA:
Store at controlled room temperature 20-25°C (68-77°F) [see USP]. Dispense in tight containers (USP).

8. **PRODUCT LINE**

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

ANDA:
10 mg and 20 mg= bottles of 90s, 1000s and 5000s (original submission)
40 mg and 80 mg= bottles of 90s, 500s and 2500s

In the amendment dated March 26, 2012, the firm did not submit final printed container labels for the 10 mg and 20 mg bottles of 1000's package configurations.

ANDA: 10 mg and 20 mg= bottles of 90s, and 5000s were submitted along with what was previously submitted for the 40 mg and 80 mg strengths.

Container label colors= 80 mg= orange, 40 mg= green, 20 mg= red, 10 mg= blue

Comments from firm: Final Container Labels Amendment dated April 24, 2012

Although the 1000-count bottles for the 10 mg and 20 mg strengths have been submitted in the application, the applicant does not intend to market these bottle sizes at the time of launch. In the event these bottle sizes are marketed at a later date, the package insert will be updated accordingly.

Labeling Amendment dated November 21, 2012
In the How Supplied section of the PI, the firm included bottles of 1000s for the 10 mg and 20 mg strength, when the firm previously decided not to launch the packaging configuration. The labels were previously provided in the amendment dated 3/4/2010. Kurt Zimmer of the firm was notified and his response is provided below.

Hi Betty,

Yes, the labels submitted in the amendment dated 3/4/10 are the true color, size, and clarity. Please let me know if you need anything else. Have a wonderful weekend!

Best regards,

Kurt

From: Turner, Betty [mailto:Betty.Turner@fda.hhs.gov]
Sent: Friday, November 30, 2012 2:20 PM
To: Zimmer Kurt
Subject: RE: ANDA 091624

Good afternoon Mr. Zimmer,

Thanks for your quick response! The labels for the 1000s count were submitted in the amendment dated 3/4/10. Can you confirm that the labels are true to color, size and clarity?

Thanks,

Betty

From: Kurt.Zimmer@ucb.com [mailto:Kurt.Zimmer@ucb.com]
Sent: Friday, November 30, 2012 1:50 PM
To: Turner, Betty
Subject: ANDA 091624

Good afternoon Ms. Turner,

I received your message. You are correct that in Sequence 0011, a statement that the 1000-count bottles were not going to be marketed at the time of launch was included in 1.14.2. Very recently, based on information obtained from our marketing and sales group, the decision was made by the applicant to launch with the 1000-count bottles for the 10 mg and 20 mg strengths. Draft labeling was submitted for these two configurations and the only differences between the current Final Container Label and the Draft Container Label is the name change from Kremers Urban, LLC to Kremers Urban Pharmaceuticals Inc. and the removal of the (b) (4) Is it acceptable to submit the 10 mg and 20 mg 1000-count Final Container Labels along with the SPL within 14 days post-approval? If you would like to discuss over the phone, feel free to call me at 812.523.5539.

Best regards,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.
1101 C Ave West
Seymour, IN 47274
Tel: 812.523.5539
Fax: 812.523.6889
Email: kurt.zimmer@ucb.com

9. CONTAINER/CLOSURE

Strength	Bottle Size	Packaging Material Description	Manufacturer/DMF
10 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

Table 34 – Container Configuration (continued)

20 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
40 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

80 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE (b) (4)	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

10. **BIOAVAILABILITY/BIOEQUIVALENCE:**

BIO is deficient on 1/12/2010

Updated BIO review 11/30/2011- overall review result Inadequate pending the outcome of the OSI inspection for the clinical site of (b) (4) (b) (4)

Updated BIO review 5/22/2012- OSI INSPECTION review adequate. The site inspection was requested for (b) (4) (b) (4). The following application contained studies conducted at these sites. Given the acceptable inspection of the sites, the bioequivalence section of the following applications is now acceptable.

ANDA	Firm	Drug Product
091624	Kudco Ireland Ltd.	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
(b) (4)		

BIO is acceptable review date 5//22/2012.

11. **SCORING:**

RLD: Not scored

ANDA: Not scored

12. **PATIENT INFORMATION SHEETS:**

Comment from labeling review dated 1/20/2010.

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

Response (AF dated 3/4/10)

KUDCO Ireland, Ltd. will ensure that the patient information sheet is available in sufficient numbers to permit the authorized dispenser to provide one sheet to each patient receiving a

prescription of at least thirty tablets.

13. **RELATED APPLICATIONS:**
    None

14. **SPL DATA ELEMENTS**
    Data elements acceptable in 3/4/2010 e-submission

    Cover letter dated 4/24/12

    The applicant commits to submitting labeling in SPL format within 14 business days of approval of the application.

15. Kremers Urban is a member of the UCB Group of Companies; note that "UCB" is the contact in the ADVERSE REACTIONS section of the HIGHLIGHTS.

16. **AMENDMENT DATED 11/21/2012**
    The firm submitted revised labeling in accordance with the labeling approved for the reference listed drug Lipitor® Tablets NDA 020702/S-062 and S-063; approved October 31, 2012. The firm also revised the labeling as requested by the Agency in the email dated 5/23/2012. (See the email below)
    Good evening Ms. Turner,

    Thank you for the update. Kremers Urban acknowledges your comments and will revise the labeling post-approval.

    Have a wonderful evening!

    Best regards,

    Kurt Zimmer
    Regulatory Affairs Manager
    Kremers Urban Pharmaceuticals Inc.
    1101 C Ave West
    Seymour, IN 47274
    Tel: 812.523.5539
    Fax: 812.523.6889
    Email: kurt.zimmer@ucb.com

    From: Turner, Betty [mailto:Betty.Turner@fda.hhs.gov]
    Sent: Wednesday, May 23, 2012 4:36 PM
    To: Zimmer Kurt
    Subject: ANDA 091624

    Good afternoon Mr. Zimmer,

I am writing to inform you of the status of your labeling for ANDA 091624, Atorvastatin Calcium Tablets. I have completed the labeling portion and would like for you to make the following revisions post-approval.

INSERT:

FULL PRESCRIBING INFORMATION: CONTENTS:

- Revise subheadings 2.1 and 2.2 to read as follows:

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)
2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

- Revise subheading 7.1 to read "7.1 Strong Inhibitors of CYP 3A4"

- Delete the following subtitles locate under subheading 7.1
  Clarithromycin
  Combination of Protease Inhibitors
  Itraconazole

- Revise subheadings 14.2 and 14.3 to read as follows:

14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)
14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

Should you have addional questions, please contact me at (240) 276-8728 or by email at betty.turner@fda.hhs.gov.

Thank you,

Betty Turner
Labeling Reviewer
Office of Generic Drugs
7520 Standish Place
Rockville, MD 20855
(240) 276-8728

Date of Review: November 29, 2012

Primary Reviewer: Betty Turner

Team Leader: Chi-Y Ann Wu

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**890**-46 90 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75885A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**890**-45 5000 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75886A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**891**-46 90 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75887A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**891**-45 5000 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75888A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**892**-46 90 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75889A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**892**-41 500 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

N 3 62175 89241 6

Lot No.
Exp.Date

CIA75890A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**892**-44 2500 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75891A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**897**-46 90 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75892A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**897**-41 500 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75893A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**897**-44

2500 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75894A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

(b) (4)

Distributed by:
Kremers Urban, LL
Princeton, NJ 08540

NDC 62175-**890**-43 1000 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010306
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**891**-43 1000 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

N 3 62175 89143 3

Lot No.
Exp.Date

4010309
Rev. 1E

Unvarnished Area

Atorvastatin Calcium Tablets

CIA75883C

℞ only

Rev. 3E 11/2012

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

Dosage and Administration (2.6)	10/2012
Warnings and Precautions (5.1)	10/2012
Drug Interactions (7)	02/2012

INDICATIONS AND USAGE

Atorvastatin Calcium Tablets is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, evascularization p ocedures, and angina in patients w thout CHD, but w th multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients w th type 2 diabetes w thout CHD, but w th multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, evascularization procedures, hospitalization for CHF, and angina in patients w th 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 w th hypertriglyceridemia and prima y dysbetalipop oteinemia (1 2).
- Reduce total-C and LDL-C in patients w th homozygous familia hype cholesterolemia (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 familia hype choleste olemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
Atorvastatin Calcium Tablets has not been studied in *Fredrickson* Types I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring la ge LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum ecommended dose: 20 mg once daily (2 2).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who a e 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 habdomyolysis): Risks inc ease when higher doses are used concomitantly with cyclosporine and st ong CYP3A4 inhibitors (e g., clar th omycin, itraconazole, HIV protease inhibitors). P edisposing factors include advanced age (> 65), uncont olled hypothy oidism, and renal impairment Rare cases of rhabdomyolysis w th acute enal failu e seconda y to myoglobinuria have been eported. Advise patients to p omptly eport to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. Atorvastatin Calcium Tablets therapy should be discontinued if myopathy is diagnosed or suspected (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 hemor hagic st oke was seen in patients without CHD but w th st oke or TIA within the p evious 6 months in the Atorvastatin Calcium Tablets 80 mg group vs. placebo (5.5).

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated w th Atorvastatin Calcium Tablets in placebo-controlled trials rega dless of causality were: nasopha yngitis, arthralgia, diar hea, pain in ext emity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at (1-866-822-0068) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drug Interactions Associated w th Inc eased Risk of Myopathy/Rhabdomyolysis (2 6, 5.1, 7, 12 3)

Interacting Agents	P escribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C p otease inhibitor (telaprevir)	Avoid atorvastatin
HIV p otease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV p otease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamp enavir, fosamp enavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV p otease inhibitor (nelfinavir) Hepatitis C protease inhibitor (bocep evir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Use w th fibrate products or lipid-modifying doses (≥1 g/day) of niacin inc eases the risk of adverse skeletal muscle effects. Caution should be used when prescribing w th Atorvastatin Calcium Tablets (7).
- Digoxin: Patients should be monit ored app opriately (7 8).
- Oral Contraceptives: Values for norethind one and ethinyl estradiol may be increased (7 9).
- Rifampin should be simultaneously co-administe ed with Atorvastatin Calcium Tablets (7.7).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients with ch onic alcoholic liver disease (12 3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy w th lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for athe osclerotic vascular disease due to hype choleste olemia. Drug therapy is ecommended as an adjunct to diet when the response to a diet restricted in saturated fat and choleste ol and other nonpharmacologic measu es alone has been inadequate. In patients w th CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously w th diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but w th multiple risk factors for co ona y heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Atorvastatin Calcium Tablets is indicated to:

- Reduce the risk of myoca dial infa ction
- Reduce the risk of st oke
- Reduce the risk for revascularization p ocedures and angina

In patients w th type 2 diabetes, and without clinically evident coronary heart disease, but w th multiple risk factors for co ona y heart disease such as etinopathy, albuminuria, smoking, or hypertension, Atorvastatin Calcium Tablets is indicated to:

- Reduce the risk of myoca dial infa ction
- Reduce the risk of st oke

In patients with clinically evident coronary heart disease, Atorvastatin Calcium Tablets 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 p ocedures
- Reduce the risk o hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin Calcium Tablets is indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to inc ease HDL-C in patients with primary hype cholesterolemia (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 prima y dysbetalipoproteinemia (*Fredrickson* Type III) who do not espond adequately to diet;
- To reduce total-C and LDL-C in patients w th homozygous familial hype choleste olemia as an adjunct to other lipid-lowering treatments (e g., LDL aphe esis) or if such t eatments 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 hypercholeste olemia if after an adequate trial of diet therapy the following findings are p esent:
  1. LDL-C emains ≥ 190 mg/dL or
  2. LDL-C emains ≥ 160 mg/dL and:
     - the e is a positive family history of p emature ca diovascular disease or
     - two or mo e other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin Calcium Tablets has not been studied in conditions where the major lipop otein abnormality is elevation of chylomic ons (*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 ecommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who equi e a la ge eduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, w th 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 acco dingly.

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

The ecommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses g eater than 20 mg have not been studied in this patient population). Doses should be individualized acco ding to the recommended goal of therapy [see cur ent *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 w th homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e g., LDL apheresis) in these patients or if such treatments a e unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used w th bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used w th 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 w th renal dysfunction is not necessa y [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 p otease 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 p escribing atorvastatin calcium tablets and the lowest dose necessa y employed. In patients taking clar thromycin, 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 taking the HIV inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and app opriate clinical assessment is recommended to ensure that the lowest dose necessa y of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who a e pregnant or may become pregnant. Atorvastatin calcium tablets may cause fetal harm when administered to a p egnant woman. Serum cholesterol and triglycerides inc ease 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 prima y hype choleste olemia. The e a e no adequate and well-cont olled studies of atorvastatin calcium tablets use during pregnancy; however in rare reports, congenital anomalies we e observed following intrauterine exposure to statins. In rat and rabbit animal ep oduction studies, atorvastatin evealed no evidence of teratogenicity. ATORVASTATIN CALCIUM TABLETS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin calcium tablets should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing Mothers

It is not known whether atorvastatin is exc eted 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 eactions in nursing infants, women who equi e atorvastatin calcium tablets treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium tablets and with other drugs in this class. A histo y of enal impairment may be a risk factor for the development of habdomyolysis. 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 w th inc eases in c eatine phosphokinase (CPK) values >10 times ULN. The concomitant use o higher doses of atorvastatin w th certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e g., clar th omycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/ habdomyolysis.

The e have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: p oximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin t eatment; muscle biopsy showing nec otizing myopathy without significant inflammation; improvement w th immunosupp essive agents.

Myopathy should be conside ed in any patient w th diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report p omptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing atorvastatin calcium tablets. Atorvastatin calcium tablets therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment w th drugs in this class is inc eased with concurrent administration of cyclosporine, fibric acid derivatives, eryth omycin, clar thromycin, the hepatitis C p otease inhibitor telap evir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamp enavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin calcium tablets and fibric acid derivatives, e ythromycin, clar thromycin, 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 ca efully 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 c eatine phosphokinase (CPK) determinations may be conside ed in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing ecommendations for interacting agents a e 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 p otease inhibitor (telap evir)	Avoid atorvastatin
HIV p otease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV p otease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamp enavir, fosamp enavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV p otease inhibitor (nelfinavir) Hepatitis C protease inhibitor (bocep evir)	Do not exceed 40 mg atorvastatin daily

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

Cases of myopathy, including habdomyolysis, have been eported w th atorvastatin co-administe ed w th colchicine, and caution should be exe cised when prescribing atorvastatin with colchicine [*see Drug Interactions (7.11)*].

Atorvastatin calcium tablets 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 w th biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium tablets in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Inc eases in liver function tests (LFT) in other patients we e not associated w th jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels eturned to or near p etreatment levels w thout sequelae. Eighteen of 30 patients with persistent LFT elevations continued t eatment with a educed dose of atorvastatin calcium tablets.

It is recommended that liver enzyme tests be obtained prior to initiating therapy w th atorvastatin calcium tablets and epeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failu e in patients taking statins, including atorvastatin. If serious liver inju y with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during t eatment w th atorvastatin calcium tablets, p omptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium tablets.

Atorvastatin calcium tablets should be used w th caution in patients who consume substantial quantities of alcohol and/or have a histo y of liver disease. Active liver disease or unexplained persistent transaminase elevations a e contraindications to the use of atorvastatin calcium tablets [see *Contraindications (4.1)*].

5.3 Endocrine Function

Inc eases in HbA_{1c} and fasting serum glucose levels have been reported w th HMG-CoA eductase inhibitors, including atorvastatin calcium tablets.

Statins interfere w th cholesterol synthesis and theo etically might blunt adrenal and/or gonadal steroid p oduction. Clinical studies have shown that atorvastatin calcium tablets does not reduce basal plasma cortisol concentration or impair ad enal 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 administe ed concomitantly w th drugs that may dec ease the levels or activity of endogenous ste oid 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 hemor hage and optic nerve vacuolation we e 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 esulted in a systemic exposure app oximately 16 times the human plasma a ea-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one t eated 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 hemor hages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs t eated w th other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of etinogeniculate 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 P evention by Agg essive Reduction in Choleste ol Levels (SPARCL) study whe e atorvastatin calcium tablets 80 mg vs. placebo was administe ed in 4,731 subjects w thout CHD who had a st oke or TIA w thin the preceding 6 months, a higher incidence o hemorrhagic st oke was seen in the atorvastatin calcium tablets 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 hemor hagic stroke was similar across treatment g oups (17 vs. 18 for the atorvastatin and placebo g oups, respectively). The incidence of nonfatal hemorrhagic st oke was significantly higher in the atorvastatin g oup (38, 1 6%) as compa ed to the placebo g oup (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, we e associated w th a higher incidence o hemorrhagic st oke in the atorvastatin g oup [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse eactions a e 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 eaction rates observed in the clinical studies of a drug cannot be di ectly compa ed to rates in the clinical trials of another drug and may not eflect the rates observed in clinical practice.

In the atorvastatin calcium tablets placebo-cont olled clinical trial database of 16,066 patients (8755 atorvastatin calcium tablets vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) w th a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium tablets and 9 5% of the patients on placebo discontinued due to adverse reactions egardless of causality. The five most common adverse eactions in patients treated w th atorvastatin calcium tablets that led to treatment discontinuation and occurred at a rate g eater than placebo we e: myalgia (0.7%), diar hea (0 5%), nausea (0 4%), alanine aminotransferase increase (0 4%), and hepatic enzyme increase (0 4%).

The most commonly eported adverse reactions (incidence ≥ 2% and g eater than placebo) regardless of causality, in patients t eated w th atorvastatin calcium tablets in placebo controlled trials (n=8755) were: nasopharyngitis (8 3%), arthralgia (6 9%), diar hea (6 8%), pain in extremity (6 0%), and urina y tract infection (5.7%).

Table 2 summarizes the f equency of clinical adverse reactions, ega dless of causality, eported in ≥ 2% and at a rate g eater than placebo in patients treated w th atorvastatin calcium tablets (n=8755), f om seventeen placebo-controlled trials.

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

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8 3	12 9	5.3	7 0	4.2	8.2
Arthralgia	6 9	8 9	11.7	10.6	4.3	6.5
Diarrhea	6 8	7 3	6.4	14.1	5.2	6.3
Pain in extremity	6 0	8 5	3.7	9 3	3.1	5 9
Urinary tract infection	5.7	6 9	6.4	8 0	4.1	5.6
Dyspepsia	4.7	5 9	3.2	6 0	3.3	4.3
Nausea	4 0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3 8	5 2	3.2	5.1	2.3	3.6
Muscle Spasms	3 6	4 6	4.8	5.1	2.4	3.0
Myalgia	3 5	3 6	5 9	8 4	2.7	3.1
Insomnia	3 0	2 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 eactions eported in placebo-controlled studies include:

Body as a whole: malaise, py exia; *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 inc ease, 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 40–80 years, 19% women; 94 6% Caucasians, 2 6% Africans, 1 5% South Asians, 1 3% mixed/other) t eated with atorvastatin calcium tablets 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability p ofile of the g oup treated w th atorvastatin calcium tablets was comparable to that of the g oup treated w th 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 39–77 years, 32% women; 94 3% Caucasians, 2 4% South Asians, 2 3% Af o-Caribbean, 1 0% other) w th type 2 diabetes treated with atorvastatin calcium tablets 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse eactions or serious adverse eactions 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 29–78 years, 19% women; 94.1% Caucasians, 2 9% Blacks, 1.0% Asians, 2 0% other) with clinically evident CHD treated w th atorvastatin calcium tablets 10 mg daily (n=5006) or atorvastatin calcium tablets 80 mg daily (n=4995), there were mo e serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1 8%; 497, 9 9%, espectively) as compared to the low-dose g oup (69, 1 4%; 404, 8.1%, respectively) during a median follow-up of 4 9 years. Persistent transaminase elevations (≥3 x ULN twice w thin 4–10 days) occur ed in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0 2%) individuals w th atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but we e higher in the high-dose atorvastatin t eatment 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 26–80 years, 19% women; 99 3% Caucasians, 0.4% Asians, 0.3% Blacks, 0 04% other) t eated with atorvastatin calcium tablets 80 mg/day (n=4439) or simvastatin 20–40 mg daily (n=4449), the e was no difference in the overall f equency of adverse eactions or serious adverse eactions between the treatment groups during a median follow-up of 4 8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21–92 years, 40% women; 93 3% Caucasians, 3 0% Blacks, 0.6% Asians, 3.1% other) w thout clinically evident CHD but w th a stroke or transient ischemic attack (TIA) within the previous 6 months t eated w th atorvastatin calcium tablets 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4 9 years, the e was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice w thin 4–10 days) in the atorvastatin group (0 9%) compa ed to placebo (0.1%). Elevations of CK (>10 x ULN) were ra e, but were higher in the atorvastatin group (0.1%) compa ed to placebo (0 0%). Diabetes was eported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium tablets 80 mg educed the incidence of ischemic st oke (218/2365, 9.2% vs. 274/2366, 11 6%) and increased the incidence of hemor hagic st oke (55/2365, 2 3% vs. 33/2366, 1 4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin calcium tablets vs. 18 placebo). The incidence of non-fata hemorrhagic st okes was significantly greater in the atorvastatin g oup (38 non-fata hemorrhagic st okes) as compa ed to the placebo g oup (16 non-fatal hemor hagic st okes). Subjects who ente ed the study w th a hemor hagic st oke appeared to be at inc eased risk for hemor hagic st oke [7 (16%) atorvastatin calcium tablets vs. 2 (4%) placebo].

The e we e no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium tablets 80 mg/day g oup vs. 211 (8 9%) in the placebo g oup. The proportions of subjects who experienced ca diovascular death were numerically smaller in the atorvastatin calcium tablets 80 mg group (3 3%) than in the placebo g oup (4.1%). The proportions of subjects who experienced non-ca diovascular death were numerically larger in the atorvastatin calcium tablets 80 mg g oup (5 0%) than in the placebo group (4 0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapp oval use of atorvastatin calcium tablets Because these eactions are eported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their f equency or establish a causal elationship to drug exposu e.

Adverse eactions associated with atorvastatin calcium tablets therapy reported since market introduction, that are not listed above, rega dless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including e ythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), habdomyolysis, fatigue, tendon rupture, fatal and non-fata hepatic failu e, dizziness, dep ession, peripheral neu opathy, and panc eatitis.

There have been ra e reports of immune-mediated necrotizing myopathy associated w th statin use [see *Warnings and Precautions (5.1)*].

The e have been ra e postmarketing reports of cognitive impairment (e g., memo y loss, fo getfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports a e generally nonserious, and eversible upon statin discontinuation, w th variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10-17 years)

In a 26-week cont olled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1 6% Asians, 4 8% other), the safety and tolerability profile of atorvastatin calcium tablets 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during t eatment w th statins is increased w th concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or st ong CYP 3A4 inhibitors (e g., clarithromycin, HIV p otease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4

Atorvastatin calcium tablets is metabolized by cytoch ome P450 3A4. Concomitant administration of atorvastatin calcium tablets with strong inhibitors of CYP 3A4 can lead to inc eases 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 inc eased with concomitant administration of atorvastatin calcium tablets 80 mg w th clarithromycin (500 mg twice daily) compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin calcium tablets 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 inc eased w th concomitant administration of atorvastatin calcium tablets w th several combinations of HIV protease inhibitors, as well as with hepatitis C p otease inhibitor telap evir, compa ed to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking HIV p otease inhibitor tipranavir plus ritonavir, or the hepatitis C p otease inhibitor telaprevir, concomitant use of atorvastatin calcium tablets should be avoided. In patients taking the HIV p otease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary should be used. In patients taking the HIV p otease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamp enavir, or fosamprenavir plus ritonavir, the dose of atorvastatin calcium tablets should not exceed 20 mg and should be used w th caution [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*]. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor bocep evir, the dose of atorvastatin calcium tablets should not exceed 40 mg and close clinical monitoring is ecommended.

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

7.2 Grapefruit Juice

Contains one or more components that inhibit CYP 3A4 and can inc ease plasma concentrations of atorvastatin, especially w th excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolites a e substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e g., cyclosporine) can inc ease the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased w th concomitant administration of atorvastatin calcium tablets 10 mg and cyclosporine 5 2 mg/kg/day compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. The co-administration of atorvastatin calcium tablets with cyclosporine should be avoided [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Gemfibrozil

Due to an inc eased risk of myopathy/ habdomyolysis when HMG-CoA reductase inhibitors a e co-administe ed with gemfibrozil, concomitant administration of atorvastatin calcium tablets with gemfib ozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 Other Fibrates

Because it is known that the risk of myopathy during treatment w th HMG-CoA eductase inhibitors is increased w th concurrent administration of other fibrates, atorvastatin calcium tablets should be administe ed w th caution when used concomitantly w th other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when atorvastatin calcium tablets is used in combination w th niacin; a eduction in atorvastatin calcium tablets dosage should be conside ed in this setting [see *Warnings and Precautions (5.1)*].

7.7 Rifampin or other Inducers of Cytochrome P450 3A4

Concomitant administration of atorvastatin calcium tablets w th inducers of cytochrome P450 3A4 (e g., efavi enz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium tablets w th rifampin is ecommended, as delayed administration of atorvastatin calcium tablets after administration of rifampin has been associated w th a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

When multiple doses of atorvastatin calcium tablets and digoxin were coadministered, steady state plasma digoxin concentrations inc eased by approximately 20%. Patients taking digoxin should be monito ed appropriately.

7.9 Oral Contraceptives

Co-administration of atorvastatin calcium tablets and an oral contraceptive increased AUC values for norethind one and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These inc eases should be conside ed when selecting an oral contraceptive for a woman taking atorvastatin calcium tablets.

7.10 Warfarin

Atorvastatin calcium tablets had no clinically significant effect on p oth ombin time when administered to patients receiving chronic warfarin t eatment.

7.11 Colchicine

Cases of myopathy, including habdomyolysis, have been eported w th atorvastatin co-administe ed w th colchicine, and caution should be exe cised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Catego y X

Atorvastatin calcium tablets is contraindicated in women who are or may become p egnant. Serum cholesterol and triglycerides increase during normal p egnancy. Lipid lowering drugs offer no benefit during p egnancy because choleste ol and cholesterol derivatives are needed for normal fetal development. Athe osclerosis is a chronic p ocess, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholeste olemia therapy.

The e a e no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare eports of congenital anomalies following intrauterine exposu e to statins. In a review of about 100 p ospectively followed p egnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a th ee-to-four-fold inc eased risk of congenital anomalies over backg ound incidence. In 89% of these cases, drug treatment started befo e pregnancy and stopped during the first trimester when pregnancy was identified.

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

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

Statins may cause fetal harm when administe ed to a pregnant woman. Atorvastatin calcium tablets should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential haza ds. If the woman becomes pregnant while taking atorvastatin calcium tablets, it should be discontinued immediately and the patient advised again as to the potentia hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in patients 10-17 years of age with hete ozygous familia hype choleste olemia have been evaluated in a cont olled clinical trial of 6 months' duration in adolescent boys and postmena chal girls. Patients t eated w th atorvastatin calcium tablets had an adverse experience profile generally similar to that of patients treated w th placebo. The most common adverse experiences observed in both groups, egardless of causality assessment, we e infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited cont olled study, the e was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10-17 years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age) (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin calcium tablets therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium tablets has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

10 OVERDOSAGE

The e is no specific treatment for atorvastatin calcium tablets overdosage. In the event of an overdose, the patient should be t eated symptomatically, and supportive measures instituted as equi ed. Due to extensive drug binding to plasma p oteins, hemodialysis is not expected to significantly enhance atorvastatin calcium tablets clearance.

11 DESCRIPTION

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

PATIENT INFORMATION

Atorvastatin Calcium Tablets

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

If you have any questions about Atorvastatin Calcium Tablets, ask your doctor or pharmacist.

What is Atorvastatin Calcium Tablets?

Atorvastatin Calcium Tablets 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 is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

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

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

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

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

Atorvastatin Calcium Tablets start to work in about 2 weeks.

What is Cholesterol?

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

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take Atorvastatin Calcium Tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin Calcium Tablets may harm your unborn baby. If you get pregnant, stop taking Atorvastatin Calcium Tablets and call your doctor right away.
- are breast feeding. Atorvastatin Calcium Tablets can pass into your breast milk and may harm your baby.
- 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 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

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

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

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

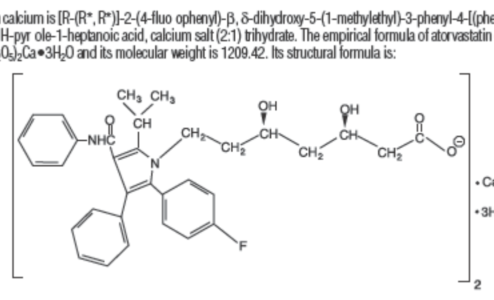
How Should I Take Atorvastatin Calcium Tablets?

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

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

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

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



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7 4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, c oscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium tablets is a selective, competitive inhibitor of HMG-CoA eductase, the rate-limiting enzyme that converts 3-hyd oxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of ste ols, including choleste ol. Cholesterol and triglycerides circulate in the bloodst eam as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (ve y-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and eleased into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human athe osclerosis and a e risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated w th a decreased cardiovascular risk.

In animal models, atorvastatin calcium tablets lower plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA eductase and choleste ol synthesis in the liver and by inc easing the number of hepatic LDL eceptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium tablets also educes LDL production and the number of LDL particles. Atorvastatin calcium tablets educes LDL-C in some patients w th homozygous familial hype cholesterolemia (FH), a population that ra ely responds to other lipid-lowering medication(s).

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

Atorvastatin calcium tablets educes total-C, LDL-C, and apo B in patients with homozygous and hete ozygous FH, nonfamilial forms of hype cholesterolemia, and mixed dyslipidemia. Atorvastatin calcium tablets also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium tablets reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and inc eases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium tablets reduces intermediate density lipoprotein choleste ol (IDL-C) in patients w th dysbetalipop oteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also p omote 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 co ona y heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermo e, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption: Atorvastatin calcium tablets is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium tablets dose. The absolute bioavailability of atorvastatin (pa ent drug) is approximately 14% and the systemic availability of HMG-CoA eductase inhibito y activity is approximately 30%. The low systemic availability is attributed to p esystemic clearance in gast ointestinal mucosa and/or hepatic first-pass metabolism. A though food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C eduction is similar whether atorvastatin calcium tablets is given w th or without food. Plasma atorvastatin calcium tablets concentrations a e lower (app oximately 30% for C and AUC) following evening drug administration compared w th morning. However, LDL-C eduction is the same rega dless of the time of day of drug administration [see *Dosage and Administration (2)*].

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

Metabolism: Atorvastatin calcium tablets is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation p oducts. *In vitro* inhibition of HMG-CoA eductase by ortho- and parahyd oxylated metabolites is equivalent to that of atorvastatin calcium tablets. App oximately 70% of circulating inhibitory activity for HMG-CoA eductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin calcium tablets metabolism by cytoch ome P450 3A4, consistent with inc eased plasma concentrations of atorvastatin calcium tablets in humans following co-administration w th eryth omycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucu onidation.

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

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium tablets are higher (approximately 40% for Cmax and 30% for AUC) in hea thy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a g eater deg ee of LDL-lowering at any dose of drug in the elderly patient population compa ed to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

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

Gender: Plasma concentrations of atorvastatin calcium tablets in women differ from those in men (app oximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C eduction w th atorvastatin calcium tablets between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C eduction of atorvastatin calcium tablets; thus, dose adjustment in patients w th renal dysfunction is not necessa y [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 w th end-stage enal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin calcium tablets since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with ch onic alcoholic liver disease, plasma concentrations of atorvastatin calcium tablets a e markedly increased. Cmax and AUC are each 4-fold g eater in patients with Childs-Pugh A disease. Cmax and AUC a e app oximately 16-fold and 11-fold increased, respectively, in patients w th Childs-Pugh B disease [see *Contraindications (4.1)*].

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

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC*	Change in Cmax*
† Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑ 10.7 fold
† Tipranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
† Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10 6 fold
†,‡ Saquinavir 400 mg BID/ ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3 9 fold	↑ 4.3 fold
† Clar thromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
† Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
† Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
† Fosamp enavir 700 mg BID/ ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
† Fosamp enavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
† Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
† Grapefruit Juice, 240 mL QD §	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
E yth omycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%¶
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
† Rifampin 600 mg QD, 7 days (co-administe ed) #	40 mg SD	↑ 30%	↑ 2.7 fold
† Rifampin 600 mg QD, 5 days (doses separated) #	40 mg SD	↓ 80%	↓ 40%
† Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less than 1%
† Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%
Boceprevir 800 mg TID, 7 days	40mg SD	↑ 2 30 fold	↑ 2.66 fold

* Data given as x-fold change rep esent a simple ratio between co-administration and atorvastatin alone (i e., 1-fold = no change). Data given as % change ep esent % difference relative to atorvastatin alone (i e., 0% = no change).
† See Sections 5.1 and 7 for clinical significance.
‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposu e 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.
§ Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported w th excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).
¶ Single sample taken 8-16 h post dose.
# Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant eduction in atorvastatin plasma concentrations.

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

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

* See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 ra e tumors were found in muscle in high-dose females: in one, the e was a habdomyosarcoma and, in another, there was a fib osarcoma. This dose epresents a plasma AUC (0-24) value of app oximately 16 times the mean human plasma drug exposu e after an 80 mg oral dose.

A 2-year ca cinogenicity study in mice given 100, 200, or 400 mg/kg/day esulted in a significant increase in liver adenomas in high-dose males and liver ca cinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of app oximately 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 w thout metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT fo ward mutation assay in Chinese hamster lung cells, and the ch omosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse mic onucleus test.

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

14 CLINICAL STUDIES

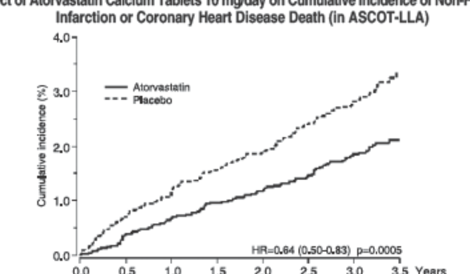
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium tablets on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infa ction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally all patients had at least 3 of the following ca diovascular risk factors: male gender (81.1%), age >55 years (84 5%), smoking (33 2%), diabetes (24 3%), history of CHD in a first-deg ee 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%), p oteinuria/albuminuria (62.4%). In this double-blind, placebo-cont olled study, patients we e t eated w th anti-hypertensive therapy (Goa BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to e ther atorvastatin calcium tablets 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients al eady en olled and minimized the imbalance of those characteristics ac oss the groups. Patients we e followed for a median duration of 3 3 years.

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

Atorvastatin calcium tablets significantly reduced the rate of co onary events [e ther fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium tablets group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium tablets g oup)] w th a relative risk eduction of 36% [(based on incidences of 1 9% for atorvastatin calcium tablets vs. 3 0% for placebo), p=0.0005 (see Figure 1)]. The risk eduction was consistent ega dless of age, smoking status, obesity or presence of enal dysfunction. The effect of atorvastatin calcium tablets was seen regardless of baseline LDL levels. Due to the small number of events, esults for women were inconclusive.

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



Atorvastatin calcium tablets also significantly decreased the elative risk for evascularization p ocedures by 42%. Although the reduction of fatal and non-fatal st okes did not reach a pre-defined significance level (p=0 01), a favorable t end was observed w th a 26% elative risk reduction (incidences of 1.7% for atorvastatin calcium tablets and 2 3% for placebo). The e was no significant diffe ence between the t eatment g oups for death due to cardiovascular causes (p=0 51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin calcium tablets on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40-75 w th type 2 diabetes based on WHO criteria, without prior history of ca diovascular disease and with LDL ≤160 mg/dL and TG ≤600 mg/dL. In addition to diabetes, subjects had 1 or mo e of the following risk factors: cur ent smoking (23%), hypertension (80%), etinopathy (30%), or mic oalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-cont olled, double-blind clinical trial, subjects we e randomly allocated to either atorvastatin calcium tablets 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3 9 years. The primary endpoint was the occurrence of any of the major ca diovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or st oke. The primary analysis was the time to first occur ence 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 52mg/dL.

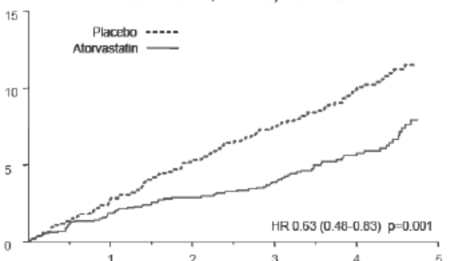
The effect of atorvastatin calcium tablets 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium tablets significantly reduced the rate of major ca diovascular events (prima y endpoint events) (83 events in the atorvastatin calcium tablets g oup vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0 63, 95% CI (0.48, 0 83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium tablets was seen egardless of age, sex, or baseline lipid levels.

Atorvastatin calcium tablets significantly educed the risk of stroke by 48% (21 events in the atorvastatin calcium tablets group vs. 39 events in the placebo group), HR 0 52, 95% CI (0.31, 0 89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium tablets group vs. 64 events in the placebo g oup), HR 0 58, 95.1% CI (0.39, 0.86) (p=0 007). There was no significant diffe ence between the treatment groups for angina, evascularization procedures, and acute CHD death.

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

Figure 2. Effect of Atorvastatin Calcium Tablets 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 Ta gets Study (TNT), the effect of atorvastatin calcium tablets 80 mg/day vs. atorvastatin calcium tablets 10 mg/day on the reduction in ca diovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a ta get LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium tablets 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium tablets and followed for a median duration of 4 9 years. The prima y endpoint was the time-to-first occur ence of any of the following major ca diovascular events (MCVE): death due to CHD, non-fatal myoca dial infa ction, resuscitated cardiac ar est, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium tablets and 99, 177, 152, 129, and 48 mg/dL during t eatment w th 10 mg of atorvastatin calcium tablets.

T eatment with atorvastatin calcium tablets 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 g oup) w th a relative risk eduction of 22%, HR 0.78, 95% CI (0 69, 0 89), p=0 0002 (see Figu e 3 and Table 5). The overall risk reduction was consistent rega dless of age (<65, ≥65) or gender.

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

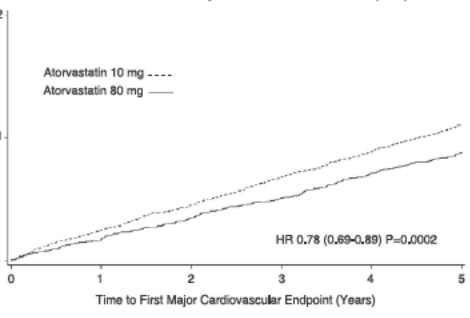


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR* (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10 9)	434	(8.7)	0.78 (0 69, 0 89)
Components of the Primary Endpoint					
CHD death	127	(2 5)	101	(2 0)	0 80 (0 61, 1 03)
Non-fatal, non-procedu e related MI	308	(6 2)	243	(4 9)	0.78 (0 66, 0 93)
Resuscitated cardiac ar est	26	(0 5)	25	(0 5)	0 96 (0 56, 1 67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2 3)	0.75 (0 59, 0 96)
SECONDARY ENDPOINTS †					
First CHF with hospitalization	164	(3 3)	122	(2 4)	0.74 (0 59, 0 94)
First PVD endpoint	282	(5 6)	275	(5 5)	0 97 (0 83, 1.15)
First CABG or other coronary evascularization p ocedure‡	904	(18.1)	667	(13 4)	0.72 (0 65, 0 80)
First documented angina endpoint‡	615	(12 3)	545	(10 9)	0 88 (0.79, 0 99)
All-cause mortality	282	(5 6)	284	(5.7)	1 01 (0 85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2 5)	0 81 (0 64, 1 03)
Noncardiovascular death	127	(2 5)	158	(3 2)	1 25 (0 99, 1 57)
Cancer death	75	(1 5)	85	(1.7)	1.13 (0 83, 1 55)
Other non-CV death	43	(0 9)	58	(1 2)	1 35 (0 91, 2 00)
Suicide, homicide, and other traumatic non-CV death	9	(0 2)	15	(0 3)	1 67 (0.73, 3 82)

HR=haza d ratio; CHD=coronary heart disease; CI=confidence interval; MI=myoca dial infa ction; CHF=congestive heart failu e; CV=cardiovascular; PVD=peripheral vascular disease; CABG=co ona y artery bypass graft
Confidence intervals for the Secondary Endpoints we e not adjusted for multiple comparisons
* Atorvastatin 80 mg: atorvastatin 10 mg
† Seconda y endpoints not included in prima y endpoint
‡ Component of other seconda y endpoints

Of the events that comprised the primary efficacy endpoint, t eatment w th atorvastatin calcium tablets 80 mg/day significantly educed the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated ca diac arrest (Table 5). Of the p edefined secondary endpoints, t eatment with atorvastatin calcium tablets 80 mg/day significantly educed the rate of corona y evascularization, angina, and hospitalization for heart failu e, but not peripheral vascular disease. The eduction in the rate of CHF with hospitalization was only observed in the 8% of patients w th a prior history of CHF.

The e was no significant difference between the treatment g oups for all-cause mortality (Table 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal st oke, were numerically smaller in the atorvastatin calcium tablets 80 mg g oup than in the atorvastatin calcium tablets 10 mg t eatment group. The proportions of subjects who experienced nonca diovascular death were numerically la ger in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg t eatment group.

In the Inc emental Dec ease in Endpoints Th ough Aggressive Lipid Lowering Study (IDEAL), t eatment w th atorvastatin calcium tablets 80 mg/day was compared to treatment with simvastatin 20-40 mg/day in 8,888 subjects up to 80 years of age w th a history of CHD to assess whether reduction in CV risk could be achieved. Patients we e mainly male (81%), white (99%) w th 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 w th no run-in period, subjects we e 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 t eatment w th 80 mg of atorvastatin calcium tablets and 105, 179, 142, 47, and 132 mg/dL during t eatment w th 20-40 mg of simvastatin.

The e was no significant difference between the treatment groups for the primary endpoint, the rate of first major co onary event (fatal CHD, non-fatal MI, and resuscitated ca diac ar est): 411 (9.3%) in the atorvastatin calcium tablets 80 mg/day g oup vs. 463 (10 4%) in the simvastatin 20-40 mg/day g oup, HR 0 89, 95% CI (0.78, 1 01), p=0 07.

The e we e no significant diffe ences between the treatment groups for all-cause mortality: 366 (8 2%) in the atorvastatin calcium tablets 80 mg/day g oup vs. 374 (8 4%) in the simvastatin 20-40 mg/day group. The p oportions of subjects who experienced CV or non-CV death were similar for the atorvastatin calcium tablets 80 mg g oup and the simvastatin 20-40 mg group.

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

Atorvastatin calcium tablets educes total-C, LDL-C, VLDL-C, apo B, and TG, and inc eases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic esponse is seen within 2 weeks, and maximum esponse is usually achieved within 4 weeks and maintained during ch onic therapy.

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

In two multicenter, placebo-cont olled, dose- esponse studies in patients with hyperlipidemia, atorvastatin calcium tablets given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG (Pooled esults a e provided in Table 6).

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

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

* Results a e pooled f om 2 dose-response studies.

In patients w th *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled f om 24 cont olled trials, the median (25th and 75th percentile) percent changes f om baseline in HDL-C for atorvastatin calcium tablets 10, 20, 40, and 80 mg were 6 4 (-1.4, 14), 8.7 (0, 17), 7 8 (0, 16), and 5.1 (-2.7, 15), espectively. Additionally, analysis of the pooled data demonstrated consistent and significant dec eases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients w th hyperlipidemia, atorvastatin calcium tablets was compared to other statins. After randomization, patients we e treated for 16 weeks with e ther atorvastatin calcium tablets 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 Calcium Tablets 10 mg	707	-27*	-36*	-28*	-17*	+7	-37*
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff †		-9.2, -6 5	-10.7, -7.1	-10 0, -6.5	-15.2, -7.1	-1.7, 2 0	-11.1, -7.1
Study 2							
Atorvastatin Calcium Tablets 10 mg	222	-25‡	-35‡	-27‡	-17‡	+6	-36‡
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff †		-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 Calcium Tablets 10 mg	132	-29§	-37§	-34§	-23§	+7	-39§
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff †		-8.7, -2.7	-10.1, -2.6	-8 0, -1.1	-15.1, -0.7	-4.3, 3 9	-9 6, -1 9

* Significantly different from lovastatin, ANCOVA, p ≤0 05
† A negative value for the 95% CI for the difference between treatments favors atorvastatin calcium tablets for all except HDL-C, for which a positive value favors atorvastatin calcium tablets. If the range does not include 0, this indicates a statistically significant difference.
‡ Significantly different from pravastatin, ANCOVA, p ≤0.05
§ Significantly different from simvastatin, ANCOVA, p ≤0.05

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

14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

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

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

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

14.4 Dysbetalipoproteinemia *(Fredrickson* Type III)

The esults of an open-label c ossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipop oteinemia *(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 Calcium Tablets 10 mg	Atorvastatin Calcium Tablets 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 concur ent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium tablets. The mean LDL-C reduction in this study was 18%. Twenty-five patients w th a reduction in LDL-C had a mean esponse of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The emaining 3 eceptor-negative patients had a mean LDL-C eduction 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 10-17 years of age (mean age 14.1 years) with hete ozygous familial hypercholesterolemia (FH) or seve e hypercholeste olemia, we e randomized to atorvastatin calcium tablets (n=140) or placebo (n=47) for 26 weeks and then all eceived atorvastatin calcium tablets for 26 weeks. Inclusion in the study requi ed 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 p ematu e cardiovascular disease in a first or second-deg ee relative. The mean baseline LDL-C value was 218 6 mg/dL (range: 138 5–385.0 mg/dL) in the atorvastatin calcium tablets g oup compared to 230 0 mg/dL (range: 160.0–324 5 mg/dL) in the placebo group. The dosage of atorvastatin calcium tablets (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium tablets-t eated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

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

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

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

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 0–242 0 mg/dL) in the atorvastatin calcium tablets group compa ed to 228 5 mg/dL (range: 152 0–385 0 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in child en. The long-term efficacy of atorvastatin calcium tablets therapy in childhood to educe morbidity and mortality in adu thood has not been established.

15 REFERENCES

[1] National Choleste ol 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 supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40, and 80 mg atorvastatin.

10 mg tablets: debossed w th "1" on one side and plain on the other.
NDC 62175-890-46 bottles of 90
NDC 62175-890-43 bottles of 1000
NDC 62175-890-45 bottles of 5000

20 mg tablets: debossed w th "2" on one side and plain on the other.
NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed w th "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed w th "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

Storage

Store at controlled oom temperature 20 - 25°C (68 - 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients taking Atorvastatin Calcium Tablets should be advised that cholesterol is a chronic condition and they should adhe e to their medication along w th their National Cholesterol Education P ogram (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 eport promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing Atorvastatin Calcium Tablets. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, w th their hea thcare professional.

17.2 Liver Enzymes

It is ecommended that liver enzyme tests be performed before the initiation Atorvastatin Calcium Tablets and if signs or symptoms of liver inju y occur. All patients treated with Atorvastatin Calcium Tablets should be advised to report promptly any symptoms that may indicate liver inju y, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using Atorvastatin Calcium Tablets. Discuss future pregnancy plans w th your patients, and discuss when to stop Atorvastatin Calcium Tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking Atorvastatin Calcium Tablets and call their healthca e professional.

17.4 Breastfeeding

Women who a e breastfeeding should be advised to not use Atorvastatin Calcium Tablets. Patients who have a lipid diso der and are b eastfeeding, should be advised to discuss the options w th their hea thcare professional.

Rx Only

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Princeton, NJ 08540, USA

CIA75883C
Rev. 3E 11/2012

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 is 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. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking Atorvastatin Calcium Tablets. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual.
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

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

The following additional side effects have been reported with Atorvastatin Calcium Tablets: tiredness, tendon problems, memory loss, and confusion.

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

These are not all the side effects of Atorvastatin Calcium Tablets. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets?

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

General Information About Atorvastatin Calcium Tablets

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

This leaflet summarizes the most important information about Atorvastatin Calcium Tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Atorvastatin Calcium Tablets that is written for health professionals. Or you can go to www.kremersurban.com.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

Rx Only

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

CIA75884B Rev. 2E 11/2012

PATIENT INFORMATION
Atorvastatin Calcium Tablets

CIA75884B Rev. 2E 11/2012

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

If you have any questions about Atorvastatin Calcium Tablets, ask your doctor or pharmacist.

What is Atorvastatin Calcium Tablets?

Atorvastatin Calcium Tablets 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 is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

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

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

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

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

Atorvastatin Calcium Tablets start to work in about 2 weeks.

What is Cholesterol?

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

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take Atorvastatin Calcium Tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin Calcium Tablets may harm your unborn baby. If you get pregnant, stop taking Atorvastatin Calcium Tablets and call your doctor right away.
- are breast feeding. Atorvastatin Calcium Tablets can pass into your breast milk and may harm your baby.
- 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 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

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

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

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

How Should I Take Atorvastatin Calcium Tablets?

- Take Atorvastatin Calcium Tablets exactly as prescribed by your doctor. Do not change your dose or stop Atorvastatin Calcium Tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with Atorvastatin Calcium Tablets. Your dose of Atorvastatin Calcium Tablets may be changed based on these blood test results.
- Take Atorvastatin Calcium Tablets each day at any time of day at about the same time each day. Atorvastatin Calcium Tablets can be taken with or without food.
  Don't break Atorvastatin Calcium Tablets before taking.
- Your doctor should start you on a low-fat diet before giving you Atorvastatin Calcium Tablets. Stay on this low-fat diet when you take Atorvastatin Calcium Tablets.
- If you miss a dose of Atorvastatin Calcium Tablets, take it as soon as you remember. Do not take Atorvastatin Calcium Tablets if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of Atorvastatin Calcium Tablets at the same time.
- If you take too much Atorvastatin Calcium Tablets or overdose, call your doctor or

Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

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

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  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

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- nausea and vomiting.
- passing brown or dark-colored urine.
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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. Or you can go to www.kremersurban.com.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

Rx Only

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

CIA75884B Rev. 2E 11/2012

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
11/30/2012

CHI-ANN Y WU
11/30/2012
For Wm. Peter Rickman

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

ANDA Number: 091624 Date of Submission: April 24, 2012 and March 26, 2012

Applicant's Name: KUDCO Ireland Limited

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

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. Electronic submission.

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

Acceptable in final print as submitted in the April 24, 2012 amendment.

Professional Package Insert Labeling:
Acceptable in final print as submitted in the April 24, 2012 amendment.

Patient Information Sheet:
Acceptable in final print as submitted in the March 26, 2012 amend met.

SPL: Data elements acceptable in 3/4/2010 e-submission

Revisions needed before full approval: Yes

INSERT:

FULL PRESCRIBING INFORMATION: CONTENTS:

- Revise subheadings 2.1 and 2.2 to read as follows:

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)
2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

- Revise subheadings 14.2 and 14.3 to read as follows:

  14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)
  14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

- Revise the subheading 7.1 to read "7.1 Strong Inhibitors of CYP 3A4"

- Delete the following subtitles locate under subheading 7.1
  Clarithromycin
  Combination of Protease Inhibitors
  Itraconazole

The above post-approval comments will be communicated to the firm to Kurt Zimmer at 812-523-5539 (phone) and by email at kurt.zimmer@ucb.com, once the review has been signed off.

Basis of Approval

Was this approval based upon a petition? No

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

NDA Number: 020702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

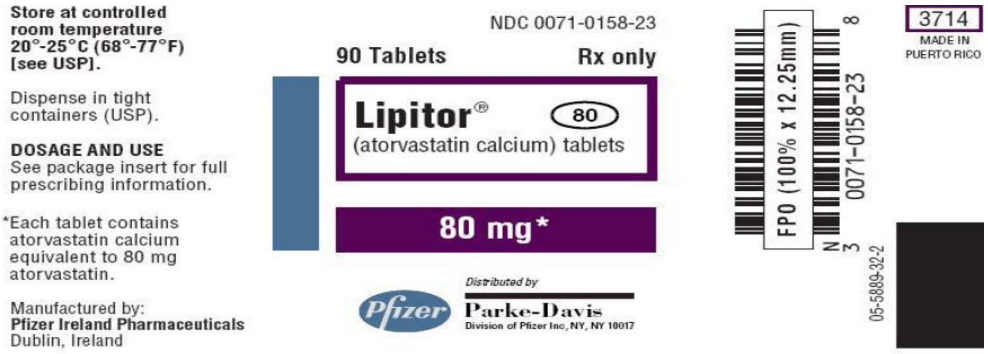
Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST: None

FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 4/27/2010 and 4/16/2012 in DARRTS.

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

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



2. **MEDWATCH**: (checked 5/11/2012)

No report of safety labeling changes since last labeling was approved February 2012.

3. **PATENTS/EXCLUSIVITIES**: (Checked 5/11/2012)

BASIS OF APPROVAL: ANDA 020702

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5686104	Nov 11, 2014 PED May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	None
5969156	Jul 8, 2016 PED Jan 8, 2017	—		IV	None
6126971	Jan 19, 2013 PED July 19, 2013	—		IV	None

Pfizer Inc. sued Kudco and Kremers Urban for the '156 patent. Case 1:09-cv-00924-UNA

Patent Amendment update 0009 submitted November 22, 2011

In the amendment dated 11/22/11, the firm notified the Agency of a Settlement Agreement that was reached between Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner-Lambert Company LLC, and the common parties of Kremers Urban LLC., Kudco Ireland LTD., and Kremers Urban Pharmaceuticals Inc.

> WHEREAS, the Parties seek to resolve the Action without further litigation with respect to U.S. Patent No. 5,969,156 and its Re-examination Certificate (together, "the '156 Patent");

Additionally, a copy of the Order of Dismissal is included in this amendment dated 11/22/2011.

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

		There is no unexpired exclusivity for this product.	None

4. **INACTIVE INGREDIENTS:** [2.3.P.1-original submission]

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: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

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

Schwarz Pharma Manufacturing, Inc.
1101 C Avenue West
Seymour, Indiana 74274

6. 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, round, film-coated tablets, debossed with “1” on one side and plain on the other.

20 mg: white, round, film-coated tablets, debossed with “2” on one side and plain on the other.

40 mg: white, round, film-coated tablets, debossed with “40” on one side and plain on the other.

80 mg: white, round, film-coated tablets, debossed with “80” on one side and plain on the other.

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

Bottle packs

Strength	Bottle Size	Packaging Material Description	Manufacturer/DMF
10 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

Table 34 – Container Configuration (continued)

20 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
40 mg	Bottles of 90	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

80 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE (b) (4)	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:

USP: Not USP (checked 5/11/12)
RLD: store at CRT 20-25°C (68-77°F) [see USP].
ANDA label: Same

9. DISPENSING STATEMENTS COMPARISON:

RLD: Dispense in tight containers (USP)
ANDA: Same as.

10. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is deficient on 1/12/2010
Updated BIO review 11/30/2011- overall review result Inadequate pending the outcome of the OSI inspection for the clinical site of (b) (4)

11. SCORING:

RLD: Not scored
ANDA: Not scored

12. PACKAGE CONFIGURATION:

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

ANDA: 10 mg and 20 mg= bottles of 90s, 1000s and 5000s (original submission)
40 mg and 80 mg= bottles of 90s, 500s and 2500s

In the amendment dated March 26, 2012, the firm did not submit final printed container labels for the 10 mg and 20 mg bottles of 1000's package configurations.

ANDA: 10 mg and 20 mg= bottles of 90s, and 5000s were submitted along with what was previously submitted for the 40 mg and 80 mg strengths.

Container label colors= 80 mg= orange, 40 mg= green, 20 mg= red, 10 mg= blue

Comments from firm: Final Container Labels Amendment dated April 24, 2012

Although the 1000-count bottles for the 10 mg and 20 mg strengths have been submitted in the application, the applicant does not intend to market these bottle sizes at the time of launch. In the event these bottle sizes are marketed at a later date, the package insert will be updated accordingly.

13. Kremers Urban is a member of the UCB Group of Companies; note that "UCB" is the contact in the ADVERSE REACTIONS section of the HIGHLIGHTS

14. PATIENT INFORMATION SHEETS:

Comment from last labeling review:

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

Response (AF dated 3/4/10)

KUDCO Ireland, Ltd. will ensure that the patient information sheet is available in sufficient numbers to permit the authorized dispenser to provide one sheet to each patient receiving a prescription of at least thirty tablets.

15. REMS:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

16. SPL: Data elements acceptable in 3/4/2010 e-submission

Cover letter dated 4/24/12
The applicant commits to submitting labeling in SPL format within 14 business days of approval of the application.

Date of Review: May 11, 2012 Date of Submission: April 24, 2012 and March 26, 2012

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

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Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**890**-46 90 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

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Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**890**-45 5000 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75886A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**891**-46 90 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75887A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**891**-45 5000 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75888A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**892**-46 90 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75889A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**892**-41 500 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

N 3 62175 89241 6

Lot No.
Exp.Date

CIA75890A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**892**-44 2500 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75891A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**897**-46 90 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

CIA75892A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**897**-41 500 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

CIA75893A
Rev. 1E

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban Pharmaceuticals Inc.
Princeton, NJ 08540, USA

NDC 62175-**897**-44

2500 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

3 62175 89744 2

Lot No.
Exp. Date

CIA75894A
Rev. 1E

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
05/14/2012

CHI-ANN Y WU
05/14/2012
For Wm. Peter Rickman

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

ANDA Number: 091624 Date of Submission: March 26, 2012

Applicant's Name: KUDCO Ireland Limited

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

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Labeling Deficiencies:

A. CONTAINER:

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

B. INSERT:

1. HIGHLIGHTS, WARNINGS AND PRECAUTIONS: second paragraph, revise the second sentence to read "Check liver enzyme tests before initiating therapy……"

2. FULL PRESCRIBING INFORMATION: CONTENTS*
   i. Revise subtitle 2.1 and 2.2 to read as follows:

      2.1 Hyperlipidemia
      2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

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

   iii. Revise subtitles 14.1, 14.2 and 14.3 to read as follows:

      14.1 Prevention of Cardiovascular Disease
      14.2 Hyperlipidemia and Mixed Dyslipidemia
      14.3 Hypertriglyceridemia

3. FULL PRESCRIBING INFORMATION:

   i. GENERAL COMMENT- Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.

   ii. 4 CONTRAINDICATIONS
      a. Revise 4.1 to read as follows.

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

      b. Revise 4.2 to read as follows.

         4.2 Hypersensitivity to any component of this medication

   iii. 16 HOW SUPPLIED
      Add "Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin."

Submit revised insert labeling electronically.

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

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

Basis of Approval

Was this approval based upon a petition? No

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

NDA Number: 020702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

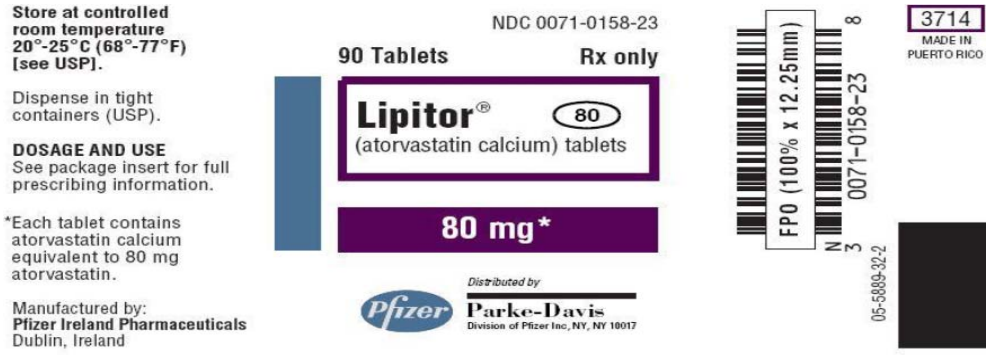
Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST: None

FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 4/27/2010 in DARRTS.

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

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



2. MEDWATCH: (checked 4/13/2012)

No report of safety labeling changes since last labeling was approved February 2012.

3. PATENTS/EXCLUSIVITIES: (Checked 4/13/2012)

BASIS OF APPROVAL: ANDA 020702

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5686104	Nov 11, 2014 PED May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	IV	None
5969156	Jul 8, 2016 PED Jan 8, 2017	—		IV	None
6126971	Jan 19, 2013 PED July 19, 2013	—		IV	None

Pfizer Inc. sued Kudco and Kremers Urban for the '156 patent. Case 1:09-cv-00924-UNA

Patent Amendment update 0009 submitted November 22, 2011

In the amendment dated 11/22/11, the firm notified the Agency of a Settlement Agreement that was reached between Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner-Lambert Company LLC, and the common parties of Kremers Urban LLC., Kudco Ireland LTD., and Kremers Urban Pharmaceuticals Inc.

> WHEREAS, the Parties seek to resolve the Action without further litigation with respect to U.S. Patent No. 5,969,156 and its Re-examination Certificate (together, "the '156 Patent");

Additionally, a copy of the Order of Dismissal is included in this amendment dated 11/22/2011.

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
		There is no unexpired exclusivity for this product.	None

4. INACTIVE INGREDIENTS: [2.3.P.1-original submission]

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: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

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

Schwarz Pharma Manufacturing, Inc.
1101 C Avenue West
Seymour, Indiana 74274

6. 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, round, film-coated tablets, debossed with "1" on one side and plain on the other.

20 mg: white, round, film-coated tablets, debossed with "2" on one side and plain on the other.

40 mg: white, round, film-coated tablets, debossed with "40" on one side and plain on the other.

80 mg: white, round, film-coated tablets, debossed with "80" on one side and plain on the other.

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

Bottle packs

Strength	Bottle Size	Packaging Material Description	Manufacturer/DMF
10 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

Table 34 – Container Configuration (continued)

20 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
40 mg	Bottles of 90	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
80 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE (b)	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON:

USP: Not USP (checked 4/13/12)
RLD: store at CRT 20-25°C (68-77°F) [see USP].

ANDA label: Same

9. DISPENSING STATEMENTS COMPARISON:

RLD: Dispense in tight containers (USP)
ANDA: Same as.

10. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is deficient on 1/12/2010
Updated BIO review 11/30/2011- overall review result Inadequate pending the outcome of the OSI inspection for the clinical site of (b) (4)

11. SCORING:

RLD: Not scored
ANDA: Not scored

12. PACKAGE CONFIGURATION:

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

ANDA: 10 mg and 20 mg= bottles of 90s, 1000s and 5000s (original submission)
40 mg and 80 mg= bottles of 90s, 500s and 2500s

In the amendment dated March 26, 2012, the firm did not submit final printed container labels for the 10 mg and 20 mg bottles of 1000's package configurations.

ANDA: 10 mg and 20 mg= bottles of 90s, and 5000s were submitted along with what was previously submitted for the 40 mg and 80 mg strengths.

Container label colors= 80 mg= orange, 40 mg= green, 20 mg= red, 10 mg= blue

13. Kremers Urban is a member of the UCB Group of Companies; note that "UCB" is the contact in the ADVERSE REACTIONS section of the HIGHLIGHTS

14. PATIENT INFORMATION SHEETS:

Comment from last labeling review:

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

Response (AF dated 3/4/10)

KUDCO Ireland, Ltd. will ensure that the patient information sheet is available in sufficient numbers to permit the authorized dispenser to provide one sheet to each patient receiving a prescription of at least thirty tablets.

15. REMS:
REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

16. SPL: Data elements acceptable in 3/4/2010 e-submission

Date of Review: April 13, 2012 Date of Submission: March 26, 2012

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

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ANDA 091624 DR#2

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

/s/

BETTY B TURNER
04/16/2012

CHI-ANN Y WU
04/16/2012
For Wm. Peter Rickman

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

ANDA Number: 091624 Date of Submission: March 4, 2010

Applicant's Name: KUDCO Ireland Limited

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

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BASIS OF TENTATIVE APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? No. Tentative approval only- draft labels and labeling.

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

Draft labels acceptable in 3/4/2010 e-submission

Professional Package Insert Labeling: Draft labeling acceptable in 3/4/1020 e-submission

Patient Information Sheet: Draft labeling acceptable in 3/4/1020 e-submission

SPL: Data elements acceptable in 3/4/2010 e-submission

Revisions needed before full approval: Yes

PACKAGE INSERT:

1. HIGHLIGHTS, INDICATIONS AND USAGE: third bullet, correct the spelling of “non-fatal”

2. FULL PRESCRIBING INFORMATION: CONTENTS: correct the spelling of “DOSAGE AND ADMINISTRATION”

3. FULL PRESCRIBING INFORMATION: General comment-

   Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.

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 PLR format.

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

Pfizer Inc. sued Kudco and Kremers Urban for the ‘156 patent. Case 1:09-cv-00924-UNA

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

[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: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

[2.3.P.1-original submission]

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

Schwarz Pharma Manufacturing, Inc.
1101 C Avenue West
Seymour, Indiana 74274

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, round, film-coated tablets, debossed with “1” on one side and plain on the other.

20 mg: white, round, film-coated tablets, debossed with “2” on one side and plain on the other.

40 mg: white, round, film-coated tablets, debossed with “40” on one side and plain on the other.

80 mg: white, round, film-coated tablets, debossed with “80” on one side and plain on the other.

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

Bottle packs

Strength	Bottle Size	Packaging Material Description	Manufacturer/DMF
10 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

Table 34 – Container Configuration (continued)

20 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccan (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
40 mg	Bottles of 90	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
80 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE (b)	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA label: Same

8. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Same as.

9. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is deficient on 1/12/2010

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

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

ANDA: 10 mg and 20 mg= bottles of 90s, 1000s and 5000s
40 mg and 80 mg= bottles of 90s, 500s and 2500s

Container label colors= 80 mg= orange, 40 mg= green, 20 mg= red, 10 mg= blue

12. Kremers Urban is a member of the UCB Group of Companies, note that "UCB" is the contact in the ADVERSE REACTIONS section of the HIGHLIGHTS

13. PATIENT INFORMATION SHEETS

Comment from last labeling review:

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

Response (AF dated 3/4/10)

KUDCO Ireland, Ltd. will ensure that the patient information sheet is available in sufficient numbers to permit the authorized dispenser to provide one sheet to each patient receiving a prescription of at least thirty tablets.

Date of Review: April 27, 2010 Date of Submission: March 4, 2010

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LL
Princeton, NJ 08540, USA

NDC 62175-**890**-45 5000 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010307
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

(b) (4)

Distributed by:
Kremers Urban, LL
Princeton, NJ 08540

NDC 62175-**890**-43 1000 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010306
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LL
Princeton, NJ 08540, USA

NDC 62175-**890**-46

90 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp. Date

4010305
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**890**-45 5000 Tablets

Atorvastatin Calcium Tablets

10 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010307
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**891**-43 1000 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

N 3 62175 89143 3

Lot No.
Exp.Date

4010309
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LL
Princeton, NJ 08540, USA

NDC 62175-**891**-46

90 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp. Date

4010308
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**891**-45 5000 Tablets

Atorvastatin Calcium Tablets

20 mg*

Rx Only

Pharmacist: please dispense with patient package insert

N 3 62175 89145 7

Lot No.
Exp.Date

4010350
Rev. 1E

Unvarnished Area

NDC 62175-**892**-41 500 Tablets

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LL
Princeton, NJ 08540

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010352
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**892**-46 90 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

4010351
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**892**-44 2500 Tablets

Atorvastatin Calcium Tablets

40 mg*

Rx Only

Pharmacist: please dispense with patient package insert

N 3 62175 89244 7

Lot No.
Exp.Date

4010353
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540

NDC 62175-**897**-41 500 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010355
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
(b) (4)
Kremers Urban, LLC
Princeton, NJ 08540, USA

NDC 62175-**897**-46 90 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010354
Rev. 1E

Unvarnished Area

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP].

Dispense in tight containers (USP).

USUAL DOSAGE
See package insert for full prescribing information.

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

Distributed by:
Kremers Urban, LLC
(b) (4)
Princeton, NJ 08540, USA

NDC 62175-**897**-44 2500 Tablets

Atorvastatin Calcium Tablets

80 mg*

Rx Only

Pharmacist: please dispense with patient package insert

Lot No.
Exp.Date

4010356
Rev. 1E

Unvarnished Area

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND 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
04/27/2010

JOHN F GRACE
04/27/2010
for Wm Peter Rickman

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

ANDA Number: 091624 Date of Submission: July 15, 2009

Applicant's Name: Kudco Ireland Ltd.

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

---

Labeling Deficiencies:

1. CONTAINER (10 mg and 20 mg= bottles of 90s, 1000s and 5000s
   40 mg and 80 mg= bottles of 90s, 500s and 2500s):

   a. Revise “DOSAGE AND USE” to “USUAL DOSAGE”.

   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

   Due to changes in the insert labeling for the reference listed drug, Lipitor (20702/S-056, approved 6/17/2009), please revise your labeling to be in accord with RLD. The RLD labeling may be accessed at the Drugs@FDA website.

3. PATIENT INFORMATION SHEET:

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

Submit labels and labeling electronically.

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

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

BASIS OF APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? No

Container Labels (all strengths in bottles of 90s and (b) (4)
No, see comments above.

Professional Package Insert Labeling: No

Patient Information Sheet: No

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

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

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-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 PLR format.

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

Pfizer Inc. sued Kudco and Kremers Urban for the ‘156 patent. Case 1:09-cv-00924-UNA

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

[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: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide.

[2.3.P.1-original submission]

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

Schwarz Pharma Manufacturing, Inc.
1101 C Avenue West
Seymour, Indiana 74274

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, round, film-coated tablets, debossed with "1" on one side and plain on the other.

20 mg: white, round, film-coated tablets, debossed with "2" on one side and plain on the other.

40 mg: white, round, film-coated tablets, debossed with "40" on one side and plain on the other.

80 mg: white, round, film-coated tablets, debossed with "80" on one side and plain on the other.

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

Bottle packs

Strength	Bottle Size	Packaging Material Description	Manufacturer/DMF
10 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

Table 34 – Container Configuration (continued)

20 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 1000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 5000	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
40 mg	Bottles of 90	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
80 mg	Bottles of 90	(b) (4) HDPE Bottle	(b) (4)
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 500	(b) (4) HDPE Bottle	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	
	Bottles of 2500	(b) (4) HDPE (b) (4)	
		(b) (4)	
		(b) (4) Desiccant (b) (4)	

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

ANDA label: Same

8. DISPENSING STATEMENTS COMPARISON

RLD: Dispense in tight containers (USP)
ANDA: Same as.

9. BIOAVAILABILITY/BIOEQUIVALENCE: BIO is deficient on 1/12/2010

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

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

ANDA: 10 mg and 20 mg= bottles of 90s, 1000s and 5000s
40 mg and 80 mg= bottles of 90s, 500s and 2500s

Container label colors= 80 mg= orange, 40 mg= green, 20 mg= red, 10 mg= blue

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Date of Review: May 11, 2009 Date of Submission: December 30, 2008

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND 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
01/14/2010

JOHN F GRACE
01/20/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

CHEMISTRY REVIEWS

ANDA 091624

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

KUDCO Ireland Limited

Haitao Li, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

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B. Description of How the Drug Product is intended to be used 7

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Chemistry Assessment **8**

III. List of Deficiencies to Be Communicated 109

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 109

Chemistry Review Data Sheet

1. ANDA 091624

2. REVIEW #: 6

3. REVIEW DATE: December 12, 2012

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	July 15, 2009
Amendment	January 12, 2011
Amendment	August 18, 2011
Amendment	May 9, 2012
Amendment	June 4, 2012
Amendment	September 7, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	November 21, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	KUDCO Ireland Limited
Address:	Shannon Industrial Estate Shannon, County State Republic of Ireland
U.S. Representative:	Elaine Siefert, Director Regulatory Affairs Kremers Urban Pharmaceuticals Inc. 1101 C Ave W Seymour IN 47274
Telephone:	(812) 523-5539
Fax:	(812) 523-6889

8. DRUG PRODUCT NAME: Proprietary Name: NA
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The firm provided both paragraph III and IV patent certification.

10. PHARMACOL. CATEGORY: Lipid Lowering Agent. Prevention of Cardiovascular Disease and Hypercholesterolemia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 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
(b) (4)	II			1	Adequate	December 17, 2012	by H. Li
(b) (4)	III			4	N/A		
	III			4			
	III				N/A		
	III				N/A		
	III			4	N/A		
(b) (4)	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
(b) (4)	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
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (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	11/21/2012	
Methods Validation	Not Applicable		
Labeling	TA	5/14/2012	TURNER, BETTY B
Bioequivalence	Adequate	5/22/2012	RAMSON, TERESA V
EA	Adequate	5/25/2010	H. Li
Radiopharmaceutical	Not Applicable		

Pharm/Tox	Not Applicable		

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:
Per DARRTS document dated 5/23/2012

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

CMC is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

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.
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide. All ingredients in the DP are (b) (4).
The manufacturing process is a (b) (4). The DS is about (b) (4) of the dosage form. The PSD of the DS may be critical since this DS is "low soluble".

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

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

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their (b) (4)

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: 0.10%, QT: 0.15%. Based on ICH Q3B, for DP: IT: 0.2%, QT: (b) (4) %.

DS is compendial now. There is a PF 37(5) In-Process Revision for Atorvastatin Calcium drug product.

B. Description of How the Drug Product is Intended to be Used
The DP is intended for long term use.

Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: debossed with "1" on one side and plain on the other.
NDC 62175-890-46 bottles of 90
NDC 62175-890-43 bottles of 1000
NDC 62175-890-45 bottles of 5000

20 mg tablets: debossed with "2" on one side and plain on the other.
NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed with "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed with "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

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

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.

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
12/23/2012

SARAH K NGUYEN on behalf of LEIGH A SEARS
12/26/2012

LAXMA R NAGAVELLI
12/26/2012

VILAYAT A SAYEED
12/28/2012

ANDA 091624

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

KUDCO Ireland Limited

Haitao Li, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

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Chemistry Assessment **8**

III. List of Deficiencies to Be Communicated 109

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 109

Chemistry Review Data Sheet

1. ANDA 091624

2. REVIEW #: 5

3. REVIEW DATE: September 22, 2012

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	July 15, 2009
Amendment	January 12, 2011
Amendment	August 18, 2011
Amendment	May 9, 2012
Amendment	June 4, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	September 7, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	KUDCO Ireland Limited
Address:	Shannon Industrial Estate Shannon, County State Republic of Ireland
U.S. Representative:	Elaine Siefert, Director Regulatory Affairs Kremers Urban LLC 1101 C Ave W Seymour IN 47274
Telephone:	(812) 523-5539
Fax:	(812) 523-6889

8. DRUG PRODUCT NAME: Proprietary Name: NA
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The firm provided both paragraph III and IV patent certification.

10. PHARMACOL. CATEGORY: Lipid Lowering Agent. Prevention of Cardiovascular Disease and Hypercholesterolemia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 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	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate with IR	September 28, 2012	by H. Li
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	III			4			
	III				N/A		
	III				N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		

Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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6 – DMF not available
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	4/18/2012	
Methods Validation	Not Applicable		
Labeling	TA	5/14/2012	TURNER, BETTY B
Bioequivalence	Adequate	5/22/2012	RAMSON, TERESA V
EA	Adequate	5/25/2010	H. Li
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Not Applicable		

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:
Per DARRTS document dated 5/23/2012

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

CMC deficiencies – Minor Deficiency (Review #5)

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

N/A

II. Summary of Chemistry Assessments

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

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.
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide. All ingredients in the DP are (b) (4).
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Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

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

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their (b) (4)

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NDC 62175-890-43 bottles of 1000
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NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed with "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed with "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

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

C. Basis for Approvability or Not-Approval Recommendation
The application is not approvable due to CMC related deficiencies.

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

/s/

HAITAO LI
10/24/2012

LEIGH A SEARS
10/24/2012

MOHAMMED K AHMED
10/24/2012

ANDA 091624

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

KUDCO Ireland Limited

Haitao Li, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

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36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 109

Chemistry Review Data Sheet

1. ANDA 091624

2. REVIEW #: 4

3. REVIEW DATE: June 5, 2012

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	July 15, 2009
Amendment	January 12, 2011
Amendment	August 18, 2011
Amendment	May 9, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 4, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	KUDCO Ireland Limited
Address:	Shannon Industrial Estate Shannon, County State Republic of Ireland
U.S. Representative:	Elaine Siefert, Director Regulatory Affairs Kremers Urban LLC 1101 C Ave W Seymour IN 47274
Telephone:	(812) 523-5539
Fax:	(812) 523-6889

8. DRUG PRODUCT NAME: Proprietary Name: NA
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The firm provided both paragraph III and IV patent certification.

10. PHARMACOL. CATEGORY: Lipid Lowering Agent. Prevention of Cardiovascular Disease and Hypercholesterolemia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 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
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate with IR	May 29,2012	by H. Li
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	III			4			
	III				N/A		
	III				N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		

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

[2] Adequate, Inadequate, or N/A (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	4/18/2012	
Methods Validation	Not Applicable		
Labeling	TA	5/14/2012	TURNER, BETTY B
Bioequivalence	Adequate	5/22/2012	RAMSON, TERESA V
EA	Adequate	5/25/2010	H. Li
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Not Applicable		

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:
Per DARRTS document dated 5/23/2012

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

CMC deficiencies NA-Minor (Review #4)

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

N/A

II. Summary of Chemistry Assessments

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

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.
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide. All ingredients in the DP are (b) (4).
The manufacturing process is a (b) (4). The DS is about (b) (4) of the dosage form. The PSD of the DS may be critical since this DS is "low soluble".

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

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

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their (b) (4)

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: 0.10%, QT: 0.15%. Based on ICH Q3B, for DP: IT: 0.2%, QT: (b) (4) %.

DS is compendial now. There is a PF 37(5) In-Process Revision for Atorvastatin Calcium drug product.

B. Description of How the Drug Product is Intended to be Used
The DP is intended for long term use.

Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: debossed with "1" on one side and plain on the other.
NDC 62175-890-46 bottles of 90
NDC 62175-890-43 bottles of 1000
NDC 62175-890-45 bottles of 5000

20 mg tablets: debossed with "2" on one side and plain on the other.
NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed with "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed with "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

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

C. Basis for Approvability or Not-Approval Recommendation
The application is not approvable due to CMC related deficiencies. The firm modified their assay method to accommodate low stability data.

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

/s/

HAITAO LI
06/08/2012

LEIGH A SEARS
06/08/2012

LAXMA R NAGAVELLI
06/08/2012

ANDA 091624

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

KUDCO Ireland Limited

Haitao Li, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

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Chemistry Assessment **8**

III. List of Deficiencies to Be Communicated 109

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 109

Chemistry Review Data Sheet

1. ANDA 091624

2. REVIEW #: 3

3. REVIEW DATE: May 23, 2012

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	July 15, 2009
Amendment	January 12, 2011
Amendment	August 18, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	May 9, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	KUDCO Ireland Limited
Address:	Shannon Industrial Estate Shannon, County State Republic of Ireland
U.S. Representative:	Elaine Siefert, Director Regulatory Affairs Kremers Urban LLC 1101 C Ave W Seymour IN 47274
Telephone:	(812) 523-5539
Fax:	(812) 523-6889

8. DRUG PRODUCT NAME: Proprietary Name: NA
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The firm provided both paragraph III and IV patent certification.

10. PHARMACOL. CATEGORY: Lipid Lowering Agent. Prevention of Cardiovascular Disease and Hypercholesterolemia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 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
(b) (4)	II	(b) (4)		1	Adequate with IR	May 29,2012	by H. Li
(b) (4)	III	(b) (4)		4	N/A		
	III			4			
	III				N/A		
	III				N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)		4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)		4	N/A		

[1] Action codes for DMF Table: 1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (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	4/18/2012	
Methods Validation	Not Applicable		
Labeling	TA	5/14/2012	TURNER, BETTY B
Bioequivalence	Deficient	5/22/2012	RAMSON, TERESA V
EA	Adequate	5/25/2010	H. Li
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Not Applicable		

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:
Per DARRTS document dated 5/23/2012

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

CMC deficiencies NA-Minor (Review #3)

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

N/A

II. Summary of Chemistry Assessments

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

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.
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide. All ingredients in the DP are (b) (4).
The manufacturing process is a (b) (4). The DS is about (b) (4) of the dosage form. The PSD of the DS may be critical since this DS is "low soluble".

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

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

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their (b) (4)

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: 0.10%, QT: 0.15%. Based on ICH Q3B, for DP: IT: 0.2%, QT: (b) (4) %.

DS is compendial now. There is a PF 37(5) In-Process Revision for Atorvastatin Calcium drug product.

B. Description of How the Drug Product is Intended to be Used
The DP is intended for long term use.

Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: debossed with "1" on one side and plain on the other.
NDC 62175-890-46 bottles of 90
NDC 62175-890-43 bottles of 1000
NDC 62175-890-45 bottles of 5000

20 mg tablets: debossed with "2" on one side and plain on the other.
NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed with "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed with "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

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

C. Basis for Approvability or Not-Approval Recommendation
The application is not approvable due to CMC related deficiencies. The firm modified their assay method to accommodate low stability data.

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
05/31/2012

LEIGH A SEARS
05/31/2012

LAXMA R NAGAVELLI
05/31/2012

ANDA 091624

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

KUDCO Ireland Limited

Haitao Li, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

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B. Description of How the Drug Product is intended to be used 7

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Chemistry Assessment **8**

III. List of Deficiencies to Be Communicated 109

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT 109

Chemistry Review Data Sheet

1. ANDA 091624

2. REVIEW #: 2

3. REVIEW DATE: March 21, 2012

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	July 15, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	January 12, 2011
Amendment	August 18, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	KUDCO Ireland Limited
Address:	Shannon Industrial Estate Shannon, County State Republic of Ireland
U.S. Representative:	Elaine Siefert, Director Regulatory Affairs Kremers Urban LLC 1101 C Ave W Seymour IN 47274
Telephone:	(812) 523-5544
Fax:	(812) 523-6889

8. DRUG PRODUCT NAME: Proprietary Name: NA
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The firm provided both paragraph III and IV patent certification.

10. PHARMACOL. CATEGORY: Lipid Lowering Agent. Prevention of Cardiovascular Disease and Hypercholesterolemia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 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	COMMENT
(b) (4)	II	(b) (4)		1	Not Adequate	March 20,2010	by H. Li
(b) (4)	III	(b) (4)		4	N/A		
	III			4			
	III				N/A		
	III				N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)		4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
(b) (4)	III	(b) (4)		4	N/A		

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

[2] Adequate, Inadequate, or N/A (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	TA	4/27/2010	T. Vu
Bioequivalence	Deficient	11/30/2011	WALTERS, JOHNETTA F
EA	Adequate	5/25/2010	H. Li
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Not Applicable		

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

I. Recommendations

1. Recommendation and Conclusion on Approvability

NA-Minor deficiencies (Review #2)

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

N/A

II. Summary of Chemistry Assessments

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

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.
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide. All ingredients in the DP are (b) (4).
The manufacturing process is a (b) (4). The DS is about (b) (4) of the dosage form. The PSD of the DS may be critical since this DS is "low soluble".

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

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their (b) (4)

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: 0.10%, QT: 0.15%. Based on ICH Q3B, for DP: IT: 0.2%, QT: (b) (4) %.

DS is compendial now. There is a PF 37(5) In-Process Revision for Atorvastatin Calcium drug product.

B. Description of How the Drug Product is Intended to be Used
The DP is intended for long term use.

Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: debossed with "1" on one side and plain on the other.
NDC 62175-890-46 bottles of 90
NDC 62175-890-43 bottles of 1000
NDC 62175-890-45 bottles of 5000

20 mg tablets: debossed with "2" on one side and plain on the other.
NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed with "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed with "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

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

C. Basis for Approvability or Not-Approval Recommendation
The application is not approvable due to CMC related deficiencies (minor).

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
04/23/2012

LEIGH A SEARS
04/24/2012

LAXMA R NAGAVELLI
04/24/2012

ANDA 091624

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

KUDCO Ireland Limited

Haitao Li, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A..... 7

II. Summary of Chemistry Assessments.....7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is intended to be used..... 7

C. Basis for Approvability or Not-Approval Recommendation..... 7

Chemistry Assessment..... 8

III. List of Deficiencies to Be Communicated.....109

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT..... 109

Chemistry Review Data Sheet

1. ANDA 091624

2. REVIEW #: 1

3. REVIEW DATE: May 26, 2010

4. REVIEWER: Haitao Li, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	July 15, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	KUDCO Ireland Limited
	Shannon Industrial Estate
Address:	Shannon, County Clare
	Republic of Ireland
U.S.	Elaine Siefert, Director Regulatory Affairs
Representative:	Kremers Urban LLC
	1101 C Ave W
	Seymour IN 47274
Telephone:	(812) 523-5544
Fax:	(812) 523-6889

8. DRUG PRODUCT NAME: Proprietary Name: NA
Non-Proprietary Name: Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION: Lipitor Tablets, NDA #: 20702
The firm provided both paragraph III and IV patent certification.

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12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 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
(b) (4)	II		(b) (4)	1	Not Adequate	May 25,2010	(b) (4) by H. Li
(b) (4)	III		(b) (4)	4	N/A		(b) (4)
	III			4			
	III				N/A		
	III				N/A		
	III			4	N/A		
(b) (4)	III		(b) (4)	4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
(b) (4)	III		(b) (4)	4	N/A		(b) (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	Deficient	1/20/2010	T. Vu
Bioequivalence	Deficient	12/18/2009	D. Mitchell
EA	Adequate	5/25/2010	H. Li
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Not Applicable		

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

I. Recommendations

1. Recommendation and Conclusion on Approvability

NA-Minor deficiencies (Review #1)

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

N/A

II. Summary of Chemistry Assessments

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

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.
Atorvastatin calcium tablets for oral administration contain 10, 20, 40 or 80 mg atorvastatin and the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, polyethylene glycol, polyvinyl alcohol, sodium stearyl fumarate, talc, titanium dioxide. All ingredients in the DP are (b) (4).
The manufacturing process is a (b) (4). The DS is about (b) (4) of the dosage form. The PSD of the DS may be critical since this DS is "low soluble".

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

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

The DS exhibit many polymorphic forms. The DS manufacturer for this ANDA claims their (b) (4)

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: 0.10%, QT: 0.15%. Based on ICH Q3B, for DP: IT: 0.2%, QT: (b) (4)%.

Neither the DS nor the DP is compendial. There is a PF 35(1) In-Process Revision for Atorvastatin Calcium.

B. Description of How the Drug Product is Intended to be Used
The DP is intended for long term use.

Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.

10 mg tablets: debossed with "1" on one side and plain on the other.
NDC 62175-890-46 bottles of 90
NDC 62175-890-43 bottles of 1000
NDC 62175-890-45 bottles of 5000

20 mg tablets: debossed with "2" on one side and plain on the other.
NDC 62175-891-46 bottles of 90
NDC 62175-891-43 bottles of 1000
NDC 62175-891-45 bottles of 5000

40 mg tablets: debossed with "40" on one side and plain on the other.
NDC 62175-892-46 bottles of 90
NDC 62175-892-41 bottles of 500
NDC 62175-892-44 bottles of 2500

80 mg tablets: debossed with "80" on one side and plain on the other.
NDC 62175-897-46 bottles of 90
NDC 62175-897-41 bottles of 500
NDC 62175-897-44 bottles of 2500

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

C. Basis for Approvability or Not-Approval Recommendation
The application is not approved due to CMC related minor deficiencies.

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

/s/

HAITAO LI
11/01/2010

LEIGH A BRADFORD
11/02/2010

LAXMA R NAGAVELLI
11/02/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE
ACCEPTABLE OSI INSPECTION REPORT REVIEW

ANDA No.	(b) (4)
Drug Product Name	
Strength(s)	
Applicant Name	
Original Submission Date(s)	
Date of Report	
Reviewer	
Clinical Site/Address	
Analytical Site/Address	
OUTCOME DECISION	**Adequate**

EXECUTIVE SUMMARY

The Office of Scientific Investigations (OSI) inspection report of the clinical site was received by the Division of Bioequivalence and found acceptable. The site inspection was requested for (b) (4). The following application contained studies conducted at these sites. Given the acceptable inspection of the sites, the bioequivalence section of the following applications is now acceptable

ANDA	Firm	Drug Product
091624	Kudco Ireland Ltd.	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
(b) (4)		

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

The Office of Scientific Investigation (OSI) inspection report of the clinical site was received by the Division of Bioequivalence on May 18, 2012 and found acceptable.

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

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

/s/

TERESA V RAMSON
05/22/2012

AIDA L SANCHEZ on behalf of DALE P CONNER
05/22/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091624		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg		
Applicant Name	KUDCO Ireland Limited		
Address	Shannon Industrial Estate Shannon, County Clare Republic of Ireland		
Authorized US Agent	Elaine Siefert, Director Regulatory Affairs, Kremers Urban LLC 1101 C Ave W Seymour IN 47274		
Contact's Telephone Number	(812) 523-5544		
Contact's Fax Number	(812) 523-6889		
Original Submission Date(s)	15 July 2009 26 February 2010 (dissolution amendment) 12 January 2011 27 June 2011		
Submission Date(s) of Amendment(s) Under Review	**31 October 2011**		
Reviewer	Johnetta F. Walters, Ph.D.		
Study Number (s)	AA77267	AA77268	
Study Type (s)	Fasting	Fed	
Strength (s)	80 mg	80 mg	
Clinical Site	MDS Pharma Services		
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE**[1]		
WAIVER REQUEST RESULT	**INADEQUATE**[1]		
OSI INSPECTION RESULT	**INADEQUATE**[1]		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**

[1] Pending the outcome of the OSI inspection for the clinical site of (b) (4)

DOCUMENT #			
9	Study Amendment	10 mg, 20 mg, 40 mg, 80 mg	INADEQUATE[1]

1 EXECUTIVE SUMMARY

This is a review of a study amendment only.

1. The firm has previously submitted the results of fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies comparing a test product, Kudco Ireland's Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfizer'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 and female subjects. The results are summarized in the tables below.

Atorvastatin, 1 X 80 mg
Fasting Bioequivalence Study No. AA77267, N=140 (Male=96 and Female=44)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	129.57	134.57	0.96	92.08	100.67
AUC∞ (ng·hr/mL)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/mL)	28.59	32.71	0.87	80.72	94.63

Atorvastatin, 1 X 80 mg
Fed Bioequivalence Study No. AA77268, N=86 (Male=56 and Female=30)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	159.22	158.02	1.01	96.54	105.16
AUC∞ (ng·hr/mL)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/mL)	37.25	40.20	0.93	82.82	103.67

The metabolite data were previously deemed supportive.

The firm's fasting and fed BE studies were found inadequate due to bioanalytical study deficiencies related to the firm's repeat assays. The firm's dissolution testing was also found incomplete. (DARRTS: REV-BIOEQ-02 (Dissolution Review) 12/18/2009 and 08/11/2010).

2. On 12 January 2011, the firm submitted an amendment. The firm submitted adequate responses to DB deficiencies which included the original and repeat values of samples that were reanalyzed for further evaluation by the DB. The firm also submitted adequate dissolution testing data. The dissolution testing, however, was deemed incomplete pending the firm's acceptance of the FDA – recommended dissolution specification.

   In the meantime, the reviewer also reviewed the OSI inspection report in this amendment. The reviewer found that one of the OSI findings pertaining to its analytical site inspection, regarding the firm's practice on chromatogram peak integration, may have affected the outcome of the current application. The

firm was asked to verify its practice of chromatogram peak integrations as related to the current ANDA[2].

3. The firm has submitted its responses (date of submission: 31 October 2011) to previous DB deficiencies which included explanation of manual reintegration of chromatograms for further evaluation by DB. The firm has also accepted the FDA – recommended dissolution method and specification. The firm's response was deemed inadequate. The firm was asked to submit the following:

   - Electronic SAS Transport data files (.xpt) for **all original concentration and PK parameter data obtained before reintegration** for its fasting (AA77267) and fed (AA77268) BE studies, as well as the summary tables of the BE results.

   - Raw pre-reintegration chromatography/numerical data for its fasting (AA77267) and fed (AA77268) BE studies.

4. In addition, it was noticed that more OSI inspections had been requested/conducted during the cycling course of the review, as listed in the following (also refer to the attachment for the communication of the PM and current reviewer for details):

   Clinical site:

   - 6/4/07, NDA 022118, NAI
   - pending (b) (4)
   - pending (b) (4)

   Analytical site:

   - 12/8/08, (b) (4), VAI
   - (b) (4), (b) (4), VAI
   - 6/29/10, (b) (4), VAI
   - (b) (4), (b) (4), VAI
   - 6/20/11, (b) (4), classification pending.

   The bioequivalence studies in this application were completed in January 2009. Please note that MDS Pharma Services (Montreal) closed in early 2010[3]. (b) (4) According to

[2] DARRTS: REV-BIOEQ-01(General Review). 04/19/2011.

[3] http://www.theglobeandmail.com/globe-investor/montreal-unit-of-mds-to-be-closed/article1462555/

the Division of Scientific Investigations, some records from Montreal may have been moved [redacted] (b) (4) Given these circumstances, the following comments have been made regarding the additional inspection reports listed above:

- For the clinical site: the clinical site is still pending the outcome of OSI inspection of [redacted] (b) (4) because the BE study of [redacted] (b) (4) was conducted at a time that is close to the date when the BE study of the current application was conducted[4].

- For the analytical site: the reviewer reviewed the analytical findings of three NDAs that the study conducted at the vicinity time of the current ANDA ([redacted] (b) (4) VAI; [redacted] (b) (4), VAI; [redacted] (b) (4), VAI) and determined that the findings in these NDAs are not expected to have impact on the outcome of the current ANDA.

5. In the *current* submission, the firm has submitted all original concentration and PK parameter data obtained **before reintegration** for the fasting (AA77267) and fed (AA77268) bioequivalence studies. The firm has also submitted raw pre-reintegration chromatography/numerical data for its fasting (AA77267) and fed (AA77268) BE studies. The reviewer verified the results which are summarized in the tables below.

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AA77267					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	129.54	134.27	0.96	92.26	100.87
AUC∞ (hr *ng/ml)	132.32	136.82	0.97	92.70	100.89
Cmax (ng/ml)	28.58	32.70	0.87	80.72	94.64

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. AA77268					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	158.85	158.09	1.00	96.32	104.83
AUC∞ (hr *ng/ml)	166.59	165.79	1.00	96.10	105.05
Cmax (ng/ml)	37.24	40.19	0.93	82.82	103.68

[4] NOTE: At the time of this review, the clinical site is still pending the outcome of the inspection. See the Additional Attachments section of this review.

The metabolite data are supportive.

The application is **inadequate** pending the outcome of the OSI inspection for the clinical site of (b) (4).

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[5]

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[6]	LIPITOR® is an inhibitor of HMG-CoA reductase (statin) indicated for the followings: **(1) Prevention of cardiovascular disease** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina • **(2) Hypercholesterolemia** LIPITOR® is indicated:

[5] Electronic Orange Book: http://www.accessdata fda.gov/scripts/cder/ob/default.cfm. Last accessed: 16 April 2010.
[6] Drugs at FDA: http://www.accessdata fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 16 April 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)	**WARNINGS** **Liver Dysfunction** HMG-CoA reductase inhibitors, like some other lipid- lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin. **Skeletal Muscle** **Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin- treated patients. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin,

	immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	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[7]
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[8]:	Draft Guidance on Atorvastatin (finalized 05/2008)

[7] 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.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

[8] Individual Product Bioequivalence Recommendations: http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. Last accessed: 16 April 2010.

3.5 Formulation

Location in appendix	DARRTS: ANDA 091624. REV-BIOEQ-01 (General Review). 08/11/2010.
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.6 In Vitro Dissolution[9]

Location of DB Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review). 12/18/2009. Amendment: DARRTS. REV-BIOEQ-01(General Review). 04/19/2011.
Source of Method (USP, FDA or Firm)	Firm
Medium	0.3% Tween 80 in 0.05 M Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
DB-recommended specifications (for the current test drug product)	NLT (b)(4)% (Q) in 30 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?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.7 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 GRANTED**
If not then why?	N/A

[9] The current dissolution data was taken from the amendment submitted on 12 January 2011 and may be found in DARRTS.

3.8 Firm's Current Responses to DB Deficiency Comments

DB's Previous Deficiency Comment No. 1 (See the review of the amendment dated 12 January 2011)**:**

On 27 June 2011, you submitted an amendment which addressed the deficiency the DBE identified in its letter dated 25 April 2011 regarding the finding identified by the Division of Scientific Investigations on the issue related to manual reintegration of the study samples in your bioequivalence studies. The DBE has reviewed your response and found that it is not adequate for the following reason:

You stated that "To evaluate the impact between the initial integration and the modified integration, the difference in peak area and percent difference of the change were included in the tables. The percent change in peak area should be equivalent to the change in calculated concentration since the internal standard response did not change between the initial integration and the reintegration of the samples listed", and that "In order to evaluate the impact of the samples for which manual reintegration was performed, analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t and Cmax PK parameters for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin for both studies under fed (AA77268) and fasted conditions (AA77267) for exploratory purposes, to determine if setting the manually integrated samples to missing had an effect on the PK conclusions. Excluding the manually reintegrated samples did not significantly impact the results nor alter the conclusion of either study. Specifically, the bioequivalence criteria were still met for the assessed parameters in both the fed and fasted studies."

However, you have not demonstrated that ***including*** *the original results of these reintegrated samples (results prior to reintegration) in the statistical analysis of both the fed and fasted studies did not change the study outcome. In addition, you did not provide all the original assay results (prior to reintegration) to the DBE for verification.*

Therefore, we ask that you submit the following additional information/data:

- *Electronic SAS Transport data files (.xpt) for* ***individual concentration and PK parameter data that are based on original integration results (i.e., obtained before reintegration)*** *for your fasting (AA77267) and fed (AA77268) studies. These bioequivalence data to be submitted in the two usual separate files as described below:*

  a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf KE_FIRSTKE_LAST (where KE_FIRST and KE_LAST are the beginning and ending time points selected for calculation of the elimination constant KE, and expressed in the order of the time points, e.g., KE_FIRST=12 means the 12th time point.)

b. SUBJ SEQ PER TRT C1 C2 C3..... Cn T1 T2 T3.…… Tn Each field should be separated with a blank space, and missing values should be indicated with a period (.).

- *The summary of your study results, based on the data of the original integration (**before** reintegration), in the following tabular format:*

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr-1)	
Study #	Fasting study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol.# p.#
Study #	Fed study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol. # p. #

Drug name Dose Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No.				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)				
AUC∞ (hr *ng/ml)				
Cmax (ng/ml)				

- *You also stated in the current amendment that "Initial chromatograms, for all manually modified chromatography for each study, were saved as word document files for each batch (AA77267 Manual Edited Chromatography and AA77268 Manual Edited Chromatography). Complete sets of chromatograms for all batches with at least one manual reintegration have been saved as pdf files (AA77267 Accepted Batch Chromatography and AA77268 Accepted Batch Chromatography). Refer to Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance". For verification, please submit all aforementioned initial chromatograms for each manually modified chromatography from both studies, together with legible raw numerical data associated with these chromatograms.*

Firm's Current Response No. 1:

The response to this deficiency was prepared by [redacted] (b) (4)

The reintegrations performed within the analytical batches for AA77267 and AA77268 were done to provide consistency for baselines and peak shape between samples. We believe that SOP GL-BIO-10610, *"Chromatographic Peak Identification, Review, and Acceptance"*, establishes adequate controls for eliminating bias, ensuring integrity of data, and accurate reporting of the results. All baseline reviews and reintegrations were performed, reviewed, and approved prior to the regression of the analytical data. The reason for each reintegration was captured in the audit trail and is available for review.

Therefore, the conclusions derived from these bioanalytical results can be considered to be accurate.

In light of the request by the Agency, the pharmacokinetic parameters for the 3 analytes of interest for studies AA77267 and AA77268 have been regenerated based on the original concentration data prior to reintegration. (Please note that the analyte concentrations from the computer generated integrations which are being referred to as the "original" results were not processed per [redacted] (b) (4) SOP, and as such, no official review by Quality Assurance can be performed.) Links to SAS transport files and related information are provided in study-aa77267.pdf and study-aa77268.pdf. Additionally,

OGD summary tables (see ogd-table-2-aa77267.pdf, ogd-table-2-aa77268.pdf, ogd-table-3-aa77267.pdf and ogd-table-3-aa77268.pdf) summarizing the pharmacokinetic results and bioequivalence assessment have been provided with this response. The results from the pharmacokinetic and bioequivalence assessment are consistent with the original results previously provided in that 90% confidence interval for the geometric mean ratio for the parent analyte atorvastatin falls entirely within the limits of 80.00 and 125.00.

To illustrate why the manual integrations were performed, example chromatograms from Study AA77267 are provided at the end of this response. Before and after reintegration chromatograms (Examples 1-10) are included along with the reason for performing the reintegration. Also included are examples of chromatography where the software parameters were sufficient to accurately integrate the analyte peak, and manual modification was not needed (Examples 11-13).

As illustrated, the manual modifications were performed to ensure consistent integration of the chromatographic peaks. Our SOPs require that integrations be performed in a consistent manner. SOP GL-BIO-10610*, "Chromatographic Peak Identification, Review, and Acceptance"* specifically stipulates:

> • A general review of the chromatograms obtained during the method development is performed before production sample analysis to ensure the data obtained is consistent (Sections 6.2.2) and
> • Baseline integration must be consistent throughout the entire batch of samples.

Whenever possible and in order to avoid bias, a single set of integration parameters will be used for within-batch peak integration. Within-batch parameter modification is only warranted so as to obtain appropriate baseline integration and avoid bias with respect to sample type. When the integration parameters are not acceptable for a chromatographic peak, adjustments to the parameters or manual integration of that peak is performed; and the reason for the adjustment is documented (Section 6.3.1).

In addition, please note that:

• by design, the software will not accept manual reintegration if the peak area change is less than 5 percent of original value.
• the software audit trail tracks peaks that were re-integrated, reason for reintegration, peak area before reintegration, peak area after reintegration and percent change in peak area.
• at least 2 individuals must review every chromatogram. This review is documented and integrations are locked prior to regression of the data.

In conclusion, we feel that the manual reintegrations were appropriate to comply within the guidelines of the SOP.

• **You also stated in the current amendment that "Initial chromatograms, for all manually modified chromatography for each study, were saved as word document**

files for each batch (AA77267 Manual Edited Chromatography and AA77268 Manual Edited Chromatography). Complete sets of chromatograms for all batches with at least one manual reintegration have been saved as pdf files (AA77267 Accepted Batch Chromatography and AA77268 Accepted Batch Chromatography). Refer to Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance". For verification, please submit all aforementioned initial chromatograms for each manually modified chromatography from both studies, together with legible raw numerical data associated with these chromatograms.

Initial chromatograms for all manually modified chromatography from each study as well as complete sets of chromatograms for all batches with at least one manual reintegration were provided in Module 1 of Amendment 0006. After a telephone conversation between Kurt Zimmer, Regulatory Affairs Manager, Kremers Urban (KU), and Nam Chun, Project Manager, OGD, the applicant discovered that the chromatograms had not been correctly linked to the response. KU apologizes for this inconvenience and herein provides links to the requested chromatography (see chromatograms.pdf) and raw numerical data in .pdf and .xlsx format (see test-concentration-data-aa77267.pdf, test-concentration-data-aa77267.xlsx, test-concentration-data-aa77268.pdf, and test-concentration-data-aa77268.xlsx).

Reviewer's Comments:

1. The firm has submitted the following additional information in response to the previous Division of Bioequivalence deficiencies:

   - Electronic SAS Transport data files (.xpt) for **individual concentration and PK parameter data that are based on original integration results (i.e., obtained before reintegration)** for its fasting (AA77267) and fed (AA77268) studies.

   - The summary of its study results, based on the data of the original integration (**before** reintegration), in tabular format.

2. The firm calculated results, based on the firm's original data, are shown below:

Summary Results of Fasting Bioequivalence Study (AA77267)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Atorvastatin Mean Parameters (+/-SD)*						Study Repor Locati
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77267	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fasting Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401 Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V	140 completing (96M/44F) Healthy subjects mean age: 39.8 years (range: 18 – 55 years)	28.58281 (68.1%) 32.72809 (46.7%)	0.750 (0.333 – 6.061) 0.750 (0.333 – 6.000)	129.595 (50.0%) 134.284 (45.9%)	135.436 (47.7%) 138.828 (45.0%)	9.897 (±5.5456) 10.112 (±4.7816)	0.09328 (±0.052196) 0.08630 (±0.046536)	study aa7726 pdf

* Geometric Mean (CV%) are presented for AUC0-t, AUC∞ and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for T½ and K

Table 3 Statistical Summary of the Comparative Bioavailability Data – AA77267 (Fasted Study)

Atorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	129.398	134.141	96.5	92.2% - 100.9%
AUC∞	135.074	139.119	97.1	93.1% - 101.2%
Cmax	28.55578	32.66518	87.4	80.8% - 94.6%

Ortho-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	144.582	151.075	95.7	90.6% - 101.1%
AUC∞	151.895	156.911	96.8	91.9% - 102.0%
Cmax	23.08694	25.63619	90.1	82.1% - 98.8%

Para-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	9.79583	9.43432	103.8	95.5% - 112.9%
AUC∞	25.8120	22.4633	114.9	103.4% - 127.6%
Cmax	0.88918	0.87315	101.8	93.1% - 111.4%

Summary Results of Fed Bioequivalence Study (AA77268)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Atorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77268	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fed Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401	86 completing (56M/30F) Healthy subjects mean age: 36.8 years (18 – 54 years)	37.16305 (61.5%)	1.667 (0.333 – 6.000)	158.299 (46.0%)	163.325 (45.7%)	9.416 (±4.3890)	0.09202 (±0.050110)	study-aa77268.pdf
			Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V		40.02698 (69.9%)	1.333 (0.667 – 5.000)	157.496 (48.5%)	162.421 (47.7%)	8.981 (±3.9088)	0.09327 (±0.045083)	

* Geometric Mean (CV%) are presented for AUC0-t, AUC∞ and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for T½ and Kel.

Table 3 Statistical Summary of the Comparative Bioavailability Data – AA77268 (Fed Study)

Atorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	158.839	158.089	100.5	96.3% - 104.8%
AUC∞	163.057	162.499	100.3	96.3% - 104.6%
Cmax	37.24389	40.19107	92.7	82.8% - 103.7%

Ortho-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	147.129	147.126	100.0	96.3% - 103.9%
AUC∞	153.309	152.445	100.6	96.8% - 104.4%
Cmax	21.27497	22.41451	94.9	87.3% - 103.3%

Para-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	12.05558	11.79499	102.2	94.4% - 110.7%
AUC∞	21.26834	22.96595	92.6	84.6% - 101.3%
Cmax	1.23938	1.24046	99.9	93.4% - 106.9%

3. The reviewer calculated results, based on the firm's original data, are shown below:

Summary Results of Fasting Bioequivalence Study (AA77267)

Fasting Bioequivalence Study, Study No. AA77267 Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)*	145.644	55.39	45.52	580.69	148.741	52.64	38.68	520.81	0.98
AUC∞ (hr *ng/ml)*	148.015	54.36	47.08	582.56	150.993	51.78	44.21	522.98	0.98
Cmax (ng/ml)*	34.024	63.76	4.57	163.00	36.359	53.16	10.20	129.00	0.94
Tmax (hr)	0.750	.	0.33	6.06	0.750	.	0.33	6.00	1.00
Kel (hr^{-1})	0.165	29.09	0.01	0.29	0.161	28.78	0.04	0.34	1.03
T1/2 (hr)	4.955	85.10	2.39	48.55	4.719	36.86	2.05	16.42	1.05

*Arithmetic mean values.

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AA77267					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	129.54	134.27	0.96	92.26	100.87
AUC∞ (hr *ng/ml)	132.32	136.82	0.97	92.70	100.89
Cmax (ng/ml)	28.58	32.70	0.87	80.72	94.64

Orthohydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AA77267					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	144.69	151.13	0.96	90.64	101.12
AUC∞ (hr *ng/ml)	149.92	155.80	0.96	91.44	101.26
Cmax (ng/ml)	23.09	25.64	0.90	82.06	98.81

Parahydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. AA77267					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	7.43	7.78	0.95	81.59	111.67
AUC∞ (hr *ng/ml)	27.64	26.84	1.03	87.09	121.80
Cmax (ng/ml)	0.81	0.83	0.98	90.23	106.90

Atorvastatin

Root mean square error, AUC0-t	0.2253	
Root mean square error, AUC∞	0.2139	
Root mean square error, Cmax	0.4017	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	140	140
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?	Yes – 3	Yes - 3

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	140	0.98	0.85	1.00
Reference	140	0.98	0.87	1.00

Comments on Pharmacokinetic and Statistical Analysis:

- The confidence interval for $\ln AUC_{\infty}$ (as calculated by the firm and reviewer - verified) falls within the bioequivalence interval of 80%-125% for the parent drug and both active metabolites. Therefore, the Division of Bioequivalence (DB) bases its bioequivalence determination on the reviewer – calculated 90% CIs data of AUC_{0-t}, AUC_{∞}, and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolites, ortho hydroxyatorvastatin, and parahydroxyatoravastatin. The DB concludes that the PK results are acceptable and metabolite data is deemed supportive.

- Subjects enrolled in this study were dosed in different days and divided into three groups (Group 1: Subject Nos. 1-48, Group 2: Subject Nos. 49-96, Group 3: Subject Nos. 97-144). The reviewer has previously used the model TRT*GRP for statistical analysis. There was no significant TRT*GRP effect ($p>0.1$) for AUC_{0-t}

(0.2195), AUC_{∞} (0.3389) and C_{MAX} (0.3250). Therefore, this term was dropped from subsequent analysis.

- The pharmacokinetic and statistical analyses are **adequate.** The reviewer used the SAS code, CALCKE, for statistical analysis of the data. The following time points were selected to calculate the Kel of the parent drug:

  Ke first: T14 (16 hours)

  Ke last: T17 (36 hours)

As noted above in the firm – calculated confidence intervals (and reviewer – verified), the 90% confidence intervals for log-transformed AUC_{∞} of an active metabolite, parahydroxy atorvastatin, of the data collected **BEFORE reintegration** meet the acceptable BE limits of 80.00% - 125.00%. The orthohydroxy – and parahydroxy atorvastatin data is adequate and considered supporting documentation.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

- The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of atorvastatin are within the acceptable BE limits of 80.00%-125.00%. Also, the 90% confidence intervals for log – transformed AUC_{0-t}, AUC_{∞} and C_{max} of the active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin, are within acceptable BE limits of 80.00% - 125.00%.

- The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of atorvastatin are comparable to that of the reviewer-calculated data. The firm has demonstrated that using the original results of these reintegrated samples (results prior to reintegration) in the statistical analysis of the fasted study did not change the study outcome. The firm's response to this portion of the DB's deficiency comment is **adequate**.

Summary Results of Fed Bioequivalence Study (AA77268)

Fed Bioequivalence Study, Study No. AA77268 Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml) *	174.987	50.04	66.13	596.50	174.502	46.89	43.64	436.81	1.00
AUC∞ (hr *ng/ml) *	184.931	47.97	70.53	601.69	181.890	45.20	49.06	440.21	1.02
Cmax (ng/ml) *	44.045	66.95	13.00	167.00	48.343	66.05	6.20	177.00	0.91
Tmax (hr)	1.667	.	0.33	6.00	1.333	.	0.67	5.00	1.25
Kel (hr^{-1})	0.064	38.02	0.00	0.12	0.068	34.45	0.00	0.14	0.94
T1/2 (hr)	10.715	27.31	5.63	23.05	11.108	45.04	4.80	39.30	0.96

* Arithmetic mean values.

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. AA77268					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	158.85	158.09	1.00	96.32	104.83
AUC∞ (hr *ng/ml)	166.59	165.79	1.00	96.10	105.05
Cmax (ng/ml)	37.24	40.19	0.93	82.82	103.68

Orthohydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. AA77268					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	147.16	147.19	1.00	96.20	103.91
AUC∞ (hr *ng/ml)	150.13	150.30	1.00	96.19	103.73
Cmax (ng/ml)	21.27	22.41	0.95	87.24	103.27

Parahydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. AA77268					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	11.30	10.76	1.05	96.07	114.66
AUC∞ (hr *ng/ml)	19.14	18.60	1.03	86.12	122.93
Cmax (ng/ml)	1.21	1.21	1.00	93.37	106.99

Atorvastatin

Root mean square error, AUC0-t	0.1667	
Root mean square error, AUC∞	0.1692	
Root mean square error, Cmax	0.4427	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	81	84
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?	Yes – 2	Yes - 2

Ratio of AUC0-t/AUC∞

Treatment	n	Mean	Minimum	Maximum
Test	80	0.97	0.89	1.00
Reference	84	0.96	0.61	0.99

- The confidence interval for $\ln AUC_{\infty}$ (as calculated by the firm and reviewer - verified) falls within the bioequivalence interval of 80%-125% for the parent drug and both active metabolites. Therefore, the Division of Bioequivalence (DB) bases its bioequivalence determination on the reviewer – calculated 90% CIs data of AUC_{0-t}, AUC_{∞}, and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolites, ortho hydroxyatorvastatin, and parahydroxyatoravastatin. The DB concludes that the PK results are acceptable and metabolite data is deemed supportive.

- Subjects enrolled in this study were dosed in different days and divided into two groups (Group 1: Subject Nos. 1-44 and Group 2: Subject Nos. 45-88). The reviewer has previously used the model TRT*GRP for statistical analysis. There was no significant TRT*GRP effect ($p>0.1$) for AUC_{0-t} (0.1736), AUC_{∞} (0.5532) and C_{MAX} (0.5439). Therefore, this term was dropped from subsequent analysis.

- The pharmacokinetic and statistical analyses are **adequate.** The reviewer used the SAS code, CALCKE, for statistical analysis of the data. The following time points were selected to calculate the Kel of the parent drug:

  Ke first: T14 (16 hours)

  Ke last: T17 (36 hours)

As noted above in the firm – calculated confidence intervals (and reviewer – verified), the 90% confidence intervals for log-transformed AUC_{∞} of an active metabolite, parahydroxy atorvastatin, of the data collected **BEFORE reintegration** meet the acceptable BE limits of 80.00% - 125.00%. The orthohydroxy – and parahydroxy atorvastatin data is adequate and considered supporting documentation.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study:

- The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of atorvastatin are within the acceptable BE limits of 80.00%-125.00%. Also, the 90% confidence intervals for log – transformed AUC_{0-t}, AUC_{∞} and C_{max} of the active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin, are within acceptable BE limits of 80.00% - 125.00%.

- The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of atorvastatin are comparable to that of the reviewer-calculated data. The firm has demonstrated that using the original results of these reintegrated samples (results prior to reintegration) in the statistical analysis of the fed study did not change the

study outcome. The firm's response to this portion of the DB's deficiency comment is **adequate**.

4. The firm was also asked to submit all aforementioned initial chromatograms for each manually modified chromatography from both studies, together with legible raw numerical data associated with these chromatograms.

   The firm has submitted original (before integration) chromatograms as identified above. The firm states the following:

   > *The reintegrations performed within the analytical batches for AA77267 and AA77268 were done to provide consistency for baselines and peak shape between samples. We believe that SOP GL-BIO-10610,"Chromatographic Peak Identification, Review, and Acceptance", establishes adequate controls for eliminating bias, ensuring integrity of data, and accurate reporting of the results. All baseline reviews and reintegrations were performed, reviewed, and approved prior to the regression of the analytical data. The reason for each reintegration was captured in the audit trail and is available for review.*

   Therefore, the conclusions derived from these bioanalytical results can be considered to be accurate.

   The Bioanalytical Method Validation Guidance states that documentation for reintegrated data should include the following:

   Documentation should include the initial and repeat integration results, the method used for reintegration, the reported result, assay run identification, the reason for the reintegration, the requestor of the reintegration, and the manager authorizing reintegration. Reintegration of a clinical or preclinical sample should be performed only under a predefined SOP[10].

5. Based on the above data and the fact that the firm's data before reintegration does not change the outcome of the fasting (AA77267) or fed (AA77268) studies, the firm's response to the deficiency comment is **adequate.**

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[10] Guidance for Industry: Bioanalytical Method Validation. May 2001. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
None	N/A

3.10 Additional Attachments

3.10.1 OSI Inspection Status – Clinical Site

From: Chun, Nam
Sent: Monday, November 14, 2011 7:59 AM
To: Walters, Johnetta F.
Subject: RE: OSI Inspection Status - (b) (4)

Good morning Johnetta,

The clinical site for (b) (4) is still pending for an inspection.

Thanks,

Nam (Esther) Chun, Pharm.D.
LCDR, U.S. Public Health Service
Regulatory Project Manager, Branch VI
Division of Bioequivalence I
Office of Generic Drugs
FDA

From: Walters, Johnetta F.
Sent: Thursday, November 10, 2011 3:40 PM
To: Chun, Nam
Cc: Walters, Johnetta F.
Subject: OSI Inspection Status - (b) (4)

Hi Esther,

I am currently working on an amendment whose clinical site is pending a OSI inspection. Could you please update me on the status of the clinical site of (b) (4)?

Thanks,

Johnetta

Johnetta F. Walters, Ph.D.
Review Pharmacologist
USFDA/CDER/OPS/OGD/DBEI
MPN1, Room 1358, HFD-650
Telephone: (240) 276 - 8802
Facsimile: (240) 276 - 8766

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
DRUG PRODUCT:	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

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

We acknowledge that you will conduct dissolution testing using the current FDA-recommended method for your test product, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The dissolution method is as follows:

Medium:	0.3% Tween 80 in 0.05 M Phosphate buffer, pH 6.8
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	Type II (Paddle)
Rotation (rpm):	75 rpm

The test product should meet the following specification:

NLT (b)(4)% (Q) of the labeled amount of Atorvastatin is dissolved in 30 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

3.11 Outcome Page

ANDA: 091624

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14598	6/27/2011	Other	Study Amendment	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/

JOHNETTA F WALTERS
11/17/2011

BING V LI
11/18/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
11/30/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091624
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg
Applicant Name	KUDCO Ireland Limited
Address	Shannon Industrial Estate Shannon, County Clare Republic of Ireland
Authorized US Agent	Elaine Siefert, Director Regulatory Affairs, Kremers Urban LLC 1101 C Ave W Seymour IN 47274
Contact's Telephone Number	(812) 523-5544
Contact's Fax Number	(812) 523-6889
Original Submission Date(s)	15 July 2009 26 February 2010 (dissolution amendment) 12 January 2011
Submission Date(s) of Amendment(s) Under Review	**27 June 2011**
Reviewer	Johnetta F. Walters, Ph.D.

Study Number (s)	AA77267	AA77268
Study Type (s)	Fasting	Fed
Strength (s)	80 mg	80 mg
Clinical Site	MDS Pharma Services	
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345	
Analytical Site	(b) (4)	
Analytical Site Address		

OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI INSPECTION RESULT	**INADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
7	**Study Amendment**	**10 mg, 20 mg, 40 mg, 80 mg**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This is a review of a study amendment only.

1. The firm has previously submitted the results of fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies comparing a test product, Kudco Ireland's Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfizer'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 and female subjects. The results are summarized in the tables below.

Atorvastatin, 1 X 80 mg
Fasting Bioequivalence Study No. AA77267, N=140 (Male=96 and Female=44)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	129.57	134.57	0.96	92.08	100.67
AUC∞ (ng·hr/mL)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/mL)	28.59	32.71	0.87	80.72	94.63

Atorvastatin, 1 X 80 mg
Fed Bioequivalence Study No. AA77268, N=86 (Male=56 and Female=30)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	159.22	158.02	1.01	96.54	105.16
AUC∞ (ng·hr/mL)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/mL)	37.25	40.20	0.93	82.82	103.67

The metabolite data were previously deemed supportive.

The firm's fasting and fed BE studies were found inadequate due to bioanalytical study deficiencies related to the firm's repeat assays. The firm's dissolution testing was also found incomplete. (DARRTS: REV-BIOEQ-02 (Dissolution Review) 12/18/2009 and 08/11/2010).

2. On 12 January 2011, the firm submitted an amendment. The firm submitted adequate responses to DBE deficiencies which included the original and repeat values of samples that were reanalyzed for further evaluation by the DBE. The firm also submitted adequate dissolution testing data. The dissolution testing, however, was deemed incomplete pending the firm's acceptance of the FDA – recommended dissolution specification.

   In the meantime, the reviewer also reviewed the DSI inspection report in this amendment. The reviewer found that one of the DSI findings pertaining to its analytical site inspection, regarding the firm's practice on chromatogram peak integration, may have affected the outcome of the current application. The

firm was asked to verify its practice of chromatogram peak integrations as related to the current ANDA[1].

3. In the *current* submission, the firm has submitted its responses to previous DBE deficiencies which included explanation of manual reintegration of chromatograms for further evaluation by DBE. The firm has also accepted the FDA – recommended dissolution method and specification. **The firm's response is still inadequate.** The firm should submit the following:

   - Electronic SAS Transport data files (.xpt) for **all original concentration and PK parameter data obtained before reintegration** for its fasting (AA77267) and fed (AA77268) BE studies, as well as the summary tables of the BE results.

   - Raw pre-reintegration chromatography/numerical data for its fasting (AA77267) and fed (AA77268) BE studies.

4. In addition, it is noticed that a few more DSI inspections had been requested/conducted during the cycling course of this review, as listed in the following (also refer to the attachment for the communication of the PM and current reviewer for details):

   Clinical site:

   - 6/4/07, NDA 022118, NAI
   - pending (b) (4)
   - pending, (b) (4)

   Analytical site:

   - 12/8/08, (b) (4), VAI
   - (b) (4), (b) (4), VAI
   - 6/29/10, (b) (4), VAI
   - (b) (4), (b) (4), VAI
   - 6/20/11, (b) (4), classification pending.

   The bioequivalence studies in this application were completed in January 2009. Please note that MDS Pharma Services (Montreal) closed in early 2010[2]. Also, (b) (4). According to

[1] DARRTS: REV-BIOEQ-01(General Review). 04/19/2011.

[2] http://www.theglobeandmail.com/globe-investor/montreal-unit-of-mds-to-be-closed/article1462555/

the Division of Scientific Investigations, some records from Montreal may have been moved to (b) (4). Given these circumstances, the following comments have been made regarding the additional inspection reports listed above:

- For the clinical site: the clinical site is pending the outcome of DSI inspection of (b) (4) because the BE study of (b) (4) was conducted at a time that is close to the date when the BE study of the current application was conducted.

- For the analytical site: the reviewer reviewed, in this report, the analytical findings of three NDAs that the study conducted at the vicinity time of the current ANDA ((b) (4), VAI; (b) (4) (b) (4) VAI; (b) (4), VAI) and determined that the findings in these NDAs are not expected to have impact on the outcome of the current ANDA.

The application is **inadequate**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[3]

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[4]	LIPITOR® is an inhibitor of HMG-CoA reductase (statin) indicated for the followings: **(1) Prevention of cardiovascular disease** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina • **(2) Hypercholesterolemia** LIPITOR® is indicated:

[3] Electronic Orange Book: http://www.accessdata fda.gov/scripts/cder/ob/default.cfm. Last accessed: 16 April 2010.
[4] Drugs at FDA: http://www.accessdata fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 16 April 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)	**WARNINGS** **Liver Dysfunction** HMG-CoA reductase inhibitors, like some other lipid- lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin. **Skeletal Muscle** **Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin- treated patients. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin,

	immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	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[5]
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[6]:	Draft Guidance on Atorvastatin (finalized 05/2008)

[5] 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.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

[6] Individual Product Bioequivalence Recommendations: http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. Last accessed: 16 April 2010.

3.5 Formulation

Location in appendix	DARRTS: ANDA 091624. REV-BIOEQ-01 (General Review). 08/11/2010.
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.6 In Vitro Dissolution[7]

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review). 12/18/2009.
Source of Method (USP, FDA or Firm)	Firm
Medium	0.3% Tween 80 in 0.05 M Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
DBE-recommended specifications (for the current test drug product)	NLT (b)(4)% (Q) in 30 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?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.7 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?	The DBE should compare the study results that are based on the original assay values (before reintegration) and the results that are based on reintegrated values.

[7] The current dissolution data was taken from the amendment submitted on 12 January 2011 and may be found in DARRTS.

3.8 Firm's Current Responses to DBE Deficiency Comments

DBE's Previous Deficiency Comment No. 1 (See the review of the amendment dated 12 January 2011)**:**

Your dissolution testing data using your newly revised dissolution method is acceptable but your proposed specification (NLT (b)(4)% (Q) in 30 minutes) is not acceptable. Based on your dissolution testing data, the DBE recommends a more appropriate specification for your test product. Please acknowledge your acceptance of the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL of 0.3% Polysorbate 80 in 0.05 M Phosphate Buffer, pH 6.8 using USP apparatus II (Paddle) at 75 rpm. The test products should meet the following specification:

Not less than (b)(4)% (Q) of the labeled amount of drug in the dosage form is dissolved in 30 minutes.

Firm's Current Response No. 1:

"The applicant accepts the proposed method and specification of "Not Less Than (b)(4)% (Q) of the labeled amount of drug in the dosage form is dissolved in 30 minutes." A revised Table 5 is included in Word and pdf to reflect this update. Additionally, 5.3.1.3 has been updated. The drug product specification section 3.2.P.5.1 will be updated to reflect the revised specification in response to the Quality Deficiency letter dated 02 November 2010. The response is in process and will be submitted shortly."

Reviewer's Comments:

The firm has accepted the proposed method and specification of "*Not Less Than (b) (4)% (Q) of the labeled amount of drug in the dosage form is dissolved in 30 minutes*." The firm has also revised Table 5 as well as module 5.3.1.3. Please see below:

Table 5 - Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm (b) (4)
	Medium:	0.3% Tween 80 in pH 6.8 Phosphate Buffer (proposed test product medium)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)% (Q) of the labeled amount is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Kremers Urban Pharmaceuticals Inc. 1101 C Avenue West – Seymour, IN 47274	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 5 min	10 min	15 min	30 min	Study Report Location
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	65	80	86	92	
					Range	(b) (4)				
					%CV	1.4	1.6	2.0	2.2	Table 5.2
Study Report[1]	11/6/10	Lipitor Tablets, 10mg / 03698V (Expires: 01 / 2010)	10 mg Tablets	12	Mean	82	92	95	98	
					Range	(b) (4)				
					%CV	4.4	2.5	1.9	1.5	
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	67	80	86	94	
					Range	(b) (4)				
					%CV	1.0	1.4	1.2	1.6	Table 5.3
Study Report[1]	11/6/10	Lipitor Tablets, 20mg / 02648V (Expires: 02 / 2010)	20 mg Tablets	12	Mean	82	91	94	97	
					Range	(b) (4)				
					%CV	4.0	3.3	2.7	1.8	
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	64	78	84	93	
					Range	(b) (4)				
					%CV	3.9	2.7	1.8	1.4	Table 5.4
Study Report[1]	11/6/10	Lipitor Tablets, 40mg / 0307048 (Expires: 03 / 2011)	40 mg Tablets	12	Mean	85	93	96	98	
					Range	(b) (4)				
					%CV	5.9	2.6	1.7	1.7	
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	58	74	81	90	
					Range	(b) (4)				
					%CV	2.1	1.4	1.3	1.2	Table 5.5
Study Report[1]	11/6/10	Lipitor Tablets, 80mg / 08107V (Expires: 04 / 2009)	80 mg Tablets	12	Mean	87	93	95	97	
					Range	(b) (4)				
					%CV	3.0	2.6	1.5	1.2	

[1]Report number is not applicable as individual results and dissolution plots can be found in the Study Report Location noted above.

Table 5.2 – 10 mg product

Vessel	Atorvastatin Calcium Tablets, 10mg Lot# P80350				Lipitor 10mg Tablets Lot# 03698V			
	5 min	10 min	15 min	30 min	5 min	10 min	15 min	30 min
1	(b) (4)				(b) (4)			
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	65	80	86	92	82	92	95	98
% CV	1.4	1.6	2.0	2.2	4.4	2.5	1.9	1.5
Minimum	(b) (4)				(b) (4)			
Maximum								

Table 5.3 – 20 mg product

Vessel	Atorvastatin Calcium Tablets, 20mg Lot# P80360				Lipitor 20mg Tablets Lot# 02648V			
	5 min	10 min	15 min	30 min	5 min	10 min	15 min	30 min
1	(b) (4)				(b) (4)			
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	67	80	86	94	82	91	94	97
% CV	1.0	1.4	1.2	1.6	4.0	3.3	2.7	1.8
Minimum	(b) (4)				(b) (4)			
Maximum								

Table 5.4 – 40 mg product

Vessel	Atorvastatin Calcium Tablets, 40mg Lot# P80370					Lipitor 40mg Tablets Lot# 0307048			
	5 min	10 min	15 min	30 min		5 min	10 min	15 min	30 min
1	(b) (4)								(b) (4)
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Average	64	78	84	93		85	93	96	98
% CV	3.9	2.7	1.8	1.4		5.9	2.6	1.7	1.7
Minimum	(b) (4)								(b) (4)
Maximum									

Table 5.5 – 80 mg product

Vessel	Atorvastatin Calcium Tablets 80 mg Lot P80340					Lipitor Tablets, 80 mg Lot 08107V			
	5 min	10 min	15 min	30 min		5 min	10 min	15 min	30 min
1	(b) (4)								(b) (4)
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Average	58	74	81	90		87	93	95	97
% RSD	2.1	1.4	1.3	1.2		3.0	2.6	1.5	1.2
Minimum	(b) (4)								(b) (4)
Maximum									

As a result, the firm's response to this deficiency is **adequate**.

DBE's Previous Deficiency Comment No. 2 (See the review of the amendment dated 12 January 2011)**:**

During February 2008, the Division of Scientific Investigation (DSI) inspected the analytical sites of (b) (4) *, for another application. This is the same site where the subject samples from the fasting (AA77267) and fed (AA77268) bioequivalence (BE)*

studies for your application were also analyzed. Following the inspection, a Form FDA-483 was issued for each site. Subsequently, the analytical sites provided its responses to Form 483 observations and these responses were included in the final evaluation by DSI, which recommended that the inspected studies be considered questionable based on the DSI's original findings and the sites' responses.

For considering the impact of similar objectionable study conduct and site practices by the same analytical facility on the BE studies submitted in your application, the DBE reviewed the above DSI inspection report and found that the following objectionable finding by the DSI at the analytical site could potentially compromise the integrity of the studies of ANDA 091624 as well:

- *Analytical results, specifically chromatogram peak integrations, were modified. These modifications were made by manually picking the baseline or changing integrations parameters.*

Please address the above specific finding by the DSI with respect to its impact on the BE studies of the current ANDA, providing any necessary supporting documents in your response, including but not limited to:

  - *Confirmation of the existence of any manual reintegration/manual baseline adjustment in any chromatograms of the BE studies, if any.*
  - *If such manual modification of chromatograms was indeed carried out for certain chromatograms, please submit:*

    - *all chromatograms of the affected runs for comparison.*
    - *In addition, for chromatograms manually modified for reintegration, please also submit the same chromatograms prior to modification, for comparison, and*
    - *the peak height/area response counts before and after modification, together with the resulting calculated concentration values associated with the unmodified and modified chromatograms.*
    - *Standard Operating Procedure (SOP) for chromatography integration/reintegration.*

Firm's Current Response No. 2:

"The response to this question was prepared by [redacted] (b) (4) ***DBE deficiency comments are bolded.***

For the inspection referenced above, the bio-analytical phase was performed at [redacted] (b) (4) *The data generated and processes used for that study are in no way related to the* [redacted] (b) (4) *site or the data generated for the studies in question in this deficiency letter. Moreover, since then,* [redacted] (b) (4) *implemented a new global SOP GL-BIO-10610*

(Attachment 1) with strict controls for performing manual reintegration. The (b) (4) *site was closed in* (b) (4) *and the records for the site are retained in* (b) (4) *Studies AA77267 and AA77268 were analyzed in 2009 in* (b) (4) *under the new SOP.*

It should be noted that in (b) (4)*, the* (b) (4) *site was inspected by FDA. The inspection included a study in which a number of chromatograms were re-integrated. The FDA inspector(s) also reviewed the SOPs used by the* (b) (4) *bio-analytical laboratory, including SOP GL-BIO-10610. At the conclusion of the inspection, there were no observations issued regarding reintegration.*

For considering the impact of similar objectionable study conduct and site practices by the same analytical facility on the BE studies submitted in your application, the DBE reviewed the above DSI inspection report and found that the following objectionable finding by the DSI at the analytical site could potentially compromise the integrity of the studies of ANDA 091624 as well;

- ***Analytical results, specifically chromatogram peak integrations, were modified. These modifications were made by manually picking the baseline or changing integrations parameters.***

Chromatographic peak integrations were performed for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin using (b) (4) (b) (4) *The software audit trail tracks peaks that were re-integrated, reason for reintegration, peak area before reintegration, peak area after reintegration and percent change in peak area. By design, the software will not accept manual reintegration if the peak area change is less than 5 percent of original value. If modification is needed to ensure consistency of integration for the entire batch, if possible the integration parameters are modified, so that all injections are re-integrated using the modified parameters. When this is not possible due to limitations of the software, adjustments to the parameters or manual integrations must be performed to ensure consistency of the integration for the batch. Chromatographic review and baseline integration/reintegration is described in* (b) (4) *Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance". Version 01 was in effect at the time these studies were performed. No changes other than format have been made since version 01.*

Please address the above specific finding by the DSI with respect to its impact on the BE studies of the current ANDA, providing any necessary supporting documents in your response, including but not limited to:

- ***Confirmation of the existence of any manual reintegration / manual baseline adjustment in any chromatograms of the BE studies, if any.***
- ***If such manual modification of chromatograms was indeed carried out for certain chromatograms, please submit:***

- ***all chromatograms of the affected runs for comparison.***
- ***In addition, for chromatograms manually modified for reintegration, please also submit the same chromatograms prior to modification, for comparison and***
- ***the peak height / area response counts before and after modification, together with the resulting calculated concentration values associated with the unmodified and modified chromatograms.***
- ***Standard Operating Procedure (SOP) for chromatography integration / reintegration.***

Chromatographic evaluation:

There were multiple manual reintegrations performed for both studies with the majority of them being made to remove a small tailing peak for para-hydroxyatorvastatin. The reintegrations (per study) are summarized in the tables below.

Study AA77267	
Total number of subject samples analyzed	*5310*
Number of system suitability (SS), QC & STD samples re-integrated	*80*
Number of subject samples re-integrated	*995*
Number of Treatment A samples re-integrated	*484*
Number of Treatment B samples re-integrated	*511*

AA77267 - Manual Reintegrations per analyte (Percent of total subject samples assayed in parenthesis)			
Analyte	*Atorvastatin*	*Ortho-hydroxyatorvastatin*	*Para-hydroxyatorvastatin*
Total Reintegrations	*122 (2.3%)*	*46 (0.9%)*	*827 (15.6%)*

Study AA77268	
Total number of subject samples analyzed	*3261*
Number of system suitability (SS), QC & STD samples re-integrated	*55*
Number of subject samples reintegrated	*386*
Number of Treatment A samples re-integrated	*185*
Number of Treatment B samples re-integrated	*201*

AA77268 - Manual Reintegrations per analyte (Percent of total subject samples assayed in parenthesis)			
Analyte	*Atorvastatin*	*Ortho-hydroxyatorvastatin*	*Para-hydroxyatorvastatin*
Total Reintegrations	*60 (1.8%)*	*31 (1.0%)*	*295 (9.0%)*

Reintegration tables have been prepared for both studies (Attachment 2 and Attachment 3). The tables include fields for compound, samples type, subject ID, period, treatment, and whether the reported result was below the limit of

quantitation (BLQ), (entered as yes or no), initial integration peak area, modified integration peak area, batch number, injection number and reason for modification.

To evaluate the impact between the initial integration and the modified integration, the difference in peak area and percent difference of the change were included in the tables. The percent change in peak area should be equivalent to the change in calculated concentration since the internal standard response did not change between the initial integration and the reintegration of the samples listed.

The reintegrations were performed in accordance with the above referenced SOP in place at the time of the study. The reintegrations were performed to ensure the integrity of the chromatography and that data was accurately reported. Each reintegration was reviewed by a second scientist of adequate experience and knowledge. A relatively low percentage of samples for the parent and main analyte, atorvastatin, as well as the more abundant metabolite, ortho-hydroxyatorvastatin, were re-integrated and these analytes have the larger contribution to the overall systemic exposure of atorvastatin from a safety and efficacy perspective.

Initial chromatograms, for all manually modified chromatography for each study, were saved as word document files for each batch (AA77267 Manual Edited Chromatography and AA77268 Manual Edited Chromatography). Complete sets of chromatograms for all batches with at least one manual reintegration have been saved as pdf files (AA77267 Accepted Batch Chromatography and AA77268 Accepted Batch Chromatography).

Refer to Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance".

Statistical evaluation:

In order to evaluate the impact of the samples for which manual reintegration was performed, analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t and Cmax PK parameters for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin for both studies under fed (AA77268) and fasted conditions (AA77267) for exploratory purposes, to determine if setting the manually integrated samples to missing had an effect on the PK conclusions.

Excluding the manually reintegrated samples did not significantly impact the results nor alter the conclusion of either study. Specifically, the bioequivalence criteria were still met for the assessed parameters in both the fed and fasted studies. The resultant QC'd summary of results tables for the 3 analytes under

fasted (AA77267) and fed (AA77268) conditions are presented in Attachment 4 and Attachment 5.

The 90% confidence intervals of the ratios of LSM derived from the analyses on the ln-transformed PK parameters AUC 0-t and Cmax of the test to reference formulation for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin in plasma were within the 80.00 – 125.00% FDA acceptance range for both studies. This analysis suggests that manual reintegration of samples for AA77268 and AA77267 does not have any effect on the assessment of bioequivalence and the original conclusions can be upheld.

In conclusion, (b) (4) considers the chromatograms to have been appropriately re-integrated per applicable SOP and the results can be considered valid. In addition, statistical re-analysis of the data with and wihout the modified data confirms the original study conclusion that the data supports bioequivalence for Atorvastatin. (b) (4) will make clarifications to its SOP GL-BIO-10603 to ensure that there is no ambiguity in interpretation."

Reviewer's Comments:

1. The firm notes the following regarding (b) (4) site located in (b) (4):

For the inspection referenced above, the bio-analytical phase was performed at (b) (4). The data generated and processes used for that study are in no way related to the (b) (4) site or the data generated for the studies in question in this deficiency letter. Moreover, since then, (b) (4)) implemented a new global SOP GL-BIO-10610 (Attachment 1) with strict controls for performing manual reintegration. The (b) (4) site was closed in 2003 and the records for the site are retained in (b) (4) Studies AA77267 and AA77268 were analyzed in 2009 in (b) (4) under the new SOP.

It should be noted that in April 2011, the (b) (4) site was inspected by FDA. The inspection included a study in which a number of chromatograms were re-integrated. The FDA inspector(s) also reviewed the SOPs used by the (b) (4) bio-analytical laboratory, including SOP GL-BIO-10610. At the conclusion of the inspection, there were no observations issued regarding reintegration.

2. The firm notes that there were multiple manual reintegrations performed for both studies with the majority of them being made to remove a small tailing peak for para-hydroxyatorvastatin. The reintegrations are summarized in the tables below:

Study AA77267	
Total number of subject samples analyzed	5310
Number of system suitability (SS), QC & STD samples re-integrated	80
Number of subject samples re-integrated	995
Number of Treatment A samples re-integrated	484
Number of Treatment B samples re-integrated	511

AA77267 - Manual Re-integrations per analyte (Percent of total subject samples assayed in parenthesis)			
Analyte	Atorvastatin	Ortho-hydroxyatorvastatin	Para-hydroxyatorvastatin
Total Re-integrations	122 (2.3%)	46 (0.9%)	827 (15.6%)

Study AA77268	
Total number of subject samples analyzed	3261
Number of system suitability (SS), QC & STD samples re-integrated	55
Number of subject samples reintegrated	386
Number of Treatment A samples re-integrated	185
Number of Treatment B samples re-integrated	201

AA77268 - Manual Re-integrations per analyte (Percent of total subject samples assayed in parenthesis)			
Analyte	Atorvastatin	Ortho-hydroxyatorvastatin	Para-hydroxyatorvastatin
Total Re-integrations	60 (1.8%)	31 (1.0%)	295 (9.0%)

3. As shown in the table above, a relatively low percentage of samples for the parent and main analyte, atorvastatin (2.3% fasting study, 1.8% fed study), as well as the more abundant metabolite, ortho-hydroxyatorvastatin (0.9% fasting study, 1.0% fed study), were re-integrated.

4. Per the Bioanalytical Method Validation Guidance[8], sample data reintegration requires a standard operating procedure (SOP) or guideline that explains the reasons for integration and how the reintegration is to be performed. The rationale for the reintegration should also be clearly described and documented. Both original and reintegration data should be reported.

5. The firm submitted its Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance". Version 01, which was in place at the time of the study. The following procedures are outlined in its SOP:

[8] Guidance for Industry: Bioanalytical Method Validation. May 2001

The reintegrations were performed per the procedures outline in the SOP.

6. As requested by DBE, the firm submitted its reintegration tables for both studies (AA77267 and AA77268). The tables include fields for compound, sample type, subject ID, period, treatment, and whether the reported result was below the limit of quantitation (BLQ), initial integration peak area, modified integration peak area, batch number, injection number and reason for modification. An example of this table is shown below (for more details please refer to Attachments 2 and 3 of the firm's current submission[9]):

[9] \\Cdsesub1\evsprod\ANDA091624\0006\m1\us\responses-to-deficiency.pdf.

[redacted] (b) (4) **Response to Deficiency**
Project No. AA77267 & AA77268

Compound	Sample Type	Subject	Period	Treatment	Timepoint	BLQ	Initial Integration Peak Area	Modified Integration Peak Area	Integration Difference	Integration % Difference	Method Used for Reintegration	Reported Integration Result	Batch #	Injection #	Reason for Modification
Parahydroxy Atorvastatin	Unknown Sample	0002	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	Unknown Sample	0003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	Unknown Sample	0004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	Unknown Sample	0004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	Unknown Sample	0005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(b) (4)

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7. The reviewer checked the firm's reintegration table. The reviewer found that for the parent drug, atorvastatin, for majority of the samples, the integration % differences are below 20%. There are few samples that have integration % differences greater than 20% (see table below). Note that none of these samples occurred at Cmax:

Fasting study (AA77267) - Atorvastatin

Subject	Treatment*	Timepoint (hours)	Integration % Difference (%)	Reason for Modification	Occurs at Cmax Value?
22	A	60	80.5	Draw Baseline Valley to Valley	No

**** Test = A; Reference = B***

Fed study (AA77268) - Atorvastatin

Subject	Treatment*	Timepoint (hours)	Integration % Difference (%)	Reason for Modification	Cmax Value?
26	A	48	71.3	Draw Baseline Valley to Valley	No
32	A	60	78.6	Integrate Entire Peak	No
51	A	30	61.1	Exclude Interference from Peak	No

56	B	36	20.8	Exclude Interference from Peak	No
64	B	60	150.2	Exclude Interference from Peak	No
81	A	0.3333	106.1	Exclude Interference from Peak	No
5	A	24	21.7	Exclude Interference from Peak	No
5	B	60	35.0	Exclude Interference from Peak	No

**** Test = A; Reference = B***

8. The firm did not submit the original assay data (before reintegration). The firm is asked to submit the following:

   - Electronic SAS Transport data files (.xpt) for **all original concentration and PK parameter data obtained before reintegration** for its fasting (AA77267) and fed (AA77268) BE studies, as well as the summary tables of the BE results.

   - Raw pre-reintegration chromatography/numerical data for its fasting (AA77267) and fed (AA77268) BE studies.

9. The firm's response to the current deficiency comment is **inadequate.**

DBE's Previous Deficiency Comment No. 3 (See the review of the amendment dated 12 January 2011)**:**

According to your standard operating procedure (SOP) for repeat analysis (SOP# GL-BIO-10601-01), "if an analytical reason for reassay can be assigned to a sample, the original result is not reported." For future submissions, please revise your SOP to include the procedure of reporting the original results of all reassays, including the analytical related reassays, if applicable.

Firm's Current Response No. 3:

"The SOP referenced in the comment is a (b) (4) *SOP. The applicant has conveyed this information to* (b) (4) *."*

Reviewer's Comments:

The firm's response to this deficiency is **adequate**.

3.9 Review of the Analytical Sites ([redacted])

3.9.1 Review of the DSI findings for [redacted]

At the request of the Division of Pulmonary and Allergy Products (DPAP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the bioequivalence studies of [redacted]. The studies (analytical portions) were conducted at [redacted]. This is the same site where the subject samples from the bioequivalence (BE) studies for the current application were also analyzed. Following the inspections [redacted] a Form FDA 483 was issued for the analytical portion[10].

[redacted]

DSI's Conclusions:

[redacted]

- *For future studies, [redacted] should conduct ISR assessments for all bioequivalence studies as per their revised SOP [redacted] for the first [redacted] samples and [redacted] thereafter for larger studies).*

DBE Reviewer's Comments About the Impact of DSI Findings on the Current Application:

[10] DARRTS [redacted]: CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review). [redacted]

The above listed DSI findings regarding the issues are not expected to have impact on the outcome of the current ANDA for the following reasons:

- Currently, the DBE does not require the calibration standards and quality control samples be prepared separate from stock solution. Per the Bioanalytical Method Validation Guidance (issued May 2001), page 18, *"Standards and QC samples can be prepared from the same spiking stock solution, provided the solution stability and accuracy have been verified. A single source of matrix may also be used, provided selectivity has been verified."*
- Currently, the Agency does not have evaluation criteria for ISR.
- The stability of the current application has been adequately demonstrated.
- The firm has listed the following batch acceptance criteria:

  Standards were rejected if they were greater than ± (b)(4)% (all standards but the LLOQ) or ± (b)(4)% (LLOQ only) of the nominal concentration.

  At least 75% of the non-zero standards were within the respective acceptance criterion.

  At least two-thirds of the low, medium, and high QCs, including at least 50% at each concentration level, were valid data points and were within ± (b)(4)% of the nominal concentration.

  For the fasting study, the firm listed only one rejected batch (batch #70) for metabolite (Parahydroxy Atorvastatin) analysis due to "std/qc fail acceptance". For the fed study, there was no rejected batch.

3.9.2 Review of the DSI findings for NDA (b) (4)

At the request of the Division of Metabolism and Endocrinology, the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the bioequivalence studies of NDA (b) (4). The analytical portion was conducted at (b) (4). Following the inspection of (b) (4) Form FDA-483 was issued. This is the same site where the subject samples from the bioequivalence (BE) studies for the current application were also analyzed[11].

DSI finding #1*: Although the run acceptance criteria for calibration standards and quality control samples were met, two analytical runs # 2 and 31 for (b) (4) were re-assayed and rejected due to improbable contaminations.*

DBE Reviewer's Comments About the Impact of DSI Finding #1 on the Current Application:

[11] DARRTS: CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review). 07/09/2010.

In the current application, there was no sample being reassayed due to improbably contaminations. This finding is not expected to have impact on the outcome of the current application.

DSI finding #2: *170 study samples identified Unacceptable Internal Standard Response (UISR) for* (b) (4) *were re-assayed and the data for these UISR samples were rejected.*

DBE Reviewer's Comments On the Impact of DSI Finding #2 on the Current Application:

In the current application, for the parent drug atorvastatin, there were only few samples that were reassays due to UISR (one sample (0.019%) reassayed in the fasting study, and 7 samples (0.215%) reassayed in the fed study). This finding is not expected to have impact on the outcome of the current application**.**

DSI finding #3: *Failure to follow your SOP, Laboratory Documentation, SOP number 03.01.009 version 19, dated 30-Apr-2009. Specifically,* (b) (4) *Maintenance Logs, LH5 SIN 550450N4507, LH2, SIN 550235N4655, in review of these logs the "Disclosed To And Understood By" section should be signed and dated within 2 business days of signature date. The disclosed signature was not signed until 8 months later, and the "Verified By Date" was signed after the Disclosed Signature. In review of LC/MS# 19 SIN 5061020B, the "disclosed To And Understood By" section is again signed late. Some pages are marked "late Review" Some are not.*

DBE Reviewer's Comments On the Impact of DSI Finding #3 on the Current Application:

This finding is not expected to have impact on the outcome of the current application**.**

3.9.3 Review of the DSI findings for NDA (b) (4)

DSI finding #1*: The stability of* (b) (4) *in the presence of the coadministered medication* (b) (4) *was not evaluated as part of method validation. Specifically, long-term and freeze-thaw stability of* (b) (4) *in human plasma in the presence of* (b) (4) *was not evaluated.*

To assure that (b) (4) *is stable in the presence of* (b) (4) *during long term storage, and during the freezing and thawing of subject plasma samples,* (b) (4)*. should provide these stability data generated in the presence of* (b) (4)

DBE Reviewer's Comments On the Impact of DSI Finding #1 on the Current Application:

In the current application, there are no issues with concomitant medications and the firm has previously submitted acceptable long-term storage stability (LTSS) data. This finding is not expected to have impact on the outcome of the current application.

3.10 Deficiency Comments

The firm did not submit its original (before reintegration) data. The firm is asked to submit the following:

- Electronic SAS Transport data files (.xpt) for **all original concentration and PK parameter data obtained before reintegration** for its fasting (AA77267) and fed (AA77268) BE studies. The bioequivalence data to be submitted in an ANDA should be provided in SAS Transport format in two separate files as described below:

  a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf KE_FIRSTKE_LAST (where KE_FIRST and KE_LAST are the beginning and ending time points selected for calculation of the elimination constant KE, and expressed in the order of the time points, e.g., KE_FIRST=12 means the 12th time point.)

  b. SUBJ SEQ PER TRT C1 C2 C3..... Cn T1 T2 T3…… Tn Each field should be separated with a blank space, and missing values should be indicated with a period (.).

- The firm should also submit a summary of its BE results, using data **before** reintegration, in the following tabular format

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	$T½$ (hr)	K_{el} (hr-1)	
Study #	Fasting study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol.# p.#
Study #	Fed study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol. # p. #

Drug name Dose Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No.				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)				
AUC∞ (hr *ng/ml)				
Cmax (ng/ml)				

Drug name Dose Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No.				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)				
AUC∞ (hr *ng/ml)				
Cmax (ng/ml)				

- The firm should also submit raw chromatography and/or numerical data recorded before reintegration

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (AA77267) incomplete due to the deficiencies mentioned above. The fasting study was conducted by Kudco Ireland, Ltd. on its Atorvastatin 80 mg Tablets (lot # P803401) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 08107V).

2. The Division of Bioequivalence finds the fed BE study (AA77268) incomplete due to the deficiencies mentioned above. The fed study was conducted by Kudco Ireland, Ltd. on its Atorvastatin 80 mg Tablets (lot # P803401) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 08107V).

3. The firm's *in vitro* dissolution testing is acceptable. The DBE acknowledges that the firm will conduct dissolution testing according to the following method:

Apparatus	USP apparatus II (Paddle)
Medium	0.3% Polysorbate 80 in 0.05 M Phosphate Buffer, pH 6.8
Volume	900 mL
Speed	75 rpm

Temperature	37 ºC ± 0.5 ºC
Specification	NLT (b)(4)% (Q) of Atorvastatin dissolved in 30 minutes

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	N/A

3.13 Additional Attachments

From: CDER DSI Bioequivalence
Sent: Thursday, July 14, 2011 1:41 PM
To: Chun, Nam
Cc: Walters, Johnetta F.
Subject: RE: Please provide DSI inspection history for below sites for ANDA 091624

Attachments: (b) (4) 06242011.doc.PDF
The BE studies in this application were done in approximately 2009. Note that MDS in Montreal closed in early 2010
http://www.theglobeandmail.com/globe-investor/montreal-unit-of-mds-to-be-closed/article1462555/
and (b) (4). It is our understanding that some records from Montreal may have been moved to (b) (4)

Inspection history:
MDS/Montreal
6/4/07, NDA 22-118, NAI
pending, (b) (4)
pending, (b) (4)

(b) (4)
12/8/08, (b) (4), VAI
(b) (4), (b) (4), VAI
6/29/10, (b) (4), VAI
(b) (4), (b) (4), VAI
6/20/11 (b) (4) classification pending:

(b) (4)

From: Chun, Nam
Sent: Thursday, July 14, 2011 10:42 AM
To: CDER DSI Bioequivalence
Cc: Walters, Johnetta F.
Subject: Please provide DSI inspection history for below sites for ANDA 091624

Clinical Site	MDS Pharma Services
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345
Analytical Site	(b) (4)
Analytical Site Address	

Thanks,

Nam (Esther) Chun, Pharm.D.
LCDR, U.S. Public Health Service
Regulatory Project Manager, Branch VI
Division of Bioequivalence I
Office of Generic Drugs
FDA

BIOEQUIVALENCE DEFICIENCIES

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
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 identified the following deficiencies:

On 27 June 2011, you submitted an amendment to address the deficiencies communicated in the DBE letter dated 25 April 2011. Regarding the objectionable finding identified by the Division of Scientific Investigations (DSI) related to the analytical site's manual reintegration practice, you provided justification for the manual reintegration of the study samples in your bioequivalence studies. The DBE has reviewed your response and found that it is not adequate for the following reason:

You stated that *"To evaluate the impact between the initial integration and the modified integration, the difference in peak area and percent difference of the change were included in the tables. The percent change in peak area should be equivalent to the change in calculated concentration since the internal standard response did not change between the initial integration and the reintegration of the samples listed"*, and that *"In order to evaluate the impact of the samples for which manual reintegration was performed, analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t and Cmax PK parameters for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin for both studies under fed (AA77268) and fasted conditions (AA77267) for exploratory purposes, to determine if setting the manually integrated samples to missing had an effect on the PK conclusions. Excluding the manually reintegrated samples did not significantly impact the results nor alter the conclusion of either study. Specifically, the bioequivalence criteria were still met for the assessed parameters in both the fed and fasted studies."*

However, you have not demonstrated that ***including*** the original results of these reintegrated samples (results prior to reintegration) in the statistical analysis of both

the fed and fasted studies did not change the study outcome. In addition, you did not provide all the original assay results (prior to reintegration) to the DBE for verification.

Therefore, we ask that you submit the following additional information/data:

- Electronic SAS Transport data files (.xpt) for **individual concentration and PK parameter data that are based on original integration results (i.e., obtained before reintegration)** for your fasting (AA77267) and fed (AA77268) studies. These bioequivalence data to be submitted in the two usual separate files as described below:

  a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf KE_FIRSTKE_LAST (where KE_FIRST and KE_LAST are the beginning and ending time points selected for calculation of the elimination constant KE, and expressed in the order of the time points, e.g., KE_FIRST=12 means the 12th time point.)

  b. SUBJ SEQ PER TRT C1 C2 C3..... Cn T1 T2 T3…… Tn Each field should be separated with a blank space, and missing values should be indicated with a period (.).

- The summary of your study results, based on the data of the original integration (**before** reintegration), in the following tabular format:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr-1)	
Study #	Fasting study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol.# p.#
Study #	Fed study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol. # p. #

Drug name Dose Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No.				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)				
AUC∞ (hr *ng/ml)				
Cmax (ng/ml)				

- You also stated in the current amendment that *"Initial chromatograms, for all manually modified chromatography for each study, were saved as word document files for each batch (AA77267 Manual Edited Chromatography and AA77268 Manual Edited Chromatography). Complete sets of chromatograms for all batches with at least one manual reintegration have been saved as pdf files (AA77267 Accepted Batch Chromatography and AA77268 Accepted Batch Chromatography). Refer to Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance".* For verification, please submit all aforementioned initial chromatograms for each manually modified chromatography from both studies, together with legible raw numerical data associated with these chromatograms.

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

3.14 Outcome Page

ANDA: 091624

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
14598	6/27/2011	Other	Study Amendment	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/

HARITHA MANDULA on behalf of JOHNETTA F WALTERS
07/25/2011

BING V LI
07/25/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/25/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091624		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg		
Applicant Name	KUDCO Ireland Limited		
Address	Shannon Industrial Estate Shannon, County Clare Republic of Ireland		
Authorized US Agent	Elaine Siefert, Director Regulatory Affairs, Kremers Urban LLC 1101 C Ave W Seymour IN 47274		
Contact's Telephone Number	(812) 523-5544		
Contact's Fax Number	(812) 523-6889		
Original Submission Date(s)	15 July 2009 26 February 2010 (dissolution amendment)		
Submission Date(s) of Amendment(s) Under Review	12 January 2011		
Reviewer	Johnetta F. Walters, Ph.D.		
Study Number (s)	AA77267	AA77268	
Study Type (s)	Fasting	Fed	
Strength (s)	80 mg	80 mg	
Clinical Site	MDS Pharma Services		
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI INSPECTION RESULT	**INADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
6	**Study Amendment**	**10 mg, 20 mg, 40 mg, 80 mg**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This is a review of a study amendment only.

The firm has previously submitted the results of fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies comparing a test product, Kudco Ireland's Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfizer'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 and female subjects. The results are summarized in the tables below.

Atorvastatin, 1 X 80 mg
Fasting Bioequivalence Study No. AA77267, N=140 (Male=96 and Female=44)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	129.57	134.57	0.96	92.08	100.67
AUC∞ (ng·hr/mL)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/mL)	28.59	32.71	0.87	80.72	94.63

Atorvastatin, 1 X 80 mg
Fed Bioequivalence Study No. AA77268, N=86 (Male=56 and Female=30)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	159.22	158.02	1.01	96.54	105.16
AUC∞ (ng·hr/mL)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/mL)	37.25	40.20	0.93	82.82	103.67

The metabolite data were previously deemed supportive.

The firm's fasting and fed BE studies were inadequate due to the deficiencies related to the bioanalytical study. The firm's dissolution testing was also incomplete. (DARRTS: REV-BIOEQ-02 (Dissolution Review) 12/18/2009 and 08/11/2010).

In the *current* submission, the firm has submitted adequate responses to previous DBE deficiencies which include the original and repeat values of samples that were reanalyzed for further evaluation by the DBE. The firm has also submitted adequate dissolution testing data. The dissolution testing data met the FDA – recommended specification at S_2 level. The dissolution testing, however, is incomplete pending the firm's acceptance of the FDA – recommended dissolution specification.

A routine inspection was completed for the clinical site on 06/14/2007 for NDA 022118. The outcome was No Action Indicated (NAI)[1]. The Division of Scientific Investigations (DSI) Inspection concluded that the findings should not significantly impact the outcome of the study. A routine inspection was completed for the analytical site on (b) (4) for (b) (4). The outcome was Voluntary Action Indicated (VAI). The current reviewer reviewed the VAI DSI inspection report for the analytical site, and found that DSI Finding #6, regarding the firm's practice on chromatogram peak integration, might have effect on the outcome of the current application. Therefore, the firm should verify its practice of chromatogram peak integrations as related to the current ANDA. Please see section 3.8 of the current review for more detail.

The application is **inadequate**.

[1] DARRTS, Search: NDA 022118. O Shaughnessy, Jacqueline A/06-14- 2007/REV-NONCLINICAL-03(General Review).

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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: **(1) Prevention of cardiovascular disease** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina • **(2) Hypercholesterolemia** LIPITOR® is indicated:

[2] Electronic Orange Book: http://www.accessdata fda.gov/scripts/cder/ob/default.cfm. Last accessed: 16 April 2010.
[3] Drugs at FDA: http://www.accessdata fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 16 April 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)	**WARNINGS** **Liver Dysfunction** HMG-CoA reductase inhibitors, like some other lipid- lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin. **Skeletal Muscle** **Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin- treated patients. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin,

	immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	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.

Summary of OGD or DBE History	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, current)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

[5] Individual Product Bioequivalence Recommendations: http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. Last accessed: 16 April 2010.
[6] DARRTS Search: Submission Search Results: http://darrts.fda.gov:7777/darrts/submissionSearch.do.

3.5 Formulation

Location in appendix	DARRTS: ANDA 091624. REV-BIOEQ-01(General Review). 08/11/2010.
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.6 In Vitro Dissolution[7]

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review). 12/18/2009.
Source of Method (USP, FDA or Firm)	Firm
Medium	0.3% Tween 80 in 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?	**METHOD ACCEPTABLE; Dissolution testing incomplete (see below)**
If not then why?	The firm should accept the FDA – recommended, data - driven specification of "NLT (b)(4)% (Q) in 30 minutes".

*From FDA Internal Dissolution Database.

3.7 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?	No
Waivers granted?	**WAIVERS NOT GRANTED**
If not then why?	See deficiency section

[7] The current dissolution data was taken from the amendment submitted on 12 January 2011 and may be found in DARRTS.

3.8 Review of DSI Inspection Reports of the Analytical Site for the Related ANDA:

A routine inspection was completed for the clinical site on 06/14/2007 for NDA 022118. The outcome was No Action Indicated (NAI)[2]. The Division of Scientific Investigations (DSI) Inspection concluded that the findings should not significantly impact the outcome of the study.

A routine inspection was completed for the analytical site on (b) (4) for NDA (b) (4) The outcome was Voluntary Action Indicated (VAI). The DSI inspection report for NDA (b) (4) identified the following DSI-findings:

Analytical Site Inspection Review:

DSI Finding #1: Accuracy of analytical runs 119, 123, 127, 130 and 142 was not assured in that >50% of low QCs were inaccurate (i.e. >15% of nominal).

Reviewer's Comments: In the current application, the percent coefficient of variation (CV) for the LQC is 6.3% for the fasting bioequivalence study and 6.0 for the fed bioequivalence study. Therefore DSI finding #1 is not applicable to the current application.

DSI Finding #2: Dilution accuracy was not demonstrated in analytical runs 118 and 144.

Reviewer's Comments: In the current application, the accuracy of sample dilution was verified by the performance of dilution QC samples. At least 50% of the diluted QC samples (denoted with the dilution factor following the QC identifier) were within (b) (4)% of the nominal. Precision (%CV) was 2.6% for atorvastatin, 3.1% for parahydroxy atorvastatin, and 2.4% for orthohydroxy atorvastatin; accuracy (%Bias) was -4.2% for atorvastatin, -1.4% for parahydroxy atorvastatin, and -2.0% for orthohydroxy atorvastatin. Therefore DSI finding #2 is not applicable to the current application.

DSI Finding #3: Not all re-assays were reported in the Repeat Analysis table of analytical report (b) (4) For example, dilution repeats from analytical run 168 were not reported in the analytical report.

Reviewer's Comments: All analytical repeats were reported in the Reanalysis of Study Samples (Table 3) in the original review[8] and the analytical reports (Attachment 3 to study reports AA77267-01 and AA77268-01) of the current ANDA. Therefore DSI finding #3 is not applicable to the current application

DSI Finding #4: Failure to reject assay runs when 100% of the 75 ng/mL Quality Control samples failed.

[8] DARRTS: ANDA 091624. REV-BIOEQ-01(General Review).08/11/2010.

Reviewer's Comments: In the current application, standards were rejected if they were greater than ± (b)(4)% (all standards but the LLOQ) or ± (b)(4)% (LLOQ only) of the nominal concentration. At least 75% of the non-zero standards were within the respective acceptance criterion. At least two-thirds of the low, medium, and high QCs, including at least 50% at each concentration level, were valid data points and were within ± (b)(4)% of the nominal concentration as outlined in SOP number GL-BIO-10602-03. Therefore DSI finding #4 is not applicable to the current application

DSI Finding #5: Accuracy of analytical run 1, 5, 13, 15, 18, 20, 23, 25, 26, 30, 31, 33, 34, 36, 40, 43, 45, 47, 64, and 67 was not assured in that >50% of QCs at a single concentration were inaccurate (i.e. > (b)(4)*% of nominal).*

Reviewer's Comments: In the current application, the CV% of all QC samples ranged from 1.9 to 5.6 for atorvastatin, 2.2 to 4.6 for orthohydroxy atorvastatin, and 2.1 to 6.4 for parahydroxy atorvastatin (i.e.< (b)(4)% of nominal). Since these values are less than (b)(4)%, the %CV and thus, the accuracy of the data is considered to be acceptable.

DSI Finding #6: Analytical results, specifically chromatogram peak integrations, were modified. These modifications were made by manually picking the baseline or changing integration parameters.

Reviewer's Comments: While there was no evidence of any modification of chromatogram peak integrations found in the ANDA submission, the firm should verify its practice of chromatogram peak integrations as related to the current ANDA (see deficiency section 3.10 for details).

As shown in the comments above, the DSI findings numbers 1 – 5 for NDA 021567 are not expected to affect the current study. The firm should, however, address finding number six as specified in the Reviewer's Comments above.

3.9 Firm's Current Responses to DBE Deficiency Comments

DBE's Previous Deficiency Comment No. 1 (See the review of the original submission dated 11 August 2010)**:**

For repeat analysis of fasting BE study (study # AA77267), there was a discrepancy in your summary tables (Table 9, Section 5.3.1.4.1 of the electronic submission) and the full analytical report (Section 5.3.1.4 of the electronic submission): The summary table reported a total of 25 reassays for non-analytical reasons; the full analytical report indicated a total of 34 reassays for non-analytical reasons. Please explain this discrepancy.

Firm's Current Response No. 1:

"*The question refers to 25 reassays for non-analytical reasons, however the applicant would like to note there were only twenty (20) samples reassayed for non-analytical reasons (as "values requiring confirmation (VRC)"). In OGD Table 9, submitted for inclusion in the electronic submission, there were seven (7) non-analytical reassays for Atorvastatin, eight (8) non-analytical reassays for orthohydroxy Atorvastatin and five (5) non-analytical reassays for parahydroxy Atorvastatin. In Table 7 of the Bioanalytical report, "Summary of Reassays for Non-analytical Reasons", the fourteen (14) bracketing samples, run with the VRC samples to confirm batch reproducibility, were also included in the total number of samples reassayed for non-analytical reasons (i.e. 34 total samples).*

The bracketing samples were not included as non-analytical reassays in OGD Table 9 because their purpose was to confirm a result for which there was no suspected analytical anomaly (similar to incurred sample reproducibility reassays) rather than to confirm or negate a value for which there was a suspected analytical anomaly. The purpose and procedure for reporting bracketing samples is described in Sections 8.4 and 8.5 of SOP GL-BIO-10603-03 "Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples" in Attachment 2 to the Bioanalytical report."

Reviewer's Comments:

The firm has decided not to include bracketing samples as non-analytical reassays in the Sample Reanalysis Table because their purpose was to confirm a result for which there was no suspected analytical anomaly. The firm has submitted the purpose and procedure for reporting bracketing samples (Sections 8.4 and 8.5 of SOP GL-BIO-10603-03 "Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples").

Per SOP No. GL-BIO-10603-03, *"Bracketing samples may be reassayed along with values requiring confirmation. The bracketing samples selected and the reason for including bracketing study samples is documented before reassay."*

Bracketing samples are adjacent to the VRC sample under event investigation in the order established either by the concentration versus time profile, extraction, or injection sequence."

The reviewer agrees with the firm's rationale of not including bracketing samples as non-analytical reassays in the Sample Reanalysis Table.

There were seven (7) samples for the fasting study and four (4) samples for the fed study that were reassayed for pharmacokinetic (PK) reasons (for the parent drug, Atorvastatin). Please see the tables below:

Study No.AA77267-01 (Atorvastatin) Additional information in AA77267-01 Section 3.7								
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	
	A	B	A	B	A	B	A	B
Pharmacokinetic[1]	2	5	.038%	.094%	1	1	.019%	.019%
AAR	6	6	.113%	.113%	6	6	.113%	.113%
ISP	1	0	.019%	.000%	1	0	.019%	.000%
UISR	1	0	.019%	.000%	1	0	.019%	.000%
Total	10	11	.188%	.207%	9	7	.169%	.132%

Study No.AA77268-01 (Atorvastatin) Additional information in AA77268-01 Section 3.7								
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	
	A	B	A	B	A	B	A	B
Pharmacokinetic[1]	3	1	.092%	.031%	2	1	.061%	.031%
AAR	10	14	.307%	.429%	10	14	.307%	.429%
IIA	0	1	.000%	.031%	0	1	.000%	.031%
ISP	1	0	.031%	.000%	1	0	.031%	.000%
UISR	0	7	.000%	.215%	0	7	.000%	.215%
Total	14	23	.429%	.705%	13	23	.399%	.705%

The reviewer has examined these reassay samples, and found that the firm's PK reassays follow its SOP for both selecting and reporting repeat values for the fasting and fed studies.

In addition, the reviewer has analyzed the firm's data using both original and repeated values, for confirmation. The 90% confidence intervals of atorvastatin are all within the BE acceptance criteria of 80.00-125.00%, as shown below:

Fasting study (using original values):

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. AA77267, N=140 (Male=96 and Female=44) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	129.57	134.57	0.96	92.08	100.67
AUC∞ (ng·hr/mL)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/mL)	28.59	32.71	0.87	80.72	94.63

Fasting study (using repeated values):

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. AA77267, N=140 (Male=96 and Female=44) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	129.58	134.61	0.96	92.04	100.68
AUC∞ (ng·hr/mL)	136.89	143.64	0.95	91.12	99.67
Cmax (ng/mL)	28.63	32.70	0.88	80.84	94.82

Fed study (using original values):

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. AA77268, N=86 (Male=56 and Female=30) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	159.22	158.02	1.01	96.54	105.16
AUC∞ (ng·hr/mL)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/mL)	37.25	40.20	0.93	82.82	103.67

Fed study (using repeated values):

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. AA77268, N=86 (Male=56 and Female=30) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	159.12	158.19	1.01	96.42	104.93
AUC∞ (ng·hr/mL)	167.44	166.02	1.01	96.48	105.43
Cmax (ng/mL)	37.25	40.20	0.93	82.82	103.67

As a result, the firm's response to this deficiency is **adequate**.

DBE's Previous Deficiency Comment No. 2 (See the review of the original submission dated 11 August 2010)**:**

For repeat analysis of both fasting and fed studies (study # AA77267 and AA77268, respectively), you only submitted the original concentrations of the samples reanalyzed due to non-analytical reasons. Please provide complete tables containing the original concentrations and repeated concentrations for all reanalyzed study samples, where possible.

Firm's Current Response No. 2:

"Reassay tables for AA77267 and AA77268 are included herein. The reassay tables list the original concentrations and the reassay concentration for all bioanalytical reassays."

Reviewer's Comments:

The firm has provided the following reassay tables:

AA77267:

ANDA 091624
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Amendment 0005: Bioequivalence Response to Information Request

Compound	Custom ID	Subject Period	Timepoint	Initial Assay Result (ng/mL)	Initial Assay Run Identification Batch #	 Injection #	Reason for Repeat Assay	Repeat Assay Result (ng/mL)	Repeat Assay Run Identification Batch #	 Injection #	Reported Result (UNITS)	Approved by
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Legend:
Reason for repeat assay are pre-defined in [redacted] (b) (4) SOP 03.01.111 Version 1
AAR - Above Analytical Range
UCR - Unacceptable Chromatography Response
UISR - Unacceptable Internal Standard Response
ISP - Incomplete Sample Processing

AA77268:

ANDA 091624
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Amendment 0005: Bioequivalence Response to Information Request

(b) (4)

Compound	Custom ID	Subject	Period	Timepoint	Initial Assay Result (ng/mL)	Initial Assay Run Identification: Batch #	Initial Assay Run Identification: Injection #	Reason for Repeat Assay	Repeat Assay Result (ng/mL)	Repeat Assay Run Identification: Batch #	Repeat Assay Run Identification: Injection #	Reported Result (ng/mL)	Approved by
Atorvastatin	[redacted]												
Atorvastatin	[redacted]												
Atorvastatin	[redacted]												
Atorvastatin	[redacted]												
Atorvastatin	[redacted]												
Atorvastatin	[redacted]												
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Atorvastatin	[redacted]												
Atorvastatin	[redacted]												

(b) (4)

						Initial Assay Run Identification				Repeat Assay Run Identification			
Compound	**Custom ID**	**Subject**	**Period**	**Timepoint**	**Initial Assay Result (ng/mL)**	**Batch #**	**Injection #**	**Reason for Repeat Assay**	**Repeat Assay Result (ng/mL)**	**Batch #**	**Injection #**	**Reported Result (ng/mL)**	**Approved by**
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthohydroxy Atorvastati	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(b) (4)

Compound	Custom ID	Subject	Period	Timepoint	Initial Assay Result (ng/mL)	Initial Assay Run Identification Batch #	Initial Assay Run Identification Injection #	Reason for Repeat Assay	Repeat Assay Result (ng/mL)	Repeat Assay Run Identification Batch #	Repeat Assay Run Identification Injection #	Reported Result (ng/mL)	Approved by
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(b) (4)

						Initial Assay Run Identification				Repeat Assay Run Identification			
Compound	Custom ID	Subject	Period	Timepoint	Initial Assay Result (ng/mL)	Batch #	Injection #	Reason for Repeat Assay	Repeat Assay Result (ng/mL)	Batch #	Injection #	Reported Result (ng/mL)	Approved by
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parahydroxy Atorvastatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Legend:
Reason for repeat assay are pre-defined in [redacted] (b) (4) SOP 03.01.111 Version 1
AAR - Above Analytical Range
IIA - Incomplete Instrument Analysis
UISR - Unacceptable Internal Standard Response
ISP - Incomplete Sample Processing
LSR - Low Standard Removed

According to the firm's SOP for repeat analysis, if an analytical reason for reassay can be assigned to a sample, the original result is not reported. Per DBE's request, the firm provided information of all analytical related repeated assays. The reviewer has evaluated these repeats. The reasons for repeat analysis are shown in the legend (above). These repeat values were obtained according to the firm's SOP for the identification of repeats as well as the firm's reporting procedures, and are acceptable. The firm's response to this deficiency is **adequate.**

For future submissions, the firm is advised to revise its SOP to include the procedure of reporting the original results of all reassays, including the analytical related reassays, if available.

DBE's Previous Deficiency Comment No. 3 (See the review of the original submission dated 11 August 2010):

Please specify the salt form of the Ethylenediaminetetraacetic Acid, (EDTA), i.e., K2EDTA, K3EDTA or NaEDTA, used in your pre-study method validation, bioanalytical studies and clinical studies.

Firm's Current Response No. 3:

"The salt form used was K_3EDTA."

Reviewer's Comments:

The firm has consistently used K_3EDTA as the salt form of Ethylenediaminetetraacetic Acid (EDTA) in its pre-study method validation, bioanalytical studies and clinical studies. The firm's response to this deficiency is **adequate**.

DBE's Previous Deficiency Comment No. 4 (See the review of the original submission dated 11 August 2010):

The dissolution data based your proposed dissolution method [900 mL of (b) (4)% Tween 80 in (b) (4) using USP Apparatus II (Paddle) at 75 rpm] indicated that this method was not sufficiently discriminative: For all strengths of your test product, more than (b) (4)% of the drug was released within 5 minutes. Please develop a new dissolution method or modify your current method for more gradual dissolution profiles by reducing the paddle speed and/or reducing the concentration of the surfactant in the medium, etc.

Firm's Current Response No. 4:

"Based on development data, a discriminative dissolution procedure has been validated. The revised analytical procedure (AP-897-02) is included herein. Additionally, revised sections 3.2.P.5.2, 3.2.P.5.3, and 5.3.1.3 are included in this amendment. The table below compares the original proposed procedure with the newly validated method.

	Original Method	Proposed Method
Dissolution Media	(b) (4) Tween 80 in (b) (4)	0.3% Tween 80 in pH 6.8 Phosphate Buffer
Media Volume	900 mL	900 mL
Paddle Speed	75 rpm (b) (4)	75 rpm (b) (4)
Media Temperature	37 ± 0.5°C	37 ± 0.5°C

The revised proposed method includes the addition of 0.3% Tween 80 to the OGD dissolution medium which is required to obtain complete release. Dissolution data (n=12) using the revised procedure is presented in the revised Table 5 (Summary of In Vitro Dissolution Studies). The method validation (890.VAL.REP9-0) is included herein.

As requested, the revised proposed procedure generates a more gradual dissolution profile versus the originally submitted method. Release of > (b) (4)% is not reached on a consistent basis until 15 minutes and the release profile is still slightly increasing at 30 minutes. The figures below provide a visual representation of the supporting data. Figure 1 compares the dissolution profiles of the 10, 20, 40 and 80 mg product using the proposed dissolution procedure. The f_2 values for Atorvastatin Calcium Tablets 10 mg, 20 mg and 40 mg versus the Atorvastatin Calcium Tablets 80 mg Registration batch are all greater than 50 indicating the dissolution profiles are similar as indicated in Table 5.1.

Figure 2 compares the release profiles of the 80 mg test product using the originally submitted procedure and the revised, more discriminating procedure."

Figure 1

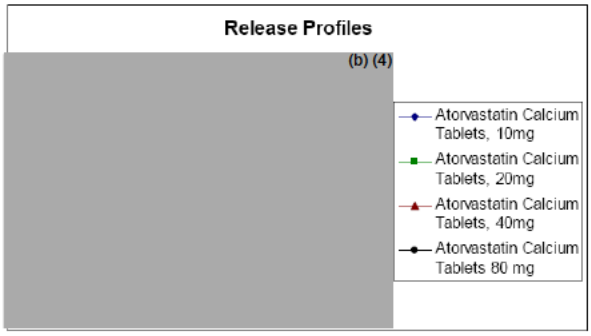
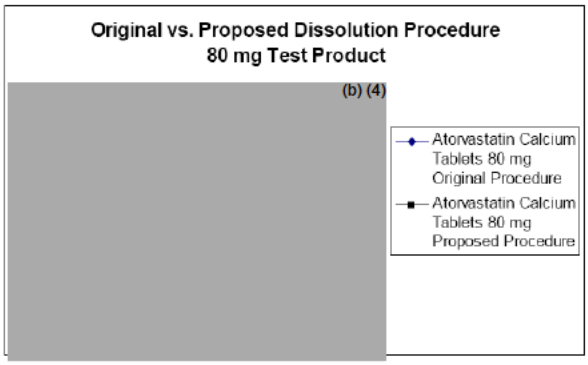


Figure 2



Reviewer's Comments:

1. The firm has currently submitted data using a newly revised dissolution method.

2. Previous submissions and dissolution history are summarized below:

   - In the original dissolution review[9], it was determined that there is no USP method for this drug product. There is, however, an FDA-recommended method (900 mL of 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm).

[9] DARRTS: REV-BIOEQ-02(Dissolution Review). 12/18/2009.

- The firm initially conducted dissolution testing using its own proposed method (900 mL of [(b) (4)]% Tween 80 in [(b) (4)] using USP Apparatus II (Paddle) at 75 rpm). Since the firm did not conduct dissolution testing using the FDA-recommended dissolution method (900 mL of 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm), it was recommended to do so.

- In the firm's previous dissolution amendment[10], the firm conducted and submitted dissolution testing on all strengths of the test and reference products (12 dosage units each) using the FDA-recommended method and sampling times.

    - Using the FDA – recommended method, the firm's test product released much slower than the reference product, especially for the higher strength (40 mg and 80 mg) which only released 52% and 45%, respectively, in 120 minutes. It was therefore deemed that the FDA's method was not suitable for the firm's test product.

    - The firm indicated that the formulation of the reference product contains Tween 80 (also known as polysorbate 80), which has been confirmed in the RLD product (NDA 020702, 11/2009 Annual Report and DARRTS: REV-QUALITY-03, Final Date 11/13/2000).

        - The amounts of Tween 80 contained in the RLD products are from [(b) (4)] to [(b) (4)] per tablets. The volume of the dissolution medium is 900 mL. Therefore, the concentrations of Tween 80 in the dissolution medium range from [(b) (4)]% to [(b) (4)]% (if the tablets are disintegrated completely) for the RLD product if the FDA-recommended method is used. The formulations of the test products do not contain Tween 80. Therefore, the different release rate of the test products, as compared with the reference products, using the FDA method may possibly be caused by the Tween 80 contained in the reference product.

    - After consulting with the DBE I dissolution focal point, Dr. Utpal Munshi, considering the borderline low 90% CIs for lnCmax in the biostudies, it was considered especially important that the method be highly discriminatory so that it could differentiate among test lots. As a result, we recommended that the firm develop a more discriminatory method by decreasing the paddle speed to 50 rpm and/or reduce the concentration of surfactant in the dissolution media.

[10] DARRTS; REV-BIOEQ-01(General Review). 08/11/2010.

3. In its *current* submission, the firm proposes a newly revised dissolution method (900 mL of 0.3% Tween 80 in 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm). The method is considered acceptable for the following reasons:

   - Using this method, the test product showed a slower and gradual release of drug, as compared to that using the firm's original dissolution method (900 mL of (b) (4)% Tween 80 in (b) (4) using USP Apparatus II (Paddle) at 75 rpm).

   - This method only differs from the FDA – recommended dissolution method by its addition of surfactant (0.3% Tween 80). As mentioned earlier, the RLD formulation contains Tween 80 as one of the inactive ingredients. The amounts of Tween 80 contained in the RLD products are from (b) (4) per tablets. The volume of the dissolution medium is 900 mL. Therefore, the concentrations of Tween 80 in the dissolution medium range from (b) (4)% to (b) (4)% for the RLD product if the FDA-recommended method is used. The concentration of Tween 80 (0.3% Tween 80) in the firm's revised dissolution medium are within the range of the (b) (4)% to (b) (4)%.

4. However, the firm's proposed specification of "NLT (b) (4)% in 30 min" is too lenient. Based on the firm's dissolution data and the firm's low limit of the Cmax 95% CI results of the BE studies (82.72 – 94.63% for fasting study and 82.82-103.67% for fed study), the DBE recommends a more stringent specification of "NLT (b) (4)% in 30 min" for the firm's test product. The firm's dissolution results meet this specification at S1 level.

5. The firm's response to this deficiency is **inadequate** pending its acceptance of the FDA - recommended specification.

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm (b) (4)
	Medium:	0.3% Tween 80 in pH 6.8 Phosphate Buffer (proposed test product medium)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4) % (Q) of the labeled amount is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Kremers Urban Pharmaceuticals Inc. 1101 C Avenue West – Seymour, IN 47274	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 5 min	10 min	15 min	30 min	Study Report Location
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	65	80	86	92	Table 5.2
					Range	(b) (4)				
					%CV	1.4	1.6	2.0	2.2	
Study Report[1]	11/6/10	Lipitor Tablets, 10mg / 03698V (Expires: 01 / 2010)	10 mg Tablets	12	Mean	82	92	95	98	
					Range	(b) (4)				
					%CV	4.4	2.5	1.9	1.5	
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	67	80	86	94	Table 5.3
					Range	(b) (4)				
					%CV	1.0	1.4	1.2	1.6	
Study Report[1]	11/6/10	Lipitor Tablets, 20mg / 02648V (Expires: 02 / 2010)	20 mg Tablets	12	Mean	82	91	94	97	
					Range	(b) (4)				
					%CV	4.0	3.3	2.7	1.8	

Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	64	78	84	93	Table 5.4
					Range	(b) (4)				
					%CV	3.9	2.7	1.8	1.4	
Study Report[1]	11/6/10	Lipitor Tablets, 40mg / 0307048 (Expires: 03 / 2011)	40 mg Tablets	12	Mean	85	93	96	98	
					Range	(b) (4)				
					%CV	5.9	2.6	1.7	1.7	
Study Report[1]	11/6/10	Atorvastatin Calcium Tablets, 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	58	74	81	90	Table 5.5
					Range	(b) (4)				
					%CV	2.1	1.4	1.3	1.2	
Study Report[1]	11/6/10	Lipitor Tablets, 80mg / 08107V (Expires: 04 / 2009)	80 mg Tablets	12	Mean	87	93	95	97	
					Range	(b) (4)				
					%CV	3.0	2.6	1.5	1.2	

[1]Report number is not applicable as individual results and dissolution plots can be found in the Study Report Location noted above.

Table 5.5 – 80 mg product

Vessel	Atorvastatin Calcium Tablets 80 mg Lot P80340				Lipitor Tablets, 80 mg Lot 08107V			
	5 min	10 min	15 min	30 min	5 min	10 min	15 min	30 min
1	(b) (4)				(b) (4)			
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	58	74	81	90	87	93	95	97
% RSD	2.1	1.4	1.3	1.2	3.0	2.6	1.5	1.2
Minimum	(b) (4)				(b) (4)			
Maximum								

Table 5.4 – 40 mg product

Vessel	Atorvastatin Calcium Tablets, 40mg Lot# P80370				Lipitor 40mg Tablets Lot# 0307048			
	5 min	10 min	15 min	30 min	5 min	10 min	15 min	30 min
1	(b) (4)				(b) (4)			
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	64	78	84	93	85	93	96	98
% CV	3.9	2.7	1.8	1.4	5.9	2.6	1.7	1.7
Minimum	(b) (4)				(b) (4)			
Maximum								

Table 5.3 – 20 mg product

Vessel	Atorvastatin Calcium Tablets, 20mg Lot# P80360				Lipitor 20mg Tablets Lot# 02648V			
	5 min	10 min	15 min	30 min	5 min	10 min	15 min	30 min
1	(b) (4)				(b) (4)			
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	67	80	86	94	82	91	94	97
% CV	1.0	1.4	1.2	1.6	4.0	3.3	2.7	1.8
Minimum	(b) (4)				(b) (4)			
Maximum								

Table 5.2 – 10 mg product

Vessel	Atorvastatin Calcium Tablets, 10mg Lot# P80350				Lipitor 10mg Tablets Lot# 03698V			
	5 min	10 min	15 min	30 min	5 min	10 min	15 min	30 min
1	(b) (4)				(b) (4)			
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	65	80	86	92	82	92	95	98
% CV	1.4	1.6	2.0	2.2	4.4	2.5	1.9	1.5
Minimum	(b) (4)				(b) (4)			
Maximum								

3.10 Deficiency Comments

1. The dissolution testing conducted with the firm's newly revised dissolution method is adequate. The firm should, however, accept the FDA - recommended specification for its test drug product.

2. During February 2008, the Division of Scientific Investigation (DSI) inspected the analytical sites of (b) (4) for another application. This is the same site where the subject samples from the fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies for your application were also analyzed. Following the inspection, a Form FDA-483 was issued for each site. Subsequently, the analytical sites provided its

responses to Form 483 observations and these responses were included in the final evaluation by DSI, which recommended that the inspected studies be considered questionable based on DSI's original findings and the site's response.

For considering the impact of a similar study conduct and site practice by the same analytical facility on the BE studies submitted in your application, the DBE reviewed the above DSI inspection report and found that the following objectionable finding by the DSI at the analytical site could potentially compromise the integrity of the studies of ANDA 091624 as well:

> Analytical results, specifically chromatogram peak integrations, were modified. These modifications were made by manually picking the baseline or changing integrations parameters.

The firm should address the above specific finding by the DSI with respect to its impact on the BE studies of the current ANDA, providing any necessary supporting documents in the firm's response, including but not limited to:

- Confirmation of the existence of any manual reintegration/manual baseline adjustment in any chromatograms of the BE studies, if any.
- If such manual modification of chromatograms was indeed carried out for certain chromatograms, the firm should submit:

  - ✓ all chromatograms of the affected runs for comparison.
  - ✓ In addition, for chromatograms manually modified for reintegration, the firm should also submit the same chromatograms prior to modification, for comparison, and
  - ✓ the peak height/area response counts before and after modification, together with the resulting calculated concentration values associated with the unmodified and modified chromatograms.
  - ✓ Standard Operating Procedure (SOP) for chromatography integration/reintegration.

3. According to the standard operating procedure (SOP) for repeat analysis (SOP# GL-BIO-10601-01), "if an analytical reason for reassay can be assigned to a sample, the original result is not reported." For future submissions, the firm should revise its SOP to include the procedure of reporting the original results of all reassays, including the analytical related reassays, if applicable.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (AA77267) incomplete. Kudco Ireland, Ltd. conducted the fasting study on its Atorvastatin 80 mg Tablets (lot

P803401) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 08107V).

2. The Division of Bioequivalence finds the fed BE study (AA77268) incomplete. Kudco Ireland, Ltd. conducted its fed study on its Atorvastatin 80 mg Tablets (lot # P803401) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 08107V).

3. The FDA - recommended dissolution method is not suitable for the firm's test product. The firm's proposed dissolution testing method is acceptable. The dissolution testing should be conducted in 900 mL of 0.3% Polysorbate 80 in 0.05 M Phosphate Buffer, pH 6.8 at 37 ºC ± 0.5 ºC using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specification(s):

   NLT (b)(4)% (Q) of Atorvastatin dissolved in 30 minutes

   NOTE: The DBE recommends a different specification.

   The firm should acknowledge the FDA-recommended dissolution method and specification.

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.

The firm should be informed the above deficiencies and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	None

BIOEQUIVALENCE DEFICIENCIES

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
DRUG PRODUCT:	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The Division of Bioequivalence (DBE) has completed its review of the submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your dissolution testing data using your newly revised dissolution method is acceptable but your proposed specification (NLT (b)(4)% (Q) in 30 minutes) is not acceptable. Based on your dissolution testing data, the DBE recommends a more appropriate specification for your test product. Please acknowledge your acceptance of the following dissolution method and specification:

   The dissolution testing should be conducted in 900 mL of 0.3% Polysorbate 80 in 0.05 M Phosphate Buffer, pH 6.8 using USP apparatus II (Paddle) at 75 rpm. The test products should meet the following specification:

   Not less than (b)(4)% (Q) of the labeled amount of drug in the dosage form is dissolved in 30 minutes.

2. During February 2008, the Division of Scientific Investigation (DSI) inspected the analytical sites of (b)(4) for another application. This is the same site where the subject samples from the fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies for your application were also analyzed. Following the inspection, a Form FDA-483 was issued for each site. Subsequently, the analytical sites provided its responses to Form 483 observations and these responses were included in the final evaluation by DSI, which recommended that the inspected studies be considered questionable based on the DSI's original findings and the sites' responses.

   For considering the impact of similar objectionable study conduct and site practices by the same analytical facility on the BE studies submitted in your application, the DBE reviewed the above DSI inspection report and found that the following objectionable finding by the DSI at the analytical site could potentially compromise the integrity of the studies of ANDA 091624 as well:

- Analytical results, specifically chromatogram peak integrations, were modified. These modifications were made by manually picking the baseline or changing integrations parameters.

Please address the above specific finding by the DSI with respect to its impact on the BE studies of the current ANDA, providing any necessary supporting documents in your response, including but not limited to:

- Confirmation of the existence of any manual reintegration/manual baseline adjustment in any chromatograms of the BE studies, if any.
- If such manual modification of chromatograms was indeed carried out for certain chromatograms, please submit:
  - all chromatograms of the affected runs for comparison.
  - In addition, for chromatograms manually modified for reintegration, please also submit the same chromatograms prior to modification, for comparison, and
  - the peak height/area response counts before and after modification, together with the resulting calculated concentration values associated with the unmodified and modified chromatograms.
  - Standard Operating Procedure (SOP) for chromatography integration/reintegration.

3. According to your standard operating procedure (SOP) for repeat analysis (SOP# GL-BIO-10601-01), "if an analytical reason for reassay can be assigned to a sample, the original result is not reported." For future submissions, please revise your SOP to include the procedure of reporting the original results of all reassays, including the analytical related reassays, if applicable.

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

3.13 Outcome Page

ANDA: 091624

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13621	1/12/2011	Other	Study Amendment	1	1
13621	1/12/2011	Other	DSI Inspection Report	1	1
				Bean Total:	2

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

/s/

JOHNETTA F WALTERS
04/15/2011

BING V LI
04/15/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
04/19/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091624	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg	
Applicant Name	KUDCO Ireland Limited	
Address	Shannon Industrial Estate Shannon, County Clare Republic of Ireland	
Authorized US Agent	Elaine Siefert, Director Regulatory Affairs, Kremers Urban LLC 1101 C Ave W Seymour IN 47274	
Contact's Telephone Number	(812) 523-5544	
Contact's Fax Number	(812) 523-6889	
Original Submission Date(s)	15 July 2009	
Submission Date(s) of Amendment(s) Under Review	26 February 2010 (dissolution amendment)	
Reviewer	Johnetta F. Walters, Ph.D.	
Study Number (s)	AA77267	AA77268
Study Type (s)	Fasting	Fed
Strength (s)	80 mg	80 mg
Clinical Site	MDS Pharma Services	
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345	
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**
4	**Dissolution**	**10 mg**	**INADEQUATE**
4	**Dissolution**	**20 mg**	**INADEQUATE**
4	**Dissolution**	**40 mg**	**INADEQUATE**

4	**Dissolution**	**80 mg**	**INADEQUATE**
1	**Fasting Study**	**80 mg**	**INADEQUATE**
1	**Fed Study**	**80 mg**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies comparing a test product, Kudco Ireland's Atorvastatin Calcium Tablets, 80 mg to the corresponding reference product, Pfizer'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 and female subjects. The firm's fasting and fed BE studies are **inadequate** due to bioanalytical deficiencies. The results are summarized in the tables below.

Atorvastatin, 1 X 80 mg
Fasting Bioequivalence Study No. AA77267, N=140 (Male=96 and Female=44)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	129.57	134.57	0.96	92.08	100.67
AUC∞ (ng·hr/mL)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/mL)	28.59	32.71	0.87	80.72	94.63

Atorvastatin, 1 X 80 mg
Fed Bioequivalence Study No. AA77268, N=86 (Male=56 and Female=30)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	159.22	158.02	1.01	96.54	105.16
AUC∞ (ng·hr/mL)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/mL)	37.25	40.20	0.93	82.82	103.67

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin as submitted by the firm, were comparable. Therefore the metabolite data are supportive and the studies are adequate. Please see the tables below (firm submitted):

Ortho-hydroxyatorvastatin
Dose (1 x 80 mg)
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t(hr*ng/ml)	144.58	151.10	0.96	90.6% - 101.1%
AUC∞(hr *ng/ml)	151.87	156.92	0.97	91.9% - 102.0%
Cmax (ng/mL)	23.087	25.64	0.90	82.1% - 98.8%
Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t(hr*ng/ml)	147.08	147.05	1.00	96.3% - 103.9%
AUC∞ (hr*ng/ml)	153.24	152.36	1.01	96.8% - 104.4%
Cmax (ng/mL)	21.27	22.41	0.95	87.3% - 103.3%

Para-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t(hr*ng/ml)	9.62	9.28	1.04	95.0% - 113.2%
AUC∞ (hr*ng/ml)	25.37	22.26	1.14	102.3% - 127.1%
Cmax (ng/mL)	0.88	0.87	1.02	92.8% - 111.00%
Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t(hr*ng/ml)	12.12	11.69	1.04	95.6% - 112.4%
AUC∞(hr *ng/ml)	20.55	22.34	0.92	85.3% - 99.2%
Cmax (ng/mL)	1.24	1.25	0.99	92.8% - 106.3%

As indicated above, in the fasting BE study, the 90% confidence intervals for the active metabolite, parahydroxy atorvastatin, did not meet the BE limits [80.00% - 125.00%] for the $AUC_{0-\infty}$ parameter. This is possibly due to the low plasma levels and highly variable PK parameters of this metabolite as compared to the parent drug, atorvastatin, and other active metabolite, orthohydroxy atorvastatin. Therefore, the Division of Bioequivalence bases bioequivalence determination on the 90% CIs data of AUC_{0-t}, AUC_{∞}, and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolite, ortho hydroxyatorvastatin, and concludes that the parahydroxy atorvastatin PK results are acceptable.

The firm's fasting and fed BE study is inadequate due to the deficiencies related to the bioanalytical study. The firm will be asked to provide the original and repeat values of all samples that were reananlyzed for futher evaluation by the DBE.

The firm's dissolution testing is incomplete. (DARRTS: REV-BIOEQ-02 (Dissolution Review). 12/18/2009 and current review). The FDA-recommended dissolution method is not suitable for the firm's test product due to the slow release rate. The firm's proposed dissolution testing method is also not suitable because it is not discriminatory enough. The firm should develop a more discriminatory method by reducing the paddle speed to 50 rpm and/or reducing the concentration of the surfactant.

The DBE does not grant the waiver request(s) for *in vivo* BE study requirements for the 10 mg, 20 mg, and 40 mg strength tablets.

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

[1] A routine inspection was completed for the clinical site on 06/14/2007 for NDA 022118. The outcome was No Action Indicated (NAI). (DARRTS, Search: NDA 022118. The DSI Inspection concluded that the findings should not significantly impact the outcome of the study. O Shaughnessy, Jacqueline A/06-14-2007/REV-NONCLINICAL-03(General Review). A routine inspection was completed for the analytical site on 03/05/2008 for NDA (b) (4) The outcome was Voluntary Action Indicated (VAI). DSI concluded that the accuracy of analyte concentrations in certain subjects was not assured. (DARRTS, Search: (b) (4). Seaton, Mark J/03-07-2008/REV-RPM-05(General Review). The application has since been approved.

The application is **inadequate** with deficiencies.

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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: **(1) Prevention of cardiovascular disease** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina • **(2) Hypercholesterolemia** LIPITOR® is indicated:

[2] Electronic Orange Book: http://www.accessdata fda.gov/scripts/cder/ob/default.cfm. Last accessed: 16 April 2010.
[3] Drugs at FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 16 April 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)	**WARNINGS** **Liver Dysfunction** HMG-CoA reductase inhibitors, like some other lipid- lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin. **Skeletal Muscle** **Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin- treated patients. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin,

	immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	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.

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, current)

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	No	--
Amendments	Yes	1

[5] Individual Product Bioequivalence Recommendations: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. Last accessed: 16 April 2010.
[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	[redacted] (b) (4) Validation Study ZZ00785-02 (Attachment 3 to study rpt AA77267-01 / AA77268-01)
Analyte	Atorvastatin
Internal standard (IS)	d_5-Atorvastatin
Method description	Liquid-liquid extraction with analysis/detection by LC-MS/MS
Limit of quantitation	0.225 ng/mL
Average recovery of drug (%)	51% at 0.525 ng/mL 50% at 5.25 ng/mL 57% at 52.5 ng/mL
Average recovery of IS (%)	47%
Standard curve concentrations (ng /mL)	0.225, 0.450, 1.80, 3.60, 9.00, 45.0, 72.0, and 90.0 ng/ml
QC concentrations (ng /mL)	LLOQ QC, 0.675, 6.75, and 67.5 ng/mL
QC Intraday precision range (%)	2.7 to 13.6%
QC Intraday accuracy range (%)	-11.6 to 4.7%
QC Interday precision range (%)	3.4 to 10.4%
QC Interday accuracy range (%)	-7.1 to 3.1%
Bench-top stability (hrs)	Short-term Stability: 20 hours in polypropylene tubes at ambient temperature under UV-shielded light Short-Term Stability: 5 hours in polypropylene tubes in an ice water bath under white light
Stock stability (days)	343 days at approximately 100 µg/mL in methanol in a polypropylene container at -20°C
Processed stability (hrs)	Post-preparative Stability: 122 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 123 hours in a polypropylene 96 well plate at 5°C
Freeze-thaw stability (cycles)	Freeze and Thaw Stability: 6 cycles in polypropylene tubes at -20°C under UV-shielded light 5 freeze (-20°C)-thaw (ice water bath) cycles in polypropylene tubes under white light
Long-term storage stability (days)	Long-term Stability: 348 days in polypropylene tubes at -20°C (LTS A, C, and D); 344 days in polypropylene tubes at -20°C (LTS E) Long-Term Stability: 14 days (LTS X) and 117 days (LTS LLOQ QC) in polypropylene tubes at -20°C Long-Term Stability: 69 days (LTS D and X) and 67 days (LTS LLOQ QC) in polypropylene tubes at -80°C
Dilution integrity	up to 450 ng/mL, diluted 10-fold
Selectivity	No significant matrix effect was observed in 9 of the 10 human plasma (EDTA) lots that were spiked at the concentration of the LLOQ (0.225 ng/mL) and in any of the 8 human plasma (EDTA) lots that were spiked at the concentration of the high QC (67.5 ng/mL) sample

Information Requested	Data
Bioanalytical method validation report location	[redacted] (b) (4) Validation Study ZZ00785-02 (Attachment 3 to study rpt AA77267-01 / AA77268-01)
Analyte	Orthohydroxy Atorvastatin
Internal standard (IS)	d5-Orthohydroxy Atorvastatin
Method description	Liquid-liquid extraction with analysis/detection by LC-MS/MS
Limit of quantitation	0.175 ng/mL
Average recovery of drug (%)	69% at 0.350 ng/mL 55% at 3.50 ng/mL 67% at 35.0 ng/mL
Average recovery of IS (%)	59%
Standard curve concentrations (ng /mL)	0.175, 0.350, 1.40, 2.80, 7.00, 35.0, 56.0, and 70.0 ng/mL
QC concentrations (ng /mL)	LLOQ QC, 0.525, 5.25, and 52.5 ng/mL
QC Intraday precision range (%)	2.2 to 15.0%
QC Intraday accuracy range (%)	-2.9 to 13.1%
QC Interday precision range (%)	4.1 to 13.3%
QC Interday accuracy range (%)	2.9 to 4.4%
Bench-top stability (hrs)	Short-term Stability: 20 hours in polypropylene tubes at ambient temperature under UV-shielded light Short-Term Stability: 5 hours in polypropylene tubes in an ice water bath under white light
Stock stability (days)	343 days at approximately 100 µg/mL in methanol in a polypropylene container at -20°C
Processed stability (hrs)	Post-preparative Stability: 122 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 123 hours in a polypropylene 96 well plate at 5°C
Freeze-thaw stability (cycles)	Freeze and Thaw Stability: 6 cycles in polypropylene tubes at -20°C under UV-shielded light 5 freeze (-20°C)-thaw (ice water bath) cycles in polypropylene tubes under white light
Long-term storage stability (days)	Long-term Stability: 348 days in polypropylene tubes at -20°C (LTS A, C, and D) Long-Term Stability: 14 days (LTS X) and 117 days (LTS LLOQ QC) in polypropylene tubes at -20°C Long-Term Stability: 71 days (LTS D and X) and 69 days (LTS LLOQ QC) in polypropylene tubes at -80°C
Dilution integrity	up to 350 ng/mL, diluted 10-fold
Selectivity	No significant matrix effect was observed in any of the 10 human plasma (EDTA) lots that were spiked at the concentration of the LLOQ (0.175 ng/mL) and in any of the 8 human plasma (EDTA) lots that were spiked at the concentration of the high QC (52.5 ng/mL) sample

Information Requested	Data
Bioanalytical method validation report location	[redacted](b) (4) Validation Study ZZ00785-02 (Attachment 3 to study rpt AA77267-01 / AA77268-01)
Analyte	Parahydroxy Atorvastatin
Internal standard (IS)	d5-Parahydroxy Atorvastatin
Method description	Liquid-liquid extraction with analysis/detection by LC-MS/MS
Limit of quantitation	0.250 ng/mL
Average recovery of drug (%)	61% at 0.750 ng/mL 57% at 7.50 ng/mL 60% at 75.0 ng/mL
Average recovery of IS (%)	55%
Standard curve concentrations (ng/mL)	0.250, 0.500, 2.00, 4.00, 10.0, 50.0, 80.0, and 100 ng/mL
QC concentrations (ng/mL)	LLOQ QC, 0.750, 7.50, and 75.0 ng/mL
QC Intraday precision range (%)	1.6 to 16.3%
QC Intraday accuracy range (%)	-14.8 to 8.9%
QC Interday precision range (%)	3.6 to 13.7%
QC Interday accuracy range (%)	-6.8 to 4.3%
Bench-top stability (hrs)	Short-term Stability: 20 hours in polypropylene tubes at ambient temperature under UV-shielded light Short-Term Stability: 5 hours in polypropylene tubes in an ice water bath under white light
Stock stability (days)	343 days at approximately 100 µg/mL in methanol in a polypropylene container at -20°C
Processed stability (hrs)	Post-preparative Stability: 122 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 123 hours in a polypropylene 96 well plate at 5°C
Freeze-thaw stability (cycles)	Freeze and Thaw Stability: 6 cycles in polypropylene tubes at -20°C under UV-shielded light 5 freeze (-20°C)-thaw (ice water bath) cycles in polypropylene tubes under white light
Long-term storage stability (days)	Long-term Stability: 348 days in polypropylene tubes at -20°C (LTS A, C, and D) Long-Term Stability: 14 days (LTS X) and 117 days (LTS LLOQ QC) in polypropylene tubes at -20°C Long-Term Stability: 69 days (LTS D and X) and 67 days (LTS LLOQ QC) in polypropylene tubes at -80°C
Dilution integrity	up to 500 ng/mL, diluted 10-fold
Selectivity	No significant matrix effect was observed in 9 of the 10 human plasma (EDTA) lots that were spiked at the concentration of the LLOQ (0.250 ng/mL) and in any of the 8 human plasma (EDTA) lots that were spiked at the concentration of the high QC (75.0 ng/mL) sample

SOPs submitted	Yes SOP Number: GL-BIO-10601-01 Title: Reporting of Data Generated from the Analysis of

	Biological Matrices and the Reassay of Samples Effective Date: 30 April 2008
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

The firm did not submit the SOP for the bioanalytical methods for analyzing the atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin. However, the firm provided the detailed methods for analyzing these analyte.

During the pre-study method validation, the average percent (%) recovery of the analyte, Atorvastatin, was 52.7%. The average percent recovery of the active metabolite, Orthohydroxy Atorvastatin, was 63.7%. The average percent recovery of the second active metabolite, Parahydroxy Atorvastatin, was 59.3%. The average percent recovery of each the internal standard (ISTD) was 47%, 59%, and 55% in assay, respectively. The percent coefficient of variation (CV), for each of the individual recoveries (LQC, MQC, and HQC) of each analyte was no greater than 12.3% of the analyte and no greater than 9.5% for the ISTD. Since these values are less than 15%, the % CV is considered to be acceptable. Ethylenediaminetetraacetic acid, EDTA, was used as the anticoagulant for both the pre-study and during study method validation. The firm did not, however, specify the salt form of the EDTA used in the bioanalytical (pre-study and during study) method validation and clinical studies. The firm will be asked to specify the salt form of EDTA.

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.**

3.6 *In Vivo* Studies

Table 1. Summary of all *in vivo* Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Atorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77267	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fasting Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401 Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V	140 completing (96M/44F) Healthy subjects mean age: 39.8 years (range: 18 – 55 years)	28.58418 (68.1%) 32.73127 (46.7%)	0.750 (0.333 – 6.061) 0.750 (0.333 – 6.000)	129.628 (49.9%) 134.325 (45.9%)	135.464 (47.7%) 138.847 (44.9%)	9.902 (±5.5432) 10.124 (±4.7704)	0.09324 (±0.052201) 0.08609 (±0.046496)	Module 5

Geometric Mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Atorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77268	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fed Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401	86 completing (56M/30F) Healthy subjects	37.16735 (61.6%)	1.667 (0.333 – 6.000)	158.361 (46.0%)	163.412 (45.7%)	9.462 (±4.4719)	0.09195 (±0.050360)	Module 5
			Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V	mean age: 36.8 years (18 – 54 years)	40.03460 (69.9%)	1.333 (0.667 – 5.000)	157.600 (48.5%)	162.504 (47.7%)	9.053 (±3.9498	0.09244 (±0.044583)	

Geometric Mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Ortho-hydroxyatorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77267	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fasting Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401 Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V	140 completing (96M/44F) Healthy subjects mean age: 39.8 years (range: 18 – 55 years)	23.07254 (80.4%) 25.64519 (48.5%)	1.000 (0.500 – 8.000) 1.000 (0.500 – 6.000)	144.620 (52.6%) 151.159 (40.6%)	152.055 (49.6%) 157.073 (39.7%)	14.437 (±4.7461) 14.181 (±4.6952)	0.05365 (±0.018650) 0.05472 (±0.019097)	Module 5

Geometric Mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Ortho-hydroxyatorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77268	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fed Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401 Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V	86 completing (56M/30F) Healthy subjects mean age: 36.8 years (18 – 54 years)	21.28986 (46.6%) 22.36015 (54.8%)	2.500 (0.333 – 6.000) 1.667 (0.667 – 6.000)	146.902 (37.2%) 146.716 (41.5%)	152.415 (36.5%) 152.453 (40.4%)	14.086 (±6.9375) 13.030 (±4.4615)	0.05621 (±0.018162) 0.05930 (±0.021385)	Module 5

Geometric Mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Para-hydroxyatorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77267	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fasting Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401 Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o Lot No.: 08107V	140 completing (96M/44F) Healthy subjects mean age: 39.8 years (range: 18 – 55 years)	0.91714 (74.1%) 0.90256 (66.3%)	6.000 (0.500 – 16.000) 6.000 (0.333 – 16.000)	10.58239 (106.8%) 10.06219 (107.5%)	25.3099 (50.8%) 23.6804 (65.6%)	16.958 (±11.7222) 17.858 (±11.7640)	0.05385 (±0.023512) 0.05491 (±0.034609)	Module 5

Geometric Mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Para-hydroxyatorvastatin Mean Parameters (+/-SD)*						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr-1)	
AA77268	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fed Conditions	Randomized single-dose crossover	Kremers Urban 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: P803401	86 completing (56M/30F) Healthy subjects	1.24689 (58.8%)	5.000 (0.667 – 16.000)	12.17872 (108.5%)	22.75684 (52.0%)	13.772 (±11.3467)	0.068750 (±0.0330254)	Module 5
			Parke-Davis (Lipitor®) 80 mg atorvastatin tablets (as atorvastatin calcium) Dose: 80 mg p.o. Lot No.: 08107V	mean age: 36.8 years (18 – 54 years)	1.27941 (70.9%)	5.000 (0.667 – 8.000)	12.14965 (116.4%)	22.40299 (54.4%)	13.410 (±9.3215)	0.067156 (±0.0302005)	

Geometric Mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Atorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. AA77267)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	129.57	134.57	0.96	92.08	100.67
AUC∞ (hr *ng/ml)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/ml)	28.59	32.71	0.87	80.72	94.63

Atorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. AA77268)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	159.22	158.02	1.01	96.54	105.16
AUC∞ (hr *ng/ml)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/ml)	37.25	40.20	0.93	82.82	103.67

Supportive metabolite data, as submitted by the firm, is below:

Ortho-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	144.58	151.10	0.96	90.6% - 101.1%
AUC∞ (hr *ng/ml)	151.87	156.92	0.97	91.9% - 102.0%
Cmax (ng/mL)	23.087	25.64	0.90	82.1% - 98.8%
Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	147.08	147.05	1.00	96.3% - 103.9%
AUC∞ (hr *ng/ml)	153.24	152.36	1.01	96.8% - 104.4%
Cmax (ng/mL)	21.27	22.41	0.95	87.3% - 103.3%

Para-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	9.62	9.28	1.04	95.0% - 113.2%
AUC∞ (hr *ng/ml)	25.37	22.26	1.14	102.3% - 127.1%
Cmax (ng/mL)	0.88	0.87	1.02	92.8% - 111.00%
Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	12.12	11.69	1.04	95.6% - 112.4%
AUC∞ (hr *ng/ml)	20.55	22.34	0.92	85.3% - 99.2%
Cmax (ng/mL)	1.24	1.25	0.99	92.8% - 106.3%

In the fasting BE study, the 90% confidence intervals for the active metabolite, parahydroxy atorvastatin, did not meet the BE limits [80.00% - 125.00%] for the $AUC_{0-\infty}$ parameter. This is due to the low plasma levels of the metabolite as compared to

the parent drug, atorvastatin, and other active metabolite, orthohydroxy atorvastatin. Therefore, the Division of Bioequivalence bases bioequivalence determination on the 90% CIs data of AUC_{0-t}, AUC_{∞}, and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolite, ortho hydroxyatorvastatin, and concludes that the parahydroxy atorvastatin PK results are acceptable.

Table 3. Reanalysis of Study Samples

Study No.AA77267-01 (Atorvastatin) Additional information in AA77267-01 Section 3.7								
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	
	A	B	A	B	A	B	A	B
Pharmacokinetic[1]	2	5	.038%	.094%	1	1	.019%	.019%
AAR	6	6	.113%	.113%	6	6	.113%	.113%
ISP	1	0	.019%	.000%	1	0	.019%	.000%
UISR	1	0	.019%	.000%	1	0	.019%	.000%
Total	10	11	.188%	.207%	9	7	.169%	.132%

Study No.AA77267-01 (Orthohydroxy Atorvastatin) Additional information in AA77267-01 Section 3.7								
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	
	A	B	A	B	A	B	A	B
Pharmacokinetic[1]	3	5	.056%	.094%	1	1	.019%	.019%
AAR	5	7	.094%	.132%	5	7	.094%	.132%
Fail	22	18	.414%	.339%	22	18	.414%	.339%
ISP	1	0	.019%	.000%	1	0	.019%	.000%
LSR/Fail	16	20	.301%	.377%	16	20	.301%	.377%
UISR	1	0	.019%	.000%	1	0	.019%	.000%
Total	48	50	.904%	.942%	46	46	.866%	.866%

Study No.AA77267-01 (Parahydroxy Atorvastatin) Additional information in AA77267-01 Section 3.7								
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**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic[1]	2	3	.038%	.056%	1	0	.019%	.000%
ISP	1	0	.019%	.000%	1	0	.019%	.000%
UCR	1	0	.019%	.000%	1	0	.019%	.000%
Fail	37	38	.697%	.716%	37	38	.697%	.716%
Total	41	41	.772%	.772%	40	38	.753%	.716%

[1] Reassays due to analytical investigations

Abbreviations

AAR Above analytical range
ISP Incomplete sample processing
LSR Low standard removed
UISR Unacceptable internal standard response
UCR Unacceptable chromatography

Study No.AA77268-01 (Atorvastatin) Additional information in AA77268-01 Section 3.7								
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**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic[1]	3	1	.092%	.031%	2	1	.061%	.031%
AAR	10	14	.307%	.429%	10	14	.307%	.429%
IIA	0	1	.000%	. .031%	0	1	.000%	.031%
ISP	1	0	.031%	.000%	1	0	.031%	.000%
UISR	0	7	.000%	.215%	0	7	.000%	.215%
Total	14	23	.429%	.705%	13	23	.399%	.705%

Study No.AA77268-01 (Orthohydroxy Atorvastatin) Additional information in AA77268-01 Section 3.7								
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	
	A	B	A	B	A	B	A	B
Pharmacokinetic[1]	3	1	.092%	.031%	1	1	.031%	.031%
AAR	0	2	.000%	.061%	0	2	.000%	.061%
IIA	0	1	.000%	.031%	0	1	.000%	.031%
ISP	1	0	.031%	.000%	1	0	.031%	.000%
UISR	0	7	.000%	.215%	0	7	.000%	.215%
Total	4	11	.123%	.337%	3	11	.092%	.337%

Study No.AA77268-01 (Parahydroxy Atorvastatin)_ Additional information in AA77268-01 Section 3.7								
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	
	A	B	A	B	A	B	A	B
Pharmacokinetic[1]	2	1	.061%	.031%	1	1	.031%	.031%
ISP	1	0	.031%	.000%	1	0	.031%	.000%
LSR	28	30	.859%	.920%	28	30	.859%	.920%
IIA	0	1	.000%	.031%	0	1	.000%	.031%
UISR	0	7	.000%	.215%	0	7	.000%	.215%
Total	31	39	.951%	1.196%	30	39	.920%	1.196%

[1] Reassays due to analytical investigations

Abbreviations

AAR Above analytical range
IIA Incomplete instrument analysis
ISP Incomplete sample processing
LSR Low standard removed
UISR Unacceptable internal standard response

Did use of recalculated plasma concentration data change study outcome?

No.

Comments from the Reviewer:

- The standard operating procedure (SOP) number GL-BIO-10603-03, Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples, effective date: 30 April 2008, allows for the following bioanalytical repeats: *(1) Above accepted range (AAR), (2) Exceeding quadratic bounds (EQB), (3) Diluted concentration unreliable (DCU), or a measureable concentration, but greater than 50% of the dilution QC samples having the same dilution factor in the same batch that did not meet the following acceptance criteria: for chromatographic methods: 15% of nominal concentrations. (4) Highest and/or lowest standard removed (HSR or LSR), (5) Incomplete instrument analysis (IIA), (6) Incomplete sample processing (ISP), (4) Unacceptable internal standard response (UISR), (7) Questionable multiple values (QMV), and (8) Unacceptable chromatography (VCR), (9) Value requiring confirmation (VRC).* The IIA (incomplete instrument analysis) indentifies a sample for which reliable data could not obtained due to processing problems that occurred during injection or instrument analysis and were documented by the analyst, while the ISP (incomplete instrument sample processing) identifies a sample for which concentration data could not be obtained due to processing problems that occurred during the extraction or assay and was documented by the analyst before instrument analysis.

- In the firm's bioanalytical report, the firm indicated that "*'fail' identifies samples for which concentration data was not accepted because the batch did not meet batch acceptance criteria"* and also indicated that this description was based on its global SOP GL-BIO-10602.

- According to the firm's SOP for repeat analysis, if an analytical reason for reassay can be assigned to a sample, the original result is not reported. The firm only provided the original and repeated concentrations for the sample reanalyzed for non-analytical reason which the firm defined as 'VRC' (values requiring confirmation). Since the 90% CIs of Cmax for atorvastatin in fasting study are marginally within the acceptable limits (80.8 – 94.8), the firm will be asked to provide the original and repeat values of all samples that were reananlyzed, where possible, for futher evaluation by the DBE.

- The firm provided the original and repeated concentrations for the samples reanalyzed for non-analytical reasons. In the firm's bioanalytical report of the fasting study, there were a total of 34 samples repeated for 'VRC' and 'Bracketing'. However, in the firm's summary tables as shown above, for the fasting study, there was a total of 25 samples (for three analytes) repeated for 'pharmacokinetic' reasons which is similar to VRC and Bracketing. The firm will be asked to explain this discrepancy. The acceptances of the repeated values were according to the firm's SOP which indicates that if the difference of the repeated values as compared with the original values is more than 20%, the repeated

values will be reported. For the fasting study, there were 5 out of 34 samples used the repeated values and for the rest of the 29 samples, the original concentrations were reported. For those 5 samples, 3 of which were pre-dose samples (0 hr) and two of them were at 24 hr time point which is during the elimination phase of all three analytes. Therefore, using the repeated values does not appear to change the outcome of the fasting BE study. For the fed BE study, there was a total of 11 samples reanalyzed for the non-analytical reasons (VRC) and concentrations of the repeated values of 8 samples (3 samples for atorvastatin, 3 samples for orthohydroxy atovastatin and 2 samples for parahydroxy atovastatin) were reported. The concentrations of these samples are not the Cmax of the specific subject, therefore, using the repeated values does not appear to change the outcome of the fed BE study.

- Incurred sample reproducibility (ISR) data was submitted in this application. To demonstrate that the analysis of incurred clinical sample concentrations were reproducible for the bioanalytical method, 100 clinical samples were reassayed. The samples were selected from multiple analytical runs and across the concentration range for clinical samples from the study. The %CV for each pair of original and repeat assay results was calculated. If the %CV was <21.2%, the pair was considered to be a match. The method was considered to be reproducible if at least two thirds (2/3) of the pairs matched. For both the fasting and fed studies, the results of ISR indicated that more than two thirds of the pairs matched. Therefore, the method is considered by the firm to be reproducible

- Based on the above comments, the firm's repeat analysis is **incomplete**. The firm should explain the discrepancy related to the number of reassays mentioned above.

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?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution[7]

Location of DBE Dissolution Review	DARRTS: REV-BIOEQ-02 (Dissolution Review). 12/18/2009.
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?	**METHOD INCOMPLETE**
If not then why?	The FDA – recommended dissolution method is not suitable for the test product. The firm's method, as proposed, is not an effectively discriminating dissolution testing. The firm should develop a more discriminatory method. The paddle speed should be reduced to 50 rpm and/or reducing the concentration of surfactant. Please see the dissolution consult included in section 4.5 of this review.

*From FDA Internal Dissolution Database.

Reviewer Comments:

1. In the original dissolution review[8], it was determined that there is no USP method for this drug product.

    a. There is, however, an FDA-recommended method (900 mL of 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm). The firm conducted dissolution testing using its own proposed method

[7] The current dissolution data was taken from the amendment submitted on 26 February 2010 and may be found here: \\Cdsesub1\evsprod\ANDA091624\0003\m2\27-clin-sum.
[8] DARRTS: REV-BIOEQ-02(Dissolution Review). 12/18/2009.

(900 mL of (b) (4)% Tween 80 in (b) (4) using USP Apparatus II (Paddle) at 75 rpm). The firm did not conduct dissolution testing using the FDA-recommended dissolution method.

b. In order to determine whether or not the FDA – recommended dissolution method is appropriate for the firm's test product, for comparison with its proposed method, the firm was asked to submit the dissolution testing data on 12 dosage units of all strengths of the test and reference products using the following FDA – recommended dissolution method:

Medium:	0.05 M Phosphate buffer, pH 6.8
Volume:	900 mL
Apparatus:	II (Paddle)
Speed:	75 rpm
Sampling Times:	5, 10, 15 and 30 minutes until (b) (4)% of the labeled amount is dissolved.

c. In addition, the firm only submitted dissolution testing data for the 80 mg strength of reference product using it proposed method. The firm was asked to submit dissolution testing data using its own proposed method for all strengths of the reference product.

2. The Division of Bioequivalence (DBE) has previously reviewed the following ANDAs for Atorvastatin Calcium Tablets:

- ANDA 077575 (10 mg, 20 mg, 40 mg, and 80 mg tablets): The dissolution testing data was found acceptable using the FDA – recommended method.

- ANDA 078773 (80 mg tablets) only: The dissolution data was found acceptable using the FDA – recommended method.

- ANDA 090548 (10 mg, 20 mg, 40 mg, and 80 mg tablets): The dissolution testing data was found acceptable on strengths of 20 mg, 40 mg and 80 mg of Atorvastatin Calcium Tablets, using the FDA - recommended method. On 24 December 2008, the firm submitted the repeated dissolution testing data for the strength of 10 mg (of the test and reference product). The firm's data for the additional dissolution testing on the 10 mg strength tablets was deemed acceptable. However, the firm's specification [(b) (4)% (Q) in (b) (4) minutes] differed from the one recommended by the FDA [(b) (4)% (Q) in 15 minutes]. The firm was requested to acknowledge its acceptance of the FDA-recommended method and specification.

NOTE: Although the above ANDAs' dissolution data were found acceptable (using the FDA-recommended method), the fast dissolving profiles were also observed for these ANDAs (i.e., ANDA 077575). However, these dissolution profiles all reached at least (b) (4)% within reasonable testing times.

3. Review of the firm's dissolution amendment (letter date of 26 February 2010):

Deficiency #1: *Your dissolution testing is incomplete. You stated in your submission that 'The dissolution was originally based on the method published by the Office of Generic Drugs (OGD). However, during execution of the validation protocol, it was determined that the dissolution media was not suitable for the tablet formulation due to the low dissolution rate. The media was changed to* (b) (4) *% Tween 80 in* (b) (4) *It should be noted that the RLD contains Polysorbate 80, which is also known as Tween 80, so the need for the addition of the surfactant to the OGD-recommended dissolution media is not immediately apparent'. However, you did not conduct dissolution using the appropriate FDA-recommended dissolution method. Therefore, please conduct and submit comparative dissolution testing on all strengths of the test and reference products (12 dosage units each) using the following FDA-recommended method and sampling times.*

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Sampling Times	5, 10, 15 and 30 minutes until (b) (4) % of the labeled amounts of atorvastatin is dissolved.

The dissolution method is currently available in the dissolution database in the FDA website: http://www.acessdata.fda.gov/scripts/cder/dissolution/index.cfm.

Firm's Resposes to Deficiency #1: "The applicant acknowledges that the reference to "OGD-recommended media" in the original ANDA was incorrect in Bioequivalence Table 5, Summary of *In Vitro* Dissolution Studies and the discussion following; therefore, relevant sections in Module 2 and Module 5 have been revised and are replaced herein.

Comparative dissolution testing was performed on all strengths of the test and reference products (12 dosage units) using the FDA-recommended media and sampling times. Please refer to 2.7.1.2 for comparative dissolution profile data for the 10, 20, 40, and 80 mg strengths. The comparative dissolution profile data includes the individual tablet data (Tables 5.5, 5.6, 5.7, and 5.8), dissolution plots of each strength (Figures 9, 10, 11, and 12) as well as the mean, range, and % coefficient of variation (%CV) at each time point for the 12 tablets tested (Table 5 - continued). Dissolution plots comparing all strengths of the test and reference products using the FDA-recommended media are presented in Figure 3 and Figure 4, respectively. Please note section 5.3.1.3 has been revised to include the comparative dissolution profile data of the 80 mg strength using the FDA-recommended media."

Reviewer's Comments:

- The firm has conducted and submitted dissolution testing on all strengths of the test and reference products (12 dosage units each) using the FDA-recommended method and sampling times. Per the firm, *"Dissolution profile data of the test and reference products using the FDA-recommended media (0.05M Phosphate Buffer, pH 6.8) are provided. Please note the sampling time for the test product was extended to 120 minutes in an attempt to achieve* (b) (4) *% dissolution, but instead reached an asymptote. It was determined during execution of the validation protocol that the dissolution media was not suitable for the tablet formulation due to the low dissolution rate."* The dissolution profiles of the test and reference products are shown as follows:

Figure 3: Dissolution Plot Comparing the Test Products (Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in 0.05M Phosphate Buffer, pH 6.8

Figure 4: Dissolution Plot Comparing the Reference Products (Lipitor Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in 0.05M Phosphate Buffer, pH 6.8

- As shown in the firm's dissolution data (attached in section 4.3) and dissolution profile, the firm's test product released much slower than the reference product, especially for the higer strength (40 mg and 80 mg) which only released 52% and 45%, respectively, in 120 minutes. Therefore, the FDA's method is not suitable for the firm's test product.

- The firm indicated that the formulation of the reference product contains Tween 80 (also known as polysorbate 80), which has been confirmed in the RLD product (NDA 020702, 11/2009 Annual Report and DARRTS: REV-QUALITY-03, Final Date 11/13/2000). The RLD formulation is below:

Table 1	Lipitor (Atorvastatin Calcium) Tablets	Composition (mg/tablet)				
Components	*Strength*	*Function*	*10*	*20*	*40*	*80*
(b) (4)						(b) (4)
(b) (4)						
(b) (4)						
(b) (4)						
(b) (4)						
(b) (4)						
(b) (4)						
(b) (4)						

As shown in the RLD's formulation table, the amounts of Tween 80 contained in the RLD products are from (b) (4) to (b) (4). The volume of the dissolution medium is 900 mL. Therefore, the concentrations of Tween 80 in the dissolution medium is from (b) (4)% to (b) (4)% (if the tablets are disintergrated completely) for the RLD product if the FDA-recommended method is used. The formulations of the test products do not contain Tween 80. Therefore, the different release rate of the test products, as compared with the reference products, using FDA-method might caused by the Tween 80 contained in the reference product.

- In the original submission, the firm conducted the dissolution testing using its own method [900 mL of (b) (4)% Tween 80 in (b) (4) using USP Apparatus II (paddle) at 75 rpm] with (b) (4)% Tween 80 in the medium. The dissolution profiles of the test products are similar to the reference products, showing as followings:

Figure 1: Dissolution Plot Comparing Test Products (Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in (b) (4) with (b) (4)% Tween 80

Figure 2: Dissolution Plot Comparing the Reference Products (Lipitor Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in (b) (4) with (b) (4)% Tween 80

However, as shown in the firm's dissolution data (attached in section 4.3) and the dissolution profiles, the firm's test product released more than (b) (4)% at 5 minutes using the firm's method, indicating the firm's dissolution method is not discriminative.

- After consulting with the DBE I dissolution focal point (please see section 4.5 for details), Dr. Munshi, considering the borderline low 90% CIs for lnCmax in the biostudies, it is especially important that the method is highly discriminatory so that it can differentiate among Test lots. We recommend the firm develop a more

discriminatory method by decreasing the paddle speed to 50 rpm and/or reduce the concentration of surfactant in the dissolution media.

(b) (4)

- The firm's response to deficiency #1 is **inadequate**.

Deficiency #2: *In addition, please provide dissolution testing data on 12 dosage units of the 10 mg, 20 mg and 40 mg strengths of the reference product, Pfizer Pharmaceutical's Lipitor® (Atorvastatin Calcium) Tablets using your proposed dissolution method.*

Firm's Resposes to Deficiency #2: "Comparative dissolution testing was performed on all strengths of the test and reference products (12 dosage units) using the proposed dissolution media ((b) (4)% Tween 80 in (b) (4) Please refer to section 2.7.1.2 for the comparative dissolution profile data for the 10, 20, 40, and 80 mg strengths. The comparative dissolution profile data includes the individual tablet data (Tables 5.1, 5.2, 5.3, and 5.4), dissolution plots of each strength (Figures 5, 6, 7, and 8) as well as the mean, range, and % coefficient of variation (%CV) at each time point for the 12 tablets tested (Table 5). Dissolution plots comparing all strengths of the test and reference products using the proposed media are presented in Figure 1 and Figure 2, respectively."

Reviewer's Comments: The firm has conducted and submitted comparative dissolution testing on all strengths of the test and reference products (12 dosage units each) using the firm's proposed method and sampling times. The firm's response to deficiency #2 is **adequate**.

Overall Dissolution Comments:

A. The firm's dissolution data using FDA-recommended method indicate that the FDA-recommended dissolution method is not suitable for the firm's test product due to the slow release rate and incomplete release over 2 hours.

B. The firm's dissolution method is not discriminative. The firm is suggested to modify its proposed dissolution method, decreasing the rotation speed and/or decreases the concentration of the surfactant in the dissolution media. Early sampling time points such as 5, 10, 15, 20 minutes should also be included in the modified method with other later time points until at least (b) (4)% of the labeled amount is dissolved.

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?	No
Waivers granted?	**WAIVERS DENIED**
If not then why?	Due to dissolution and bioanalytical deficiencies in the BE studies.

3.10 Deficiency Comments

1. For repeat analysis of fasting BE study, there is a discrepancy in the firm's summary tables and the full analytical report. For example, the firm's summary table reports a total of **20** reassays for non-analytical reasons; the full analytical report dictates a total of **34** reassays for non-analytical reasons. The firm should clearly explain this discrepancy.

2. For repeat analysis of both fasting and fed studies, the firm only submitted the original concentrations of the samples reanalyzed due to non-analytical reasons. The firm should provide complete tables containing the original concentrations and repeated concentrations for **all** reanalyzed study samples.

3. The firm did not specify the salt form of the Ethylenediaminetetraacetic Acid (EDTA), used in the bioanalytical method validation and clinical studies. The firm should provide this information.

4. The dissolution data using the firm's own dissolution method indicated that the dissolution method that the firm used is not discriminative. For example, for all strengths of the test products, more than (b)(4)% of the drug released within 5 minutes. The firm should develop a more discriminatory method. One option might be reducing the paddle speed and/or reducing the concentration of the surfactant in the medium.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (AA77267) incomplete due to the deficiencies mentioned above. Kudco Ireland, Ltd. conducted the fasting BE study on its Atorvastatin 80 mg Tablets (lot # P803401) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 08107V).

2. The Division of Bioequivalence finds the fed BE study (AA77268) incomplete due to the deficiencies mentioned above. Kudco Ireland, Ltd. conducted the fasting BE study on its Atorvastatin 80 mg Tablets (lot # P803401) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 08107V).

3. The *in vitro* dissolution testing on the 10 mg, 20 mg, 40 mg and 80 mg strengths conducted by the firm, using the Firm's dissolution method and FDA-recommended dissolution method, is **inadequate** due to the above mentioned Deficiency #4. The firm should develop a more discriminatory dissolution method for its test product.

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.

The firm should be informed the above deficiencies and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	None.

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	AA77267
Study Title	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fasting Conditions
Clinical Site (Name & Address)	MDS Pharma Services 2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345
Principal Investigator	Gaetano Morelli, M.D.
Dosing Dates	Group 1: Period 1 – January 19, 2009, Period 2 – February 2, 2009 Group 2: Period 1 – January 22, 2009, Period 2 – February 5, 2009 Group 3: Period 1 – January 26, 2009, Period 2 – February 9, 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Samples were analyzed between 20-Feb-2009 and 17-Mar-2009
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)	57 days During sample collection, study samples were initially stored at -20°C. On 28-Jan-2009, the samples were moved to -80°C storage. Sample storage at -20°C did not exceed 10 days. Study samples were stored from 28-Jan-2009 to the end of sample analysis at a nominal temperature of -80°C for a duration not exceeding 49 days.

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium Tablets	Lipitor® (atorvastatin calcium)

	80 mg* *80 mg atorvastatin (as atorvastatin calcium)	tablets 80 mg** **Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin
Manufacturer	Schwarz Pharma Manufacturing, Inc.	Pfizer Ireland Pharmaceuticals Dublin, Ireland (b) (4) Distributed by Parke-Davis
Batch/Lot No.	P803401	08107V
Manufacture Date	12/02/08	
Expiration Date		Apr 09
Strength	80 mg	80 mg
Dosage Form	tablet	tablet
Bio-Batch Size	(b) (4)	
Production Batch Size	(b) (4)	
Potency (Assay)	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	99.0%, 0.9%	
Dose Administered	80 mg	80 mg
Route of Administration	oral	oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	A total of 144 healthy adult volunteers (97 males and 47 females), who had satisfied the screening evaluation, were admitted to the study center. One hundred and forty (140) subjects completed the study (96 males and 44 females) and the data of 139 subjects were used in the statistical analysis.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	3
Washout Period	14 days

Randomization Scheme	Group 1 – AB: 01, 03, 04, 06, 08, 10, 12, 13, 15, 16, 19, 22, 24, 25, 27, 28, 30, 34, 39, 41, 43, 44, 46, Group 1 – BA: 02, 05, 07, 09, 11, 17, 18, 20 ,21, 23, 26, 29, 31, 32, 33, 35, 36, 37, 38, 40, 42, 45, 47, 48 Group 2 – AB; 50, 51, 52, 56, 58, 61, 62, 63, 67, 68, 69, 72, 73, 74, 75, 78, 79, 84, 85, 86, 89, 92, 93, 94 Group 2 – BA: 49, 53, 54, 55, 57, 59, 60, 64, 65, 66, 70, 71, 76, 77, 80, 81, 82, 83, 87, 88, 90, 91, 95, 96 Group 3 – AB: 98, 99, 100, 103, 106, 109, 110, 111, 112, 116, 117, 118, 121, 123, 125, 127, 129, 131, 132, 134, 135, 138, 140, 141 Group 3 – BA: 97, 101, 102, 104, 105, 107, 108, 113, 114, 115, 119, 120, 122, 124, 126, 128, 130, 133, 136, 137, 139, 142, 143, 144
Blood Sampling Times	Blood samples (1 x 5 mL) were collected in blood collection tubes containing EDTA before dosing (hour 0) and at the following times thereafter: 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 16, 24, 30, 36, 48 and 60 hours post-dose.
Blood Volume Collected/Sample	Blood samples (1 x 5 mL) were collected from subjects prior to dosing and up to 60 hours post-dose.
Blood Sample Processing/Storage	Blood samples were collected at the times specified under Study Design section, cooled in an ice bath and centrifuged under refrigeration as soon as possible. Plasma samples were divided into 2 aliquots and stored in suitably labeled tubes at -20±10°C following completion of processing. Samples were then transferred and stored at -80°C ± 15°C pending assay. Atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin in plasma were analyzed using a validated LC/MS/MS method developed at (b) (4). The analytical ranges were 0.225 – 90.0 ng/mL, 0.175 – 70.0 ng/mL and 0.250 - 100 ng/mL, respectively.
IRB Approval	Yes; 16 December 2008
Informed Consent	Yes; 22 December 2008
Length of Fasting	All subjects fasted overnight for at least 10 hours before dosing and for at least 4 hours thereafter. Water was not permitted from 1 hour before until 1 hour after dosing, but was allowed at all other times.
Length of Confinement	In each period, subjects were housed from at least 10 hours before dosing until after the 36-hour blood draw.
Safety Monitoring	Physical examination, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event (AE) assessments were evaluated at various phases during this study.

Comments on Study Design:

The firm did not specify the salt form of the EDTA used in the bioanalytical (pre-study and during study) method validation and clinical studies. The firm will be asked to provide this information.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. AA77267			
		Treatment Groups	
		Test Product N = 140	Reference Product N = 140
Age (years)	Mean ± SD	39.8 ± 9.4	39.8 ± 9.4
	Range	18 - 55	18 - 55
	18 – 39	62 (44.3%)	62 (44.3%)
	40 – 64	78 (55.7%)	78 (55.7%)
Sex	Male	98 (68.6%)	96 (68.6%)
	Female	44 (31.4%)	44 (31.4%)
Race	Asian	2 (1.4%)	2 (1.4%)
	African American	3 (2.1%)	3 (2.1%)
	Caucasian	135 (96.4%)	135 (96.4%)
BMI	Mean + SD	24.3 ± 2.3	24.3 ± 2.3
	Range	19.4 - 28.0	19.4 - 28.0
Height	Mean + SD	171.3 ± 8.0	171.3 ± 8.0
	Range	149 - 190	149 - 190
Weight	Mean + SD	71.7 ± 10.1	71.7 ± 10.1
	Range	46.9 - 98.9	46.9 - 98.9

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
15	Subject withdrew from the study for personal reasons (release date: 02-Feb-2009 at 08:59) prior to Period 2 dosing (treatment: reference).	Prior to Period 2 dosing	No
55	Subject withdrew from the study for personal reasons (release date: 26-Jan-2009 at 13:42) prior to Period 2 check-in (treatment: test).	Prior to Period 2 check-in	No
89	Subject did not return (release date: 05-Feb-2009 at 07:20) for Period 2 (treatment: reference).	Period 2	No
121	Subject was withdrawn from the study (release date: 09-Feb-2009 at 07:30) by the study manager due to late arrival (treatment: reference).	Period 2	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Adverse Event (Classified according to MedDRA Version 12.0) System Organ Class Preferred Term	Test		Reference		Total	
Number of Subjects Dosed	143	(100%)	141	(100%)	144	(100%)
Number of Subjects Without Adverse Events	117	(81.8%)	123	(87.2%)	108	(75%)
Number of Subjects With Adverse Events	26	(18.2%)	18	(12.8%)	36	(25%)
Nervous system disorders	14	(9.8%)	9	(6.4%)	19	(13.2%)
Headache	12	(8.4%)	8	(5.7%)	16	(11.1%)
Dizziness	2	(1.4%)	3	(2.1%)	5	(3.5%)
Hypoaesthesia	1	(0.7%)	0	(0%)	1	(0.7%)
Somnolence	1	(0.7%)	0	(0%)	1	(0.7%)
Respiratory, thoracic and mediastinal disorders	5	(3.5%)	4	(2.8%)	9	(6.3%)
Rhinorrhoea	4	(2.8%)	2	(1.4%)	6	(4.2%)
Sneezing	2	(1.4%)	0	(0%)	2	(1.4%)
Cough	0	(0%)	1	(0.7%)	1	(0.7%)
Nasal congestion	1	(0.7%)	0	(0%)	1	(0.7%)
Nasal dryness	0	(0%)	1	(0.7%)	1	(0.7%)
Wheezing	0	(0%)	1	(0.7%)	1	(0.7%)
Gastrointestinal disorders	6	(4.2%)	2	(1.4%)	8	(5.6%)
Nausea	4	(2.8%)	1	(0.7%)	5	(3.5%)
Vomiting	2	(1.4%)	1	(0.7%)	3	(2.1%)
Dyspepsia	1	(0.7%)	0	(0%)	1	(0.7%)
General disorders and administration site conditions	5	(3.5%)	2	(1.4%)	7	(4.9%)
Vessel puncture site pain	4	(2.8%)	1	(0.7%)	5	(3.5%)
Asthenia	0	(0%)	1	(0.7%)	1	(0.7%)
Catheter site pain	1	(0.7%)	0	(0%)	1	(0.7%)
Chills	0	(0%)	1	(0.7%)	1	(0.7%)
Feeling hot	0	(0%)	1	(0.7%)	1	(0.7%)
Pyrexia	1	(0.7%)	0	(0%)	1	(0.7%)
Vessel puncture site paraesthesia	1	(0.7%)	0	(0%)	1	(0.7%)
Injury, poisoning and procedural complications	2	(1.4%)	3	(2.1%)	5	(3.5%)
Procedural dizziness	1	(0.7%)	2	(1.4%)	3	(2.1%)

Adverse Event (Classified according to MedDRA Version 12.0) System Organ Class Preferred Term	Test		Reference		Total	
Foreign body trauma	1	(0.7%)	0	(0%)	1	(0.7%)
Skin laceration	0	(0%)	1	(0.7%)	1	(0.7%)
Vascular disorders	0	(0%)	1	(0.7%)	1	(0.7%)
Hot flush	0	(0%)	1	(0.7%)	1	(0.7%)
Skin and subcutaneous tissue disorders	1	(0.7%)	0	(0%)	1	(0.7%)
Acne	1	(0.7%)	0	(0%)	1	(0.7%)
Renal and urinary disorders	1	(0.7%)	0	(0%)	1	(0.7%)
Urine odor abnormal	1	(0.7%)	0	(0%)	1	(0.7%)
Musculoskeletal and connective tissue disorders	0	(0%)	1	(0.7%)	1	(0.7%)
Musculoskeletal pain	0	(0%)	1	(0.7%)	1	(0.7%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
As per protocol, plasma samples were to be divided into 2 aliquots and stored at -20±10°C, pending assay. However, following discussion between bioanalytical and the Sponsor, agreement was reached that it would be preferable to store the plasma samples at -80°C, pending assay. Therefore, all samples in Period 1 were transferred from -20°C to -80°C storage on 28-Jan-2008. All Period 2 samples were processed and stored directly at -80°C, pending assay.	1, 3, 4, 6, 8, 10, 12, 13, 15, 16, 19, 22, 24, 25, 27, 28, 30, 34, 35, 39, 41, 43, 44, 46, 50 - 52, 56, 58, 61 - 63, 67 - 69, 72 - 75, 78, 79, 84 - 86, 89, 92 - 94, 98 - 100, 103, 106, 109 - 112, 116 - 118, 121, 123, 125, 127, 129, 131, 132, 134, 135, 138, 140, 141	2, 5, 7, 9, 11, 14, 17, 18, 20, 21, 23, 26, 29, 31 – 33, 36 – 38, 40, 42, 45, 47 – 49, 53 - 55, 57, 59, 60, 64 - 66, 70, 71, 76, 77, 80 – 83, 87, 88, 90, 91, 95 – 97, 101, 102, 104, 105, 107, 108, 113 -115, 119, 120, 122, 124, 126, 128, 130, 133, 136, 137, 139, 142 -144
As per SOP, all protocol requirements were to be documented as evidence that they were performed. The stop time for the activity restriction in Period 1 was not completed until 13 days after the fact; therefore the restriction stop time is questionable.	1, 3, 4, 6, 8, 10, 12, 13, 15, 16, 19, 22, 24, 25, 27, 28, 30, 34, 35, 39, 41, 43, 44, 46, 50 - 52, 56, 58, 61 - 63, 67 - 69, 72 - 75, 78, 79, 84 - 86, 89, 92 - 94, 98 - 100, 103, 106, 109 - 112, 116 - 118, 121, 123, 125, 127, 129,	2, 5, 7, 9, 11, 14, 17, 18, 20, 21, 23, 26, 29, 31 – 33, 36 – 38, 40, 42, 45, 47 – 49, 53 - 55, 57, 59, 60, 64 - 66, 70, 71, 76, 77, 80 – 83, 87, 88, 90, 91, 95 – 97, 101, 102, 104, 105, 107, 108, 113 -115, 119, 120, 122, 124, 126,

	131, 132, 134, 135, 138, 140, 141	128, 130, 133, 136, 137, 139, 142 -144
As per protocol, medication, including over-the-counter or herbal products, was prohibited during the time of sample collection, or during the washout period between drug administrations. Subject took 200 mcg of Salbutamol on 20-Jan-2009 for an episode of wheezing in Period 1.		7
As per protocol, plasma samples were to be divided into 2 aliquots. There was no 2nd aliquot of plasma for the 48-hour time point in Period 1.		14
As per protocol, postdose meals plans were to be identical for both periods. Subject did not consume the 9-hour meal in Period 1 at the schedule time due to adverse events. Subject had ginger ale approximately 13 hours following dosing.	15	
As per protocol, medication, including over-the-counter or herbal products, was prohibited during the time of sample collection, or during the washout period between drug administrations. Subject received 100 mg of Gravol on 19-Jan-2009 for an episode of Nausea in Period 1.	15	
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subject did not return for the 48- and 60-hour blood draws in Period 1 and for the 48-hour blood draw in Period 2.	46	46
As per Memo-to-file, plasma samples were to be divided into 2 aliquots and stored at -80±15°C, pending assay. Due to activity in the unit, there was a temperature excursion which lasted approximately 99 minutes, reaching a high temperature reading of -59°C, affecting samples from the -0.75- to the 60-hour time points in Period 1. There were no temperature excursions during the conduct of Period 2.	50 - 52, 56, 58, 61, 62, 63, 67 - 69, 72 - 75, 78, 79, 84 - 86, 89, 92 - 94, 98 - 100, 103, 106, 109 - 112, 116 - 118, 121, 123, 125, 127, 129, 131, 132, 134, 135, 138, 140, 141	49, 53 - 55, 57, 59, 60, 64 - 66, 70, 71, 76, 77, 80 – 83, 87, 88, 90, 91, 95 – 97, 101, 102, 104, 105, 107, 108, 113 -115, 119, 120, 122, 124, 126, 128, 130, 133, 136, 137, 139, 142 - 144
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subject did not return for the 60-hour blood draw in Period 2.	65	
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subjects did not return for the 60-hour blood draw in Period 1.	89, 121	87, 107
As per protocol, medication was prohibited (with the exception of hormonal contraceptives and hormonal replacement therapy) or herbal products during the time of the sample collection or during the washout period between drug administrations. Subject took Fiorinal, 40 mg, for an episode of headache in Period 1.	89	
As per protocol, postdose meals plans were to be identical for both periods. Subject received a pack of crackers following an episode of vomiting in Period 1.	89	
As per protocol, subjects who had participated in another clinical trial within 28 days prior to the first dose were not	99	

to be enrolled in the study. At each check-in and return visit, subjects were asked if they had participated in any clinical trials within the 28 days prior to dosing. Subject omitted to answer this question at Period 1 check-in. However, subject answered "no" to this question on every check-in and return questionnaire thereafter.		
As per protocol, blood samples were to be obtained at various time points throughout the study. There were no samples obtained for the 6-hour time point in Period 2 due to difficult venipuncture.	133	99
As per protocol, standard meals had to be provided at approximately 4 and 9 hours after dosing, and at appropriate times thereafter. The following subjects did not entirely consume their meal(s): Sub. No. / Time Point / Period / Reason 19 / 13 / 1 and 2 / not hungry 51 / 33 / 2 / not hungry 65 / 13 / 2 / adverse events 107 / 13 / 2 / not hungry 143 / 13 / 2 / not hungry 143 / 13 / 1 / not hungry	19, 65, 107, 143	19, 51, 143
As per protocol, blood samples were to be obtained at various time points throughout the study. There was no sample obtained for the 3-hour time point in Period 1 due to difficulties with the catheter.		115
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subject did not return for the 48-hour blood draw in Period 2.	144	

Comments on Dropouts/Adverse Events/Protocol Deviations:

- No serious adverse events were reported. Each adverse event was resolved.

- The following subjects experienced emesis during the fasting bioequivalence study:

    - Subject 89, Period I, Test treatment, 12 hours post-dose
    - Subject 107, Period I, Reference treatment, 19 hours post-dose
    - Subject 142, Period II, Test treatment, 4 hours post-dose

  For the fasting study, the median Tmax of the parent drug and two metabolites are 0.75 hrs (test and reference), 1.67/1.33 hrs (test/reference) and 1 hour (test and reference), respectively. The vomiting adverse events mentioned above occurred outside the two times the median Tmax window, therefore, according to BA/BE Guidance, the data of these subjects were still included for the statistical analysis.

- Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points. Most sample collection time

deviations were not significant (± 5%). In this case for statistical analysis, nominal times were used by the firm and the reviewer. For times in which the deviation varied greater than ±5%, actual times were used by the reviewer. The reviewer agrees with the firm's decision.

- Subjects 07, 15, and 89 required administration of concomitant therapy (Salbutamol, Gravol, and Fiorinal, respectively). According to the labeling of this drug product, there are no expected interactions.

- The dropouts and data presented above were generated in accordance with standard operating procedures (SOPs).

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.225	0.450	1.80	3.60	9.00	45.0	72.0	90.0
Inter day Precision (%CV)	2.5	4.9	3.3	2.6	2.4	2.1	2.3	1.9
Inter day Accuracy (%Actual)	99.6	100.4	101.1	100.0	100.9	99.6	99.2	99.3
Linearity	0.9946-1.0000							
Linearity Range (ng/mL)	0.225-90.0							
Sensitivity/LOQ (ng/mL)	0.225							

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.675	6.75	35.0	67.5	450
Inter day Precision (%CV)	6.3	3.8	8.3	5.5	2.6
Inter day Accuracy (%Actual)	100.3	98.7	99.4	98.4	95.8

Orthohydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.175	0.350	1.40	2.80	7.00	35.0	56.0	70.0
Inter day Precision (%CV)	2.2	4.3	2.9	2.4	2.5	2.6	2.4	2.3
Inter day Accuracy (%Actual)	99.4	101.4	100.0	99.6	100.6	99.4	99.3	100.0
Linearity	0.9961-0.9999							
Linearity Range (ng/mL)	0.175-70.0							
Sensitivity/LOQ (ng/mL)	0.175							

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.525	5.25	32.0	52.5	350
Inter day Precision (%CV)	6.1	4.3	7.5	5.7	2.4
Inter day Accuracy (%Actual)	101.3	99.4	100.3	99.6	98.0

Parahydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.250	0.500	2.00	4.00	10.0	50.0	80.0	100
Inter day Precision (%CV)	3.2	6.4	3.1	3.0	2.6	2.1	2.3	2.4
Inter day Accuracy (%Actual)	99.2	102.0	100.0	100.0	101.0	99.6	99.2	99.1
Linearity	0.9949-0.9999							
Linearity Range (ng/mL)	0.250-100							
Sensitivity/LOQ (ng/mL)	0.250							

Parameter	Quality Control Samples				
Concentration (ng/mL)	0.750	2.00	7.50	75.0	500
Inter day Precision (%CV)	6.1	245.7*	4.3	9.2	3.1
Inter day Accuracy (%Actual)	98.9	121.5*	98.4	97.1	98.6

* Event Investigation (b) (4)-EIR-2009-61 was initiated due to an unexpected result on Batch 10. QC C, injection 49, and QC E, injection 60, had greater than 50% bias from nominal. During the processing (i.e. aliquotting and extracting) of Batch 10, the analyst noted that QC C and E at the end of the batch (Injections 91 and 102) had been switched. The runlog was edited and verified accordingly. After further investigation, it appeared that the first replicates of QC C and E had also been switched during processing, but since this was noted after the batch was instrumented and regressed, QC C (injection 49) and QC E (injection 60) were rejected. Batch 10 met acceptance for all analytes. There was no impact on the study data. As a result of the high bias from nominal concentrations, the %CV and %Bias for QC C and QC E for parahydroxy atorvastatin are high in the QC statistics.

Comments on Study Assay Validation:

The firm did not specify the salt form of the EDTA used in the bioanalytical (pre-study and during study) method validation and clinical studies. The firm should provide this information.

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
GL-BIO-10603-03	30-Apr-2008	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	No
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 issues with repeat analysis of study samples. Please see section 3.6 for details.

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[9]

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. AA77267 Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	145.671	55.37	45.52	580.69	149.014	52.47	38.68	520.81	0.98
AUC∞ (hr *ng/ml)	155.066	52.92	52.34	584.82	158.595	49.18	61.44	525.82	0.98
Cmax (ng/ml)	34.024	63.74	4.57	163.00	36.361	53.15	10.20	129.00	0.94
Tmax* (hr)	0.750	.	0.33	6.06	0.750	.	0.33	6.00	1.00
Kel (hr^{-1})	0.067	43.34	0.00	0.14	0.070	40.38	0.00	0.18	0.96
T1/2 (hr)	10.224	31.91	4.82	24.74	10.107	31.18	3.88	27.06	1.01

Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. AA77267				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	129.431	134.182	96.5	92.2% - 100.9%
AUC∞ (hr *ng/ml)	135.101	139.138	97.1	93.2% - 101.2%
Cmax (ng/ml)	28.557	32.668	87.4	80.8% - 94.6%

[9] It should be noted, that as per the firm, geometric mean (CV%) are presented for AUC0-t, AUC∞ and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel in tables the firm's Table 1 in section 3.6. As a result, the arithmetic values presented above for atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin for AUC0-t, AUC∞ and Cmax will differ from Table 1 shown in section 3.6.

Orthohydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. AA77267				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	144.582	151.099	95.7	90.6% - 101.1%
AUC∞ (hr *ng/ml)	151.868	156.919	96.8	91.9% - 102.0%
Cmax (ng/ml)	23.087	25.637	90.1	82.1% - 98.8%

Parahydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. AA77267				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	9.624	9.28264	103.7	95.0% - 113.2%
AUC∞ (hr *ng/ml)	25.37	22.2560	114.0	102.3% - 127.1%
Cmax (ng/ml)	0.880	0.86653	101.5	92.8% - 111.00%

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. AA77267					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	129.57	134.57	0.96	92.08	100.67
AUC∞ (hr *ng/ml)	137.13	143.87	0.95	91.18	99.63
Cmax (ng/ml)	28.59	32.71	0.87	80.72	94.63

Table 17. Additional Study Information, Fasting Study No. AA77267

Atorvastatin

Root mean square error, AUC0-t	0.2252	
Root mean square error, AUC∞	0.2109	
Root mean square error, Cmax	0.4017	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	126	130
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1	0

first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	Yes – 3	Yes - 3

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	127	0.96	0.76	0.99
Reference	131	0.96	0.85	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The confidence interval for $\ln AUC_{\infty}$ (as calculated by the firm) does not fall within the interval of 80%-125% for Parahydroxy Atorvastatin. This is also observed in other in-house data (ANDA 077575). This is due to the low plasma levels of the metabolite as compared to the parent drug, atorvastatin, and other active metabolite, orthohydroxy atorvastatin. Therefore, the Division of Bioequivalence bases bioequivalence determination on the 90% CIs data of AUC_{0-t}, AUC_{∞}, and C_{max} for atorvastatin and comparable pharmacokinetic (PK) parameter results for the active metabolite, ortho hydroxyatorvastatin, and concludes that the parahydroxyatorvastatin PK results are acceptable.
- Subject 141 (period I, test product) shows a measureable drug concentration at zero (0) hours for the parent drug and both active metabolites. Since this drug concentration is less than 5% of the C_{MAX} for this subject, no further analysis is needed[10].

- The Atorvastatin and Orthohydroxy Atorvastatin data for subject 143 (period II) show an AUC0-t/AUC∞ ratio of 0.76 and 0.69, respectively (shown as the minimum test ratio in the table above).

- Subjects enrolled in this study were dosed in different days and divided into three groups (Group 1: Subject Nos. 1-48, Group 2: Subject Nos. 49-96, Group 3: Subject Nos. 97-144). For period 1 and period 2, the study dosing dates were Group 1: 19/Jan/2009, 02/Feb/2009; Group 2: 22/Jan/2009, 05/Feb/2009 and Group 3: 26/Jan/2009, 09/Feb/2009. The reviewer used the model TRT*GRP for statistical analysis. There was no significant TRT*GRP effect ($p>0.1$) for AUC_{0-t} (0.2195), AUC_{∞} (0.3389) and C_{MAX} (0.3250). Therefore, this term was dropped from subsequent analysis.

- It was noted that there were five subjects in which AUC_{∞} was not calculated by the firm: subject 24 (test and reference), subject 99 (reference), 122 (test and reference), 128 (test), and 143 (test). It was also noted that the elimination phase of these subjects was not linear for the respective treatments. Also, there were 14 subjects in which AUC_{∞} was not calculated by the reviewer (see table below). It was also noted that the elimination phase was not completely linear with respect to the mentioned

[10] Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations: March 2003.

treatments. Since the sampling times for these subjects are adequate, they were included in the final statistical analysis by the reviewer and thusly, are included in the 90% confidence intervals.

Subject Number	Treatment
10	T, R
12	T, R
24	T
30	R
33	T
43	T
73	T, R
77	T, R
83	R
86	T
90	T, R
98	R
109	T, R
119	T, R

- Low AUC0-t/AUC∞ ratios for parahydroxy atorvastatin are more than likely attributed to low CMAX values for the metabolite as well as low sensitivity within the study. Since the 90% confidence intervals are with the acceptable range of 80%-125%, the metabolite data is considered acceptable supporting documentation.

- Due to the low sensitivity of the metabolite, parahydroxy atorvastatin, the terminal K_{EL} and thusly, $AUC_{0-\infty}$ cannot be reliably determined. Similarly, ANDA 077575 [11] reports low concentrations for parahydroxy atorvastatin.

- The pharmacokinetic and statistical analyses are **adequate.** The reviewer used the SAS code, CALCKE, for statistical analysis of the data. The following time points were selected to calculate the Kel of the parent drug:

  Ke first: T14 (16 hours)

  Ke last: T17 (36 hours)

  As noted above in the firm – calculated confidence intervals (and reviewer – verified), the 90% confidence intervals for log-transformed AUC_{∞} of an active metabolite, parahydroxy atorvastatin, do not meet the acceptable BE limits of 80.00% - 125.00%. As a result, the orthohydroxy – and parahydroxy atorvastatin data is adequate and considered supporting documentation.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of atorvastatin are within the acceptable BE limits of 80.00% - 125.00%. Also, the 90%

[11] DARRTS Search: 077575. 05/07/2010. REV-BIOEQ-01(General Review).

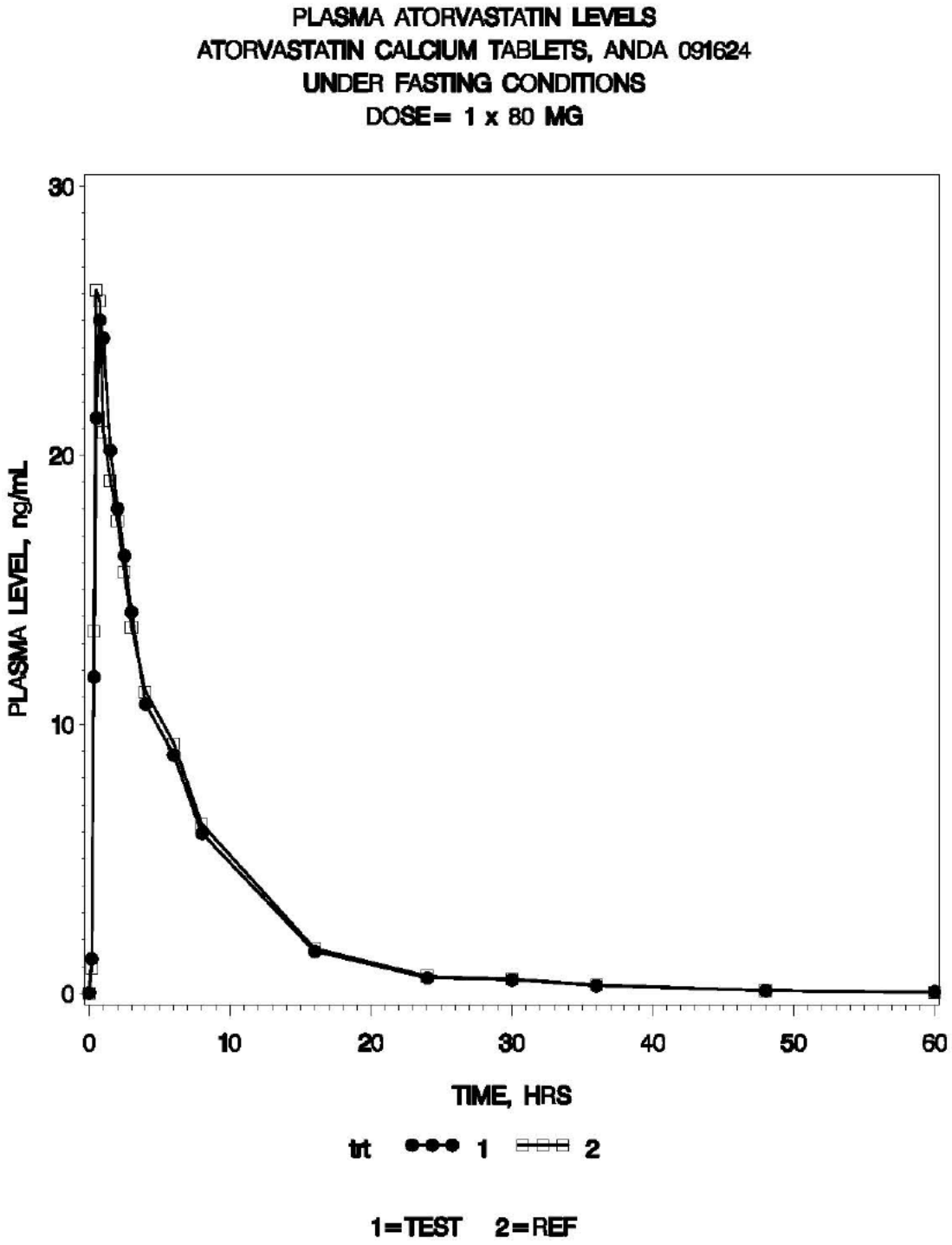
confidence intervals for log – transformed AUC_{0-t}, AUC_{∞} and C_{max} of the active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin, are within acceptable BE limits of 80.00% - 125.00%. However, the study is **inadequate** due to deficiencies noted in Section 3.10 (Deficiency Comments).

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n= 140)		Reference (n= 140)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	1183.22	0.00	.	.
0.17	1.28	145.61	0.93	292.25	1.38
0.33	11.75	98.58	13.46	109.40	0.87
0.50	21.37	85.77	26.14	68.50	0.82
0.75	25.02	71.97	25.72	64.96	0.97
1.00	24.34	81.80	20.85	62.61	1.17
1.50	20.17	77.60	19.06	63.21	1.06
2.00	18.01	75.89	17.57	65.27	1.03
2.50	16.26	78.18	15.65	77.80	1.04
3.00	14.16	76.04	13.60	86.11	1.04
4.00	10.74	71.66	11.20	109.07	0.96
6.00	8.85	55.90	9.28	58.30	0.95
8.00	5.94	56.09	6.28	56.90	0.95
16.00	1.55	71.41	1.66	66.07	0.94
24.00	0.56	73.54	0.63	88.15	0.89
30.00	0.50	67.94	0.53	64.89	0.94
36.00	0.28	94.03	0.32	82.82	0.88
48.00	0.09	173.82	0.10	169.41	0.88
60.00	0.05	231.05	0.04	266.80	1.29

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	AA77268
Study Title	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fed Conditions
Clinical Site (Name & Address)	MDS Pharma Services 2350 Cohen Street Saint-Laurent, Montréal, Québec H4R 2N6 Canada Phone: (514) 333-0042 Fax: (514) 335-8345
Principal Investigator	Gaetano Morelli, M.D.
Dosing Dates	Group 1: Period 1 – January 23, 2009, Period 2 – February 6, 2009 Group 2: Period 1 – January 28, 2009, Period 2 – February 11, 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Samples were analyzed between 27-Feb-2009 and 18-Mar-2009
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)	54 days During sample collection, study samples were initially stored at -20°C. On 28-Jan-2009, the samples were moved to -80°C storage. Sample storage at -20°C did not exceed 5 days. Study samples were stored from 28-Jan-2009 to the end of sample analysis at a nominal temperature of -80°C for a duration not exceeding 49 days.

Table 20. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium Tablets 80 mg* *80 mg atorvastatin (as atorvastatin calcium)	Lipitor® (atorvastatin calcium) tablets 80 mg** **Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin
Manufacturer	Schwarz Pharma Manufacturing, Inc.	Pfizer Ireland Pharmaceuticals Dublin, Ireland (b) (4)

		Distributed by Parke-Davis
Batch/Lot No.	P803401	08107V
Manufacture Date	12/02/08	
Expiration Date		Apr 09
Strength	80 mg	80 mg
Dosage Form	tablet	tablet
Bio-Batch Size	(b) (4)	
Production Batch Size	(b) (4)	
Potency (Assay)	(b) (4) %	(b) (4) %
Content Uniformity (mean, %CV)	99.0%, 0.9%	
Dose Administered	80 mg	80 mg
Route of Administration	oral	oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	A total of 88 subjects (57 males and 31 females) were enrolled in the study, and 86 subjects (56 males and 30 females) completed the study. Eighty-six subjects were analyzed and included in the PK and statistical analyses.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	14 days
Randomization Scheme	Group I – AB: 01, 02, 03, 05, 08, 10, 12, 15, 18, 20, 22, 23, 26, 27, 31, 32, 35, 37, 41, 42, 43 Group I – BA: 04, 06, 09, 11, 13, 14, 16, 17, 19, 21, 24, 25, 28, 29, 30, 33, 34, 36, 38, 39, 40, 44 Group II – AB: 45, 46, 48, 49, 51, 54, 56, 59, 62, 64, 67, 69, 71, 72, 76, 77, 80, 81, 82, 85, 86, 87 Group II – BA: 47, 50 ,51, 52, 53, 55, 57, 58, 60, 61, 63, 65, 66, 68, 70, 73, 74, 75, 78, 79, 83, 84, 88
Blood Sampling Times	Blood samples (1 x 5 mL) were collected in blood collection tubes containing EDTA before dosing (hour 0) and at the following times thereafter: 0.333, 0.667, 1, 1.333, 1.667, 2, 2.5, 3, 4, 5, 6, 8, 16, 24, 30, 36, 48 and 60 hours post-dose.
Blood Volume Collected/Sample	Blood samples (1 x 5 mL) were collected from subjects prior to dosing and up to 60 hours post-dose.
Blood Sample Processing/Storage	Blood samples were collected at the times specified under Study Design section, cooled in an ice bath and centrifuged under refrigeration as soon as possible. Plasma samples were divided into 2 aliquots and stored in suitably labeled tubes at -20±10°C following completion of processing. Samples were then transferred and stored at -80°C ± 15°C pending assay. Atorvastatin, ortho-hydroxyatorvastatin and para hydroxyatorvastatin in plasma were analyzed using a validated LC/MS/MS method developed at (b) (4) . The analytical ranges were 0.225 – 90.0 ng/mL, 0.175 – 70.0 ng/mL and 0.250 - 100 ng/mL, respectively.
IRB Approval	Yes; 16 December 2008
Informed Consent	Yes; 22 December 2008
Length of Fasting Before Meal	On Day -1 of each period, subjects received a dinner at 20:00, and then commenced a 10-hour overnight fast until 30 minutes prior to their scheduled dosing times, when they were given a standard high fat breakfast.
Length of Confinement	In each period, subjects were housed from at least 10 hours before dosing until after the 36 - hour blood draw. Subjects were to return for the 48-and 60-hour blood draws.
Safety Monitoring	Physical examination, clinical laboratory tests, vital signs, electrocardiogram (ECG), and adverse event (AE) assessments were evaluated at various phases during this study.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The firm did not specify the salt form of the EDTA used in the bioanalytical (pre-study and during study) method validation and clinical studies. The firm should provide this information.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. AA77268			
		Treatment Groups	
		Test Product N = 86	Reference Product N = 86
Age (years)	Mean ± SD	36.8 ± 9.0	36.8 ± 9.0
	Range	18 - 54	18 – 54
	18 – 39	48 (55.%)	48 (55.%)
	40 – 64	38 (44.2%)	38 (44.2%)
Sex	Male	30 (34.9%)	30 (34.9%)
	Female	56 (65.1%)	56 (65.1%)
	African American	4 (4.7%)	4 (4.7%)
	Caucasian	82 (95.3%)	82 (95.3%)
BMI	Mean + SD	24.3 ± 2.3	24.3 ± 2.3
	Range	18.9 – 27.9	18.9 – 27.9
Height	Mean±SD	170.7 ± 8.2	170.7 ± 8.2
	Range	147 - 188	147 - 188
Weight	Mean±SD	71.0 ± 9.5	71.0 ± 9.5
	Range	49.0 – 89.3	49.0 – 89.3

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
11	Subject was withdrawn from study (release date: 24-Jan-2009 at 16:10) due to adverse events (headache, nausea, chills, dizziness, sinusitis) in Period 1 (treatment: reference) [12].	Period 1	No
66	Subject was withdrawn from the study (release date: 11-Feb-2009 at 08:31) due to elevated Creatine Phosphokinase (CPK) level prior to Period 2 dosing (treatment: test)	Prior to Period 2 dosing	No

[12] Both the chills and nausea were noted prior to drug administration.

Table 24. Study Adverse Events, Fed Bioequivalence Study

Adverse Event (Classified according to MedDRA Version 12.0) System Organ Class Preferred Term	Test		Reference		Total	
Number of Subjects Dosed	86	(100%)	88	(100%)	88	(100%)
Number of Subjects Without Adverse Events	74	(86%)	76	(86.4%)	67	(76.1%)
Number of Subjects With Adverse Events	12	(14%)	12	(13.6%)	21	(23.9%)
Nervous system disorders	5	(5.8%)	4	(4.5%)	8	(9.1%)
Headache	4	(4.7%)	4	(4.5%)	7	(8%)
Dizziness	1	(1.2%)	0	(0%)	1	(1.1%)
General disorders and administration site conditions	3	(3.5%)	2	(2.3%)	5	(5.7%)
Asthenia	1	(1.2%)	0	(0%)	1	(1.1%)
Catheter site pain	1	(1.2%)	0	(0%)	1	(1.1%)
Chest pain	0	(0%)	1	(1.1%)	1	(1.1%)
Chills	0	(0%)	1	(1.1%)	1	(1.1%)
Feeling hot	1	(1.2%)	0	(0%)	1	(1.1%)
Pyrexia	0	(0%)	1	(1.1%)	1	(1.1%)
Vessel puncture site haematoma	1	(1.2%)	0	(0%)	1	(1.1%)
Vessel puncture site pain	0	(0%)	1	(1.1%)	1	(1.1%)
Gastrointestinal disorders	3	(3.5%)	2	(2.3%)	4	(4.5%)
Nausea	3	(3.5%)	0	(0%)	3	(3.4%)
Constipation	0	(0%)	2	(2.3%)	2	(2.3%)
Musculoskeletal and connective tissue disorders	1	(1.2%)	2	(2.3%)	3	(3.4%)
Arthralgia	0	(0%)	2	(2.3%)	2	(2.3%)
Myalgia	1	(1.2%)	0	(0%)	1	(1.1%)
Skin and subcutaneous tissue disorders	0	(0%)	2	(2.3%)	2	(2.3%)
Alopecia	0	(0%)	1	(1.1%)	1	(1.1%)
Erythema	0	(0%)	1	(1.1%)	1	(1.1%)
Injury, poisoning and procedural complications	1	(1.2%)	1	(1.1%)	2	(2.3%)
Procedural dizziness	0	(0%)	1	(1.1%)	1	(1.1%)
Skin laceration	1	(1.2%)	0	(0%)	1	(1.1%)

Adverse Event (Classified according to MedDRA Version 12.0) System Organ Class Preferred Term	Test		Reference		Total	
Vascular disorders	1	(1.2%)	0	(0%)	1	(1.1%)
Pallor	1	(1.2%)	0	(0%)	1	(1.1%)
Respiratory, thoracic and mediastinal disorders	1	(1.2%)	0	(0%)	1	(1.1%)
Oropharyngeal pain	1	(1.2%)	0	(0%)	1	(1.1%)
Reproductive system and breast disorders	1	(1.2%)	1	(1.1%)	1	(1.1%)
Breast discomfort	1	(1.2%)	1	(1.1%)	1	(1.1%)
Infections and infestations	0	(0%)	1	(1.1%)	1	(1.1%)
Acute sinusitis	0	(0%)	1	(1.1%)	1	(1.1%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
As per protocol, blood samples were to be taken before dosing and at 0.333, 0.667, 1, 1.333, 1.667, 2, 2.5, 3, 4, 5, 6, 8, 16, 24, 30, 36, 48 and 60 hours postdose. The following subjects had blood draw time deviations reported. Please refer to Appendix 16.2.2 of the report for blood draw time deviation listings.	3, 4, 14, 27, 33, 34, 41, 45, 49, 51, 54, 56, 58, 63, 64, 67, 71, 72, 77, 84	9, 11, 14, 16, 17, 23, 27, 30, 34, 36, 39, 46, 58, 67, 68, 73, 76, 77, 86, 88
As per protocol, plasma samples were to be divided into 2 aliquots and stored at -20±10°C, pending assay. However, following discussion between bioanalytical and the Sponsor, agreement was reached that it would be preferable to store the plasma samples at -80°C, pending assay. Therefore, all samples in Period 1 for Subject Nos. 1-44, and samples for Subject Nos. 45-88 from predose to the 4-hour time point in Period 1 were transferred from -20°C to -80°C storage on 28-Jan-2008. All Period 2 samples were processed and stored directly at -80°C, pending assay.	1 – 3, 5, 7, 8, 10, 12, 15, 18, 20, 22, 23, 26, 27, 31, 32, 35, 37, 41- 43, 45, 46, 48, 49, 51, 54, 56, 59, 62, 64, 67, 69, 71, 72, 76, 77, 80, 81, 82, 85 -87	4, 6, 9, 11, 13, 14, 16, 17, 19, 21, 24, 25, 28, 29, 30, 33, 34, 36, 38 - 40, 44, 47, 50, 52, 53, 55, 57, 58, 60, 61, 63, 65, 66, 68, 70, 73, 74, 75, 78, 79, 83, 84, 88
As per protocol, during housing, postdose meal plans were to be identical for both periods. Subject received 6 oz of prune juice on 07-Feb-2009 for an episode of constipation in Period 2.		1
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subjects did not return for the 60-hour blood draw in Period 1.	8, 22, 31	
As per protocol, medication, including over-the-counter or		11

herbal products, was prohibited during the time of sample collection, or during the washout period between drug administrations. Subject took 400 mg of Advil on 24-Jan-2009 for an episode of fever in Period 1.		
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subjects did not return for the 48-hour blood draw in Period 1.	23, 45	
As per protocol, plasma samples were to be divided into 2 aliquots. There was no 2nd aliquot of plasma for the 6-hour time point in Period 2.	30	
As per protocol, subjects were to return for the 48-and 60-hour blood draws. Subject did not return for the 48- and 60-hour blood draws in Period 1.		38
As per Memo-to-file, plasma samples were to be divided into 2 aliquots and stored at -80±15°C, pending assay. Due to activity in the unit, there was a temperature excursion which lasted approximately 99 minutes, reaching a high temperature reading of -59°C, affecting samples from the -1- to the 4-hour time points in Period 1. There were no temperature excursions during the conduct of Period 2.	45, 46, 48, 49, 51, 54, 56, 59, 62, 64, 67, 69, 71, 72, 76, 77, 80, 81, 82, 85, 86, 87	47, 50, 52, 53, 55, 57, 58, 60, 61, 63, 65, 66, 68, 70, 73, 74, 75, 78, 79, 83, 84, 88
As per protocol, during housing, postdose meal plans were to be identical for both periods. Subject received 125 ml of prune juice on 12-Feb-2009 for an episode of constipation in Period 2.		85

Comments on Adverse Events/Protocol Deviations:

- No serious adverse events were reported. Each adverse event was resolved.

- Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points. Most sample collection time deviations were not significant (± 5%). In this case for statistical analysis, nominal times were used by the firm. For the reviewer's verification, actual times were used for cases in which the deviation varied greater than ±5%. The reviewer agrees with the firm's decision.

- The dropouts and data presented above were generated in accordance with standard operating procedures (SOPs).

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.225	0.450	1.80	3.60	9.00	45.0	72.0	90.0
Inter day Precision (%CV)	2.7	5.6	4.2	3.0	2.2	2.4	3.0	2.1
Inter day Accuracy (%Actual)	99.6	101.1	98.9	100.0	100.9	100.4	99.6	99.8
Linearity	0.9957-0.9997							
Linearity Range (ng/mL)	0.225-90.0							
Sensitivity/LOQ (ng/mL)	0.225							

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.675	6.75	35.0	67.5	450
Inter day Precision (%CV)	6.0	3.3	11.3	3.7	5.0
Inter day Accuracy (%Actual)	99.9	99.7	99.7	100.9	99.3

Orthohydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.175	0.350	1.40	2.80	7.00	35.0	56.0	70.0
Inter day Precision (%CV)	2.4	4.6	3.0	3.1	2.6	2.7	2.8	3.2
Inter day Accuracy (%Actual)	99.4	101.7	100.0	98.9	99.4	100.3	99.6	100.6
Linearity	0.9952-1.0000							
Linearity Range (ng/mL)	0.175-70.0							
Sensitivity/LOQ (ng/mL)	0.175							

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.525	5.25	32.0	52.5	350
Inter day Precision (%CV)	5.9	3.7	11.5	3.9	4.2
Inter day Accuracy (%Actual)	101.7	101.7	101.3	102.3	102.3

Parahydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.250	0.500	2.00	4.00	10.0	50.0	80.0	100
Inter day Precision (%CV)	3.0	5.8	4.4	2.9	2.8	2.6	2.7	2.7
Inter day Accuracy (%Actual)	98.8	101.8	100.5	99.7	101	99.6	99.1	99.3
Linearity	0.9957-0.9997							
Linearity Range (ng/mL)	0.250-100							

Sensitivity/LOQ (ng/mL)	0.250

Parameter	Quality Control Samples				
Concentration (ng/mL)	0.750	2.00	7.50	75.0	500
Inter day Precision (%CV)	7.9	11.8	3.7	4.3	3.1
Inter day Accuracy (%Actual)	100.5	97.5	99.9	99.7	100.2

Comments on Study Assay Validation:

The firm did not specify the salt form of the EDTA used in the bioanalytical (pre-study and during study) method validation and clinical studies.

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
GL-BIO-10603-03	30-Apr-2008	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	No
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[13]

Mean plasma concentrations are presented in Table 33 and Figure 2

Fed Bioequivalence Study, Study No. AA77268 Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	175.471	50.03	66.68	596.50	174.317	46.76	43.64	436.14	1.01
AUC∞ (hr *ng/ml)	195.240	65.26	71.26	1012.65	181.951	45.20	49.06	442.15	1.07
Cmax (ng/ml)	44.055	66.96	13.00	167.00	48.353	66.06	6.20	177.00	0.91
Tmax* (hr)	1.667	.	0.33	6.00	1.333	.	0.67	5.00	1.25
Kel (hr^{-1})	0.064	37.96	0.00	0.12	0.067	35.18	0.00	0.14	0.96
T1/2 (hr)	11.749	77.62	5.63	88.23	11.774	59.55	4.80	56.77	1.00

* Tmax values are presented as median, range

Fed Bioequivalence Study, Study No. AA77268 Orthohydroxy Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	156.610	34.60	59.88	296.42	157.795	37.80	51.26	317.16	0.99
AUC∞ (hr *ng/ml)	161.566	33.79	64.51	298.60	165.046	38.02	57.13	341.83	0.98
Cmax (ng/ml)	23.419	44.10	7.14	53.40	25.407	53.73	5.06	80.40	0.92
Tmax* (hr)	2.500	.	0.33	6.00	1.667	.	0.67	6.00	1.50
Kel (hr^{-1})	0.067	24.23	0.01	0.10	0.065	24.38	0.01	0.11	1.02
T1/2 (hr)	11.533	55.32	7.14	61.37	12.398	91.92	6.54	108.69	0.93

* Tmax values are presented as median, range

[13] It should be noted, that as per the firm, geometric mean (CV%) are presented for AUC0-t, AUC∞and Cmax. Median (Range) are presented for Tmax. Arithmetic Mean (±SD) are presented for t½ and Kel in tables the firm's Table 1 in section 3.6. As a result, the arithmetic values presented above for atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin for AUC0-t, AUC∞and Cmax will differ from Table 1 shown in section 3.6.

Fed Bioequivalence Study, Study No. AA77268 Parahydroxy Atorvastatin									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	16.173	74.58	0.39	61.82	16.601	78.86	0.45	62.27	0.97
AUC∞ (hr *ng/ml)	37.970	79.95	17.76	229.34	37.840	35.98	18.47	70.34	1.00
Cmax (ng/ml)	1.417	58.87	0.27	4.33	1.505	74.52	0.00	5.58	0.94
Tmax* (hr)	5.000	.	0.67	16.00	5.000	.	0.67	60.00	1.00
Kel (hr^{-1})	0.026	93.69	0.00	0.09	0.023	104.30	0.00	0.09	1.13
T1/2 (hr)	33.684	224.50	7.47	550.21	28.826	93.13	7.37	157.38	1.17

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. AA77268				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	158.900	158.192	100.4	96.3% - 104.8%
AUC∞ (hr *ng/ml)	163.145	162.584	100.3	96.3% - 104.6%
Cmax (ng/ml)	37.248	40.199	92.7	82.8% - 103.7%

Orthohydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. AA77268				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	147.082	147.054	100.0	96.3% - 103.9%
AUC∞ (hr *ng/ml)	153.242	152.363	100.6	96.8% - 104.4%
Cmax (ng/ml)	21.272	22.411	94.9	87.3% - 103.3%

Parahydroxy Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study, Study No. AA77268				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	12.119	11.690	103.7	95.6% - 112.4%
AUC∞ (hr *ng/ml)	20.554	22.342	92.0	85.3% - 99.2%
Cmax (ng/ml)	1.241	1.249	99.3	92.8% - 106.3%

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 1 X 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. AA77268					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	159.22	158.02	1.01	96.54	105.16
AUC∞ (hr *ng/ml)	170.54	166.00	1.03	96.81	109.02
Cmax (ng/ml)	37.25	40.20	0.93	82.82	103.67

Table 32. Additional Study Information

Atorvastatin

Root mean square error, AUC0-t	0.1686	
Root mean square error, AUC∞	0.2270	
Root mean square error, Cmax	0.4426	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	81	84
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	1	0
Were the subjects dosed as more than one group?	Yes – 2	Yes - 2

NOTE: Subject 29 (Period II, test treatment) has a maximum concentration (C_{MAX}) value as the first measurable time point. As per the General Guidance[10], "Collection of an early time point between 5 and 15 minutes after dosing followed by additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient to assess early peak concentrations. If this sampling approach is followed, we recommend that data sets be considered adequate, even when the highest observed concentration occurs at the first time point.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	81	0.96	0.22	1.00
Reference	84	0.96	0.61	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- Subjects enrolled in this study were dosed in different days and divided into two groups (Group 1: Subject Nos. 1-44 and Group 2: Subject Nos. 45-88). For Period 1 and Period 2, the study dosing dates were Group 1: 23/Jan/2009, 06/Feb/2009 and Group 2: 28/Jan/2009, 11/Feb/2009. The reviewer used the model TRT*GRP for statistical analysis. There was no significant TRT*GRP effect ($p>0.1$) for AUC_{0-t}

(0.1736), AUC_{∞} (0.5532) and C_{MAX} (0.5439). Therefore, this term was dropped from subsequent analysis.

- It was noted that there were two subjects in which AUC_{∞} was not calculated by the firm: subject 02 (test and reference) and subject 51 (test). It was also noted that the elimination phase of these subjects was not linear for the respective treatments. Also, there were five subjects in which AUC_{∞} was not calculated by the reviewer: subject 19 (test), 26 (test), 32 (test), 42 (test and reference), and 50 (test and reference). It was also noted that the elimination phase was not completely linear with respect to the mentioned treatments. Since the sampling times for these subjects are adequate, they were included in the final statistical analysis by the reviewer and thusly, are included in the 90% confidence intervals.

- Subjects 51 (test product) and 02 (reference product) show Atorvastatin $_{AUC0\text{-}t/}AUC_{\infty}$ ratios of 0.22 and 0.61, respectively (shown as the minimum test ratio in the table above).

- Low minimum values for AUC0-t/AUC∞ ratios of orthohydroxy and parahydroxy atorvastatin are more than likely attributed to low C_{MAX} values for the metabolite as well as low sensitivity within the study. Since the 90% confidence intervals are with the acceptable range of 80%-125%, the metabolite data is considered acceptable supporting documentation.

- Due to the low sensitivity of the metabolite, parahydroxy atorvastatin, the terminal K_{EL} and thusly, $AUC_{0\text{-}\infty}$ cannot be reliably determined. Similarly, ANDA 077575 [14] reports low concentrations for parahydroxy atorvastatin

- The pharmacokinetic and statistical analyses are **adequate.** The reviewer used the SAS code, CALCKE, for statistical analysis of the data. The following time points were selected to calculate the Kel of the parent drug:

  Ke first: T14 (16 hours)

  Ke last: T17 (36 hours)

  Also, the orthohydroxy – and parahydroxy atorvastatin data is adequate and considered supporting documentation.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The 90% confidence intervals for log-transformed $AUC_{0\text{-}t}$, AUC_{∞} and C_{max} of atorvastatin are within the acceptable BE limits of 80.00%-125.00%. Also, the 90% confidence intervals for log – transformed $AUC_{0\text{-}t}$, AUC_{∞} and C_{max} of the active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin, are within

[14] DARRTS Search: 077575. 05/07/2010. REV-BIOEQ-01(General Review).

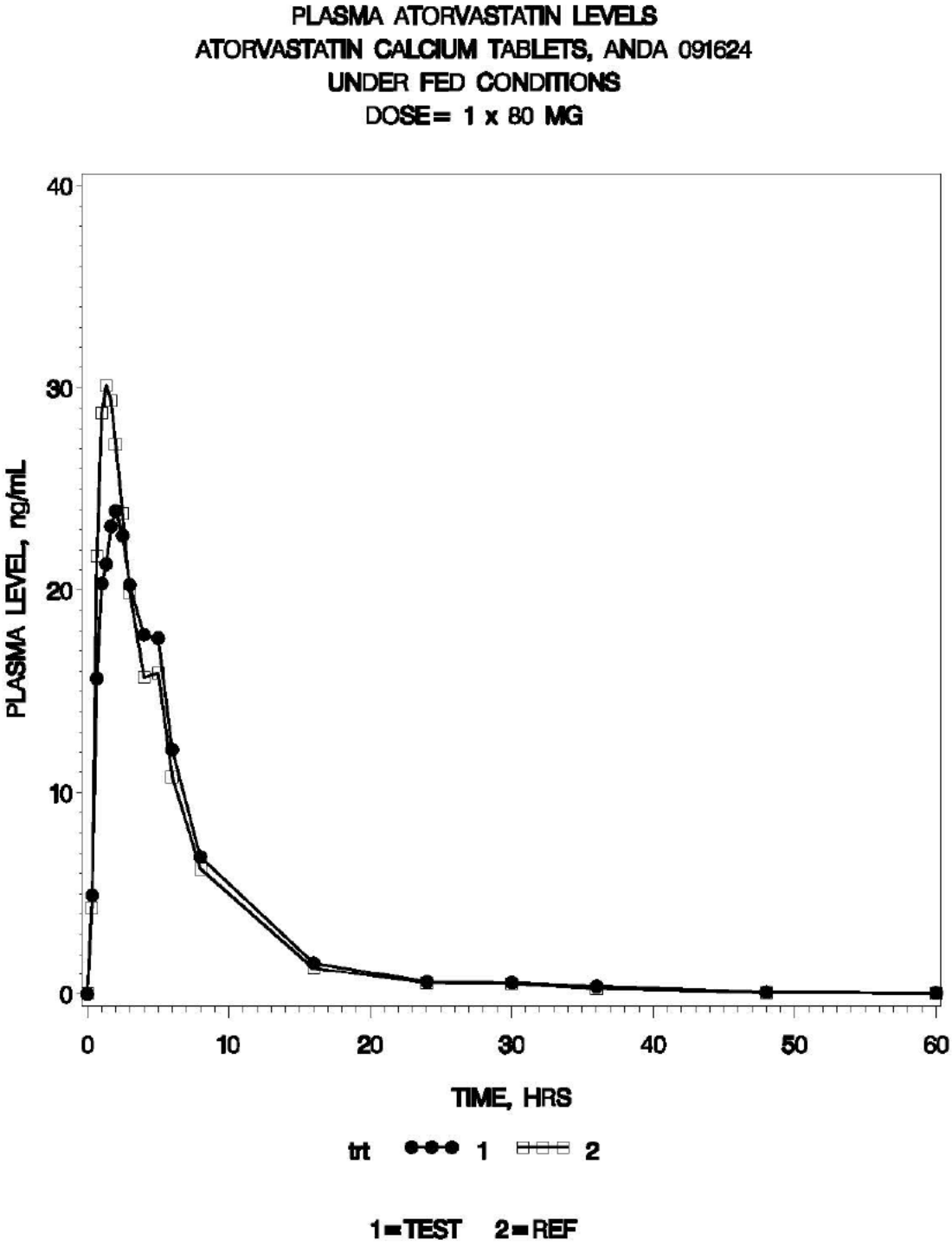
acceptable BE limits of 80.00% - 125.00%. However, the study is **inadequate** due to deficiencies listed in section 3.10 (Deficiency Comments) of this review.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n= 86)		Reference (n= 86)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.33	4.93	294.23	4.31	307.80	1.14
0.67	15.64	190.46	21.71	171.15	0.72
1.00	20.33	137.10	28.76	101.22	0.71
1.33	21.29	101.16	30.12	84.55	0.71
1.67	23.16	83.35	29.38	68.65	0.79
2.00	23.92	77.43	27.22	60.88	0.88
2.50	22.69	63.82	23.78	59.80	0.95
3.00	20.27	57.61	19.91	59.73	1.02
4.00	17.79	80.85	15.70	57.29	1.13
5.00	17.62	59.34	15.90	54.60	1.11
6.00	12.12	57.02	10.78	53.25	1.12
8.00	6.82	60.21	6.23	54.17	1.09
16.00	1.57	68.95	1.31	54.44	1.20
24.00	0.59	73.99	0.54	64.23	1.09
30.00	0.55	81.48	0.49	67.92	1.11
36.00	0.37	191.42	0.27	104.41	1.38
48.00	0.08	212.75	0.07	223.37	1.26
60.00	0.05	308.88	0.03	476.34	1.92

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin



4.2 Formulation Data

4.2.1 Test Formulation Data

Ingredient	Amount (%) / Tablet	Amount (mg) / Tablet			
		10 mg	20 mg	40 mg	80 mg
					(b) (4)
Atorvastatin Calcium Trihydrate (b) (4)					(b) (4)
Croscarmellose Sodium (b) (4)					
Amino Methacrylate Copolymer (b) (4)					
Lactose Monohydrate (b) (4)					
Sodium Stearyl Fumarate					
Colloidal Silicon Dioxide (b) (4)					
Core Tablet					
					(b) (4)
Total Weight (mg)					(b) (4)

Ingredient	Maximum Amount Based on MDD (mg)[15]				Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit or Justified with MDD (mg)	Test formulation Acceptable?
	10 mg	20 mg	40 mg	80 mg		
Croscarmellose Sodium (b) (4)	(b) (4)				(b) (4)	Yes
Amino Methacrylate Copolymer (b) (4)						Yes
Lactose Monohydrate (b) (4)						Yes
Sodium Stearyl Fumarate						Yes
Colloidal Silicon Dioxide (b) (4)						Yes

[15] Based on Clinical Pharmacology: http://www.clinicalpharmacology-ip.com/Default.aspx. Last accessed: 23 April 2010 and drug labeling, The MDD for the drug product is 80 mg/day.

4.2.2 Components of (b) (4)

Table 2 – Quantitative Composition of (b) (4)

Name	Reference	Amount % w/w	Function
(b) (4) containing:			
Polyethylene Glycol			
Titanium Dioxide			
Polyvinyl Alcohol			
Talc			

Ingredient	Maximum Amount Based on MDD (mg)[15]				Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit or Justified with MDD (mg)	Test formulation Acceptable?
	10 mg	20 mg	40 mg	80 mg		
(b) (4) (b) (4)						
Polyethylene Glycol					(b) (4)	Yes
Titanium Dioxide						Yes
Polyvinyl Alcohol						Yes
Talc						Yes

Reviewer's Comments: Each inactive ingredient of the coating, (b) (4) falls within acceptable limits listed in the FDA's Inactive Ingredient Guidance (IIG) limits. Based on the Maximum Daily Dosage (MDD) of this drug product (80 mg per day)[16], the components of the (b) (4) are **adequate**.

[16] Clinical Pharmacology: http://www.clinicalpharmacology-ip.com/Default.aspx. Last accessed: 23 April 2010.

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	1. There is no overage of active pharmaceutical ingredient (API). 2. Each inactive ingredient of the test product also falls within acceptable limits listed in the FDA's Inactive Ingredient Guidance (IIG) limits and are acceptable based on MDD (per CSO's Checklist review located in DARRTS (REV-RPM-03(Filing Review), 10/192009 and also reviewer verified). 3. The formulation for the lower strengths, 10 mg, 20 mg, and 40 mg, of Atorvastatin Calcium Tablets are proportionally similar to the firm's higher strength, 80 mg Atorvastatin Calcium Tablets. The formulations are **adequate**.

4.3 Dissolution Data

Dissolution Review Path	DARRTS: REV-BIOEQ-02(Dissolution Review). 12/18/2009.

1. Dissolution test using the firm's method:

Dissolution Conditions		
	Apparatus:	USP Apparatus 2 (Paddle)
	Speed of Rotation:	75 rpm
	Medium:	(b) (4)% Tween 80 in (b) (4)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		NLT (b) (4)% (Q) of the labeled amount is dissolved in 30 minutes
Dissolution Testing Site (Name, Address)		Schwarz Pharma Manufacturing, Inc. 1101 C Avenue West – Seymour, IN 47274

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times				Study Report Location
						5 min	10 min	15 min	30 min	
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets, 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	86	90	93	96	Table 5.1 Figure 5
					Range	(b) (4)				
					%CV	1.6	1.8	2.2	2.1	
Study Report[1]	6/15/09	Lipitor Tablets, 10mg / 03698V (Expires: 01 / 2010)	10 mg Tablets	12	Mean	71	85	92	100	
					Range	(b) (4)				
					%CV	6.7	3.0	3.2	2.1	
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets, 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	89	93	95	99	Table 5.2 Figure 6
					Range	(b) (4)				
					%CV	2.3	1.7	2.0	1.8	
Study Report[1]	6/15/09	Lipitor Tablets, 20mg / 02648V (Expires: 02 / 2010)	20 mg Tablets	12	Mean	74	86	91	95	
					Range	(b) (4)				
					%CV	3.7	3.0	1.7	2.9	

Study Report[1]	6/12/09	Atorvastatin Calcium Tablets, 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	87	91	93	97	Table 5.3 Figure 7
					Range	(b) (4)				
					%CV	1.9	1.8	1.7	1.7	
Study Report[1]	6/15/09	Lipitor Tablets, 40mg / 0307048 (Expires: 03 / 2011)	40 mg Tablets	12	Mean	78	88	91	95	
					Range	(b) (4)				
					%CV	2.4	1.9	2.2	2.0	
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets, 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	89	93	95	99	Table 5.4 Figure 8
					Range	(b) (4)				
					%CV	1.4	1.0	1.4	1.5	
Study Report[1]	6/15/09	Lipitor Tablets, 80mg / 08107V (Expires: 04 / 2009)	80 mg Tablets	12	Mean	72	85	90	95	
					Range	(b) (4)				
					%CV	1.5	0.9	1.4	1.4	

2. Dissolution test using the FDA-recommended method (submitted in the firm's dissolution amendment dated 2/26/2010):

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	0.05M Phosphate Buffer, pH 6.8
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	N/A	
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							Study Report Location
						5 min	10 min	15 min	30 min	60 min	90 min	120 min	
Study Report[1]	2/3/10	Atorvastatin Calcium Tablets, 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	48	57	61	67	72	75	77	Table 5.5 Figure 9
					Range	(b) (4)							
					%CV	2.5	2.6	2.5	2.9	2.0	1.6	1.8	
Study Report[1]	1/28/10	Lipitor Tablets, 10mg / 03698V (Expires: 01 / 2010)	10 mg Tablets	12	Mean	81	90	93	96	n/a	n/a	n/a	
					Range	(b) (4)							
					%CV	5.2	2.7	2.6	2.0	n/a	n/a	n/a	
Study Report[1]	2/1/10	Atorvastatin Calcium Tablets, 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	49	57	60	65	69	70	72	Table 5.6 Figure 10
					Range	(b) (4)							
					%CV	1.3	2.0	1.7	1.4	1.6	1.3	1.7	
Study Report[1]	2/1/10	Lipitor Tablets, 20mg / 02648V (Expires: 02 / 2010)	20 mg Tablets	12	Mean	80	89	92	94	n/a	n/a	n/a	
					Range	(b) (4)							
					%CV	3.2	2.9	2.3	1.8	n/a	n/a	n/a	

Study Report[1]	1/28/10	Atorvastatin Calcium Tablets, 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	39	44	47	49	52	52	52	Table 5.7 Figure 11
					Range	(b) (4)							
					%CV	3.7	2.6	1.7	1.3	1.7	1.5	1.1	
Study Report[1]	1/27/10	Lipitor Tablets, 40mg / 0307048 (Expires: 03 / 2011)	40 mg Tablets	12	Mean	87	95	98	101	n/a	n/a	n/a	
					Range	(b) (4)							
					%CV	2.3	1.7	1.4	0.9	n/a	n/a	n/a	
Study Report[1]	1/28/10	Atorvastatin Calcium Tablets, 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	39	44	45	46	45	45	45	Table 5.8 Figure 12
					Range	(b) (4)							
					%CV	1.8	0.7	0.5	0.5	0.5	0.5	0.6	
Study Report[1]	2/1/10	Lipitor Tablets, 80mg / 08107V (Expires: 04 / 2009)	80 mg Tablets	12	Mean	78	90	93	97	n/a	n/a	n/a	
					Range	(b) (4)							
					%CV	5.8	2.1	1.8	1.5	n/a	n/a	n/a	

Reviewer's Comments: The FDA – recommended dissolution method is not suitable for the test product. The firm's method, as proposed, is not an effectively discriminating assay. The firm should develop a more discriminatory method. Please see the dissolution consult included in section 4.5 of this review.

Figure 3. Dissolution Profiles

1. **Firm's Proposed Dissolution Method:**

Figure 1: Dissolution Plot Comparing Test Products (Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in (b) (4) with (b) (4) % Tween 80

Figure 2: Dissolution Plot Comparing the Reference Products (Lipitor Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in (b) (4) with (b) (4) % Tween 80

2. FDA - recommended Dissolution Method:

Figure 3: Dissolution Plot Comparing the Test Products (Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in 0.05M Phosphate Buffer, pH 6.8

Figure 4: Dissolution Plot Comparing the Reference Products (Lipitor Tablets 10 mg, 20 mg, 40 mg, and 80 mg strengths) in 0.05M Phosphate Buffer, pH 6.8

4.4 Detailed Regulatory History (If Applicable)

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

Johnetta:

1. The firm argues that the FDA method is not appropriate for its product due to the slow dissolution rate. Based on the data that you have provided in your email, I agree with the firm that the FDA method is not appropriate for the proposed product given that dissolution does not reach (b) (4)% for any of the Test strengths even after two hours. The slow dissolution rate is most readily apparent for the 40 mg and 80 mg strengths.

2. The firm's proposed method uses surfactant (b) (4)% Tween 80). The firm justifies this approach by citing the presence of Tween 80 in the RLD formulation. I confirmed the presence of Tween 80 in the RLD product (NDA 020702, 11/2009 Annual Report and DARRTS: REV-QUALITY-03, Final Date 11/13/2000). The RLD formulation is below:

Table 1	Lipitor (Atorvastatin Calcium) Tablets	Composition (mg/tablet)				
Components	*Strength*	*Function*	*10*	*20*	*40*	*80*
(b) (4)						

3. While the presence of surfactant in the RLD product and the known insolubility of atorvastatin in aqueous media would support inclusion of Tween 80 in the firm's proposed method, it seems that the amount of surfactant leads to an indiscriminatory assay[17]. Considering the borderline low 90% CIs for lnCmax in the biostudies, it is especially important that the method we choose is highly discriminatory so that we can differentiate among Test lots.

[17] I note that the Test product contains sodium stearyl fumarate. The presence of this excipient in the tablet may exacerbate the effect of (b) (4)% Tween 80 on the discriminatory power of the method.

4. Given point 3 above, we should suggest to the firm that it develop a more discriminatory method. I propose that we suggest to reduce the paddle speed to 50 rpm and/or reduce the concentration of surfactant.

Please note that these are just recommendations. Please consult your Team Leader for additional input and decision-making.

-Utpal

4.6 SAS Output

4.6.1 Fasting Study Data – Atorvastatin

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	treat	grp	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	T1	T2
1																										(b) (4)
2																										
3																										
4																										
5																										
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4.7 Additional Attachments

N/A

BIOEQUIVALENCE DEFICIENCIES

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
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 repeat analysis of fasting BE study (study # AA77267), there was a discrepancy in your summary tables (Table 9, Section 5.3.1.4.1 of the electronic submission) and the full analytical report (Section 5.3.1.4 of the electronic submission): The summary table reported a total of **25** reassays for non-analytical reasons; the full analytical report indicated a total of **34** reassays for non-analytical reasons. Please explain this discrepancy.

2. For repeat analysis of both fasting and fed studies (study # AA77267 and AA77268, respectively), you only submitted the original concentrations of the samples reanalyzed due to non-analytical reasons. Please provide complete tables containing the original concentrations and repeated concentrations for **all** reanalyzed study samples, where possible.

3. Please specify the salt form of the Ethylenediaminetetraacetic Acid, (EDTA), i.e., K_2EDTA, K_3EDTA or NaEDTA, used in your pre-study method validation, bioanalytical studies and clinical studies.

4. The dissolution data based your proposed dissolution method [900 mL of 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm] indicated that this method was not sufficiently discriminative: For all strengths of your test product, more than (b)(4)% of the drug was released within 5 minutes. Please develop a new dissolution method or modify your current method for more gradual dissolution profiles by reducing the paddle speed and/or reducing the concentration of the surfactant in the medium, etc.

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

4.8 Outcome Page

ANDA: 091624

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
11383	7/15/2009	Bioequivalence Study	Fasting Study	1	1
11383	7/15/2009	Bioequivalence Study	Fed Study	1	1
11383	7/15/2009	Other	Dissolution Waiver	1	1
11383	7/15/2009	Other	Dissolution Waiver	1	1
11383	7/15/2009	Other	Dissolution Waiver	1	1
11383	2/26/2010	Other	Dissolution Amendment	1	1
				Bean Total:	6

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND 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/

JOHNETTA L FARRAR
08/11/2010

BING V LI
08/11/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/11/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091624	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength (s)	10 mg, 20 mg, 40 mg, and 80 mg	
Applicant Name	KUDCO Ireland Ltd. (KUDCO)	
Address	1101 C Avenue West Seymour, IN 47274	
Applicant's Point of Contact	Jeff Siefert, Kremers Urban/ Schwarz Pharma	
Contact's Phone Number	812-523-5475	
Contact's Fax Number	812-523-1887	
Submission Date(s)	July 15, 2009	
First Generic	No	
Reviewer	Deanah L. Mitchell, Ph.D.	
Study Number (s)	AA77267	AA77268
Study Type (s)	Fasting	Fed
Strength(s)	80 mg	80 mg
Clinical Site	MDS Pharma Services	
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montreal, Quebec H4R 2N6 Canada	
Analytical Site	(b) (4)	
Analytical Address		

OVERALL REVIEW RESULT	**INADEQUATE**
DSI INSPECTION RESULT	**ADEQUATE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
#1	DISSOLUTION	10 MG	INADEQUATE
#1	DISSOLUTION	20 MG	INADEQUATE
#1	DISSOLUTION	40 MG	INADEQUATE
#1	DISSOLUTION	80 MG	INADEQUATE

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 (900 mL of 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm). The firm conducted dissolution testing using its own proposed method (900 mL of (b) (4)% Tween 80 in (b) (4) using USP Apparatus II (Paddle) at 75 rpm). The firm did not conduct dissolution testing using the FDA-recommended dissolution method.

Therefore, in order to determine whether or not the FDA-recommended dissolution method is appropriate for the firm's test product, for comparison with its proposed method, the firm will be asked to submit the dissolution testing data on 12 dosage units of all strengths of the test and reference products using the following FDA-recommended dissolution method:

Medium:	0.05 M Phosphate buffer, pH 6.8
Volume:	900 mL
Apparatus:	II (Paddle)
Speed:	75 rpm
Sampling Times:	5, 10, 15 and 30 minutes
Specification:	NLT (b) (4)% (Q) in 15 minutes

In addition, the firm only submitted dissolution testing data for the 80 mg strength of reference product using it proposed method. The firm will be asked to submit dissolution testing data using its own proposed method for all strengths of the reference product.

No Division of Scientific Investigations (DSI) inspections for the clinical site[1] and analytical site[2] are necessary or pending.

The DBE will review the fasted and fed BE studies, along with the waiver requests at a later date.

---

[1] A routine inspection was completed for the clinical site on 06/14/2007 for NDA 022118. The outcome was No Action Indicated (NAI). (DARRTS, Search: NDA 022118. The DSI Inspection concluded that the findings should not significantly impact the outcome of the study. O Shaughnessy, Jacqueline A/06-14-2007/REV-NONCLINICAL-03(General Review).

[2] A routine inspection was completed for the analytical site on 03/05/2008 for (b) (4). The outcome was Voluntary Action Indicated (VAI). DSI concluded that the accuracy of analyte concentrations in certain subjects was not assured. (DARRTS, Search (b) (4). Seaton, Mark J/03-07-2008/REV-RPM-05(General Review). The application has since been approved.

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: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	(b) (4) % Tween 80 in (b) (4) HCl (proposed test product media)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4) % (Q) of the labeled amount is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Schwarz Pharma Manufacturing, Inc. 1101 C Avenue West – Seymour, IN 47274	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 5 min	10 min	15 min	30 min	Study Report Location
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	86	90	93	96	Table 5.2
					Range	(b) (4)				
					%CV	1.6	1.8	2.2	2.1	
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	89	93	95	99	Table 5.3
					Range	(b) (4)				
					%CV	2.3	1.7	2.0	1.8	
Study Report[1]	6/14/09	Atorvastatin Calcium Tablets 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	87	91	93	97	Table 5.4
					Range	(b) (4)				
					%CV	1.9	1.8	1.7	1.7	
Study Report[1]	6/14/09	Atorvastatin Calcium Tablets 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	89	93	95	99	Table 5.5
					Range	(b) (4)				
					%CV	1.4	1.0	1.4	1.5	
Study Report[1]	6/16/09	Lipitor Tablets, 80mg / 08107v (Expires: 04 / 2009)	80 mg Tablets	12	Mean	72	85	90	95	Table 5.5
					Range	(b) (4)				
					%CV	1.5	0.9	1.4	1.4	

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	(b) (4) (OGD recommended media)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		NLT (b) (4) % (Q) of the labeled amount is dissolved in 30 minutes
Dissolution Testing Site (Name, Address)		Schwarz Pharma Manufacturing, Inc. 1101 C Avenue West – Seymour, IN 47274

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times				Study Report Location
						5 min	10 min	15 min	30 min	
Study Report[1]	5/13/09	Atorvastatin Calcium Tablets 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	70	73	75	77	Table 5.6
					Range	(b) (4)				
					%CV	1.7	1.7	1.9	1.8	
Study Report[1]	5/11/09	Atorvastatin Calcium Tablets 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	71	74	75	78	Table 5.7
					Range	(b) (4)				
					%CV	1.7	1.4	1.7	1.6	
Study Report[1]	6/27/09	Atorvastatin Calcium Tablets 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	69	72	74	75	Table 5.8
					Range	(b) (4)				
					%CV	3.0	2.2	2.1	1.7	
Study Report[1]	5/12/09	Atorvastatin Calcium Tablets 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	70	73	74	76	Table 5.9
					Range	(b) (4)				
					%CV	1.9	1.0	1.1	1.6	
Study Report[1]	5/12/09	Lipitor Tablets, 80mg / 08107v (Expires: 04 / 2009)	80 mg Tablets	12	Mean	35	39	42	46	Table 5.9
					Range	(b) (4)				
					%CV	3.9	1.7	2.3	2.8	

II. COMMENTS:

1. Currently, there is no USP method for Atorvastatin Calcium Tablets but there is an FDA-recommended dissolution method. The firm conducted dissolution testing using its own proposed method (900 mL of (b) (4) % Tween 80 in (b) (4) using USP Apparatus II (Paddle) at 75 rpm), which is different from the FDA-recommended method. The dissolution testing is incomplete. The firm should conduct dissolution testing using the FDA-recommended method, which is currently available on the public dissolution database on the Office of Generic Drugs website: http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.

2. The firm did not conduct dissolution using the appropriate FDA-recommended dissolution method. According to the website provided in comment # 1 above, the FDA-recommended dissolution media is 0.05 M Phosphate Buffer, pH 6.8. However, the firm conducted dissolution testing using (b) (4) (all other dissolution parameters are consistent). Based on using an incorrect method, the firm determined that the method was not suitable for its drug product.

   The firm states the following in its submission, "*The dissolution was originally based on the method published by the Office of Generic Drugs (OGD). However, during execution of the validation protocol, it was determined that the dissolution media was not suitable for the tablet formulation due to the low dissolution rate. The media was changed to* (b) (4) *% Tween 80 in* (b) (4) *It should be noted that the RLD contains Polysorbate 80, which is also known as Tween 80, so the need for the addition of the surfactant to the OGD-recommended dissolution media is not immediately apparent.*"[3]

3. The firm conducted dissolution testing on all strengths of its test product using its proposed method. However, the firm only conducted dissolution testing on the 80 mg strength of the reference product using it proposed method and the incorrect FDA-recommended method.

4. Based the above comments, the firm will be asked to conduct and submit additional dissolution testing for the test and reference products using the appropriate FDA-recommended method. Along with conducting dissolution testing on all strengths of the reference product using its proposed dissolution method.

III. DEFICIENCY COMMENTS:

1. The firm did not conduct and/or submit dissolution testing using the FDA-recommended dissolution method. Therefore, the firm should conduct and submit dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA-recommended dissolution method:

---

[3] EDR. ANDA 091624. Original Application 7/15/2009. Module 2.3. Quality Overall Summary. Last accessed: 12/15/09.

Medium:	0.05 M Phosphate buffer, pH 6.8
Volume:	900 mL
Apparatus:	II (Paddle)
Speed:	75 rpm
Sampling Times:	5, 10, 15 and 30 minutes
Specification:	NLT (b)(4)% (Q) in 15 minutes

The firm should provide the complete dissolution testing data of 12 units of both the test and reference products including all raw data, range, mean, and % coefficient of variation (%CV).

2. The firm did not submit dissolution testing data for the 10 mg, 20 mg and 40 mg of the reference product using its proposed dissolution method. The firm will be asked to provide this information.

IV. RECOMMENDATION

The in vitro dissolution testing conducted by Kudco Ireland Ltd. on its test product, Atorvastatin Calcium Tablets, 10 mg (Lot #P80350), 20 mg (Lot #P80360), 40 mg (Lot # P80370) and 80 mg (Lot #P80340) comparing to Pfizer Pharmaceutical's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg (Lot # 08107v) is incomplete due to the deficiency comments above.

The firm should be informed of the above deficiency comments and recommendation.

V. ADDITIONAL ATTACHMENTS

From: Solana-Sodeinde, Diana A
Sent: Tuesday, December 15, 2009 10:16 AM
To: Mitchell, Deanah
Subject: RE: Inspection Site

Hi Deanah

More than likely the Clinical address is the same. There's just a mistake with the Zip code but all is the same. Please use the DSI inspection history you found earlier.

Thank you,

Diana (Lola) Solana-Sodeinde, Pharm. D.

LT, U.S. Public Health Service
Regulatory Project Manager, Branch IV and VI
Division of BioEquivalence I
OGD/CDER/FDA
Diana.Solana-Sodeinde@fda.hhs.gov
work: (240) 276-8782
fax: (240) 276-8766

From: Mitchell, Deanah
Sent: Tuesday, December 15, 2009 10:09 AM
To: Solana-Sodeinde, Diana A
Cc: Mitchell, Deanah
Subject: FW: Inspection Site

Hello Diana,

Has DSI responded to this request?

Thanks,

Deanah

From: Mitchell, Deanah
Sent: Friday, December 11, 2009 3:30 PM
To: Solana-Sodeinde, Diana A
Subject: Inspection Site

Hello Diana,

Could you please confirm with DSI whether the inspection sites are the same:

FOR ANDA 91624

Clinical Site	MDS Pharma Services
Clinical Site Address	2350 Cohen Street Saint-Laurent, Montreal, Quebec H4R 2N6 Canada

In the DSI Database:

A routine inspection was completed for the Clinical site on 06/14/2007 for NDA 022118. The outcome was No Action Indicated (NAI).

Address: MDS Pharma, 2350 Cohen Street, Saint-Laurent, Montreal, Quebec, H4R 2N4 Canada

Thank you in advance for your help,

Deanah L. Mitchell, Ph.D.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 091624

APPLICANT: KUDCO Ireland Ltd.

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

The Division of Bioequivalence (DBE) has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the fasting and fed studies along with the waiver requests will be conducted at a later date. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. You stated in your submission that '*The dissolution was originally based on the method published by the Office of Generic Drugs (OGD). However, during execution of the validation protocol, it was determined that the dissolution media was not suitable for the tablet formulation due to the low dissolution rate. The media was changed to* (b) (4) *% Tween 80 in* (b) (4) *It should be noted that the RLD contains Polysorbate 80, which is also known as Tween 80, so the need for the addition of the surfactant to the OGD-recommended dissolution media is not immediately apparent.*' However, you did not conduct dissolution using the appropriate FDA-recommended dissolution method. Therefore, please conduct and submit comparative dissolution testing on all strengths of the test and reference products (12 dosage units each) using the following FDA-recommended method and sampling times:

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed of Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Sampling Times	5, 10, 15 and 30 minutes until (b) (4) % of the labeled amounts of atorvastatin is dissolved.

The dissolution method is currently available in the dissolution database in the FDA website: http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.

2. In addition, please provide dissolution testing data on 12 dosage units of the 10 mg, 20 mg, and 40 mg strengths of the reference product, Pfizer Pharmaceutical's Lipitor® (Atorvastatin Calcium) Tablets using your proposed dissolution method.

When you submit the additional dissolution data requested above, the DBE will compare the data from the FDA-recommended method with those from your proposed method, and determine which dissolution method is more suitable for your test product.

For all dissolution testing data, please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (%CV) at each time point for the 12 tablets tested and dates of dissolution testing. The dissolution testing data summary tables should be submitted in the DBE-recommended Electronic Common Technical Document (eCTD) format.

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

VI. OUTCOME

ANDA: 091624

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
9928	7/15/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND 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/

DEANAH L MITCHELL
12/17/2009

APRIL C BRADDY
12/17/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/18/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091624

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 #:091624
Firm Name:Kudco Ireland Limited
ANDA Name:Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base)
RLD Name:Lipitor by Pfizer

Electronic AP Routing Summary Located:
Z:\Chemistry Division III\Team 34\Electronic AP Summary\91624.ap.doc

AP/TA Letter Located:
Z:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\91624.apltr.DOC

Project Manager Evaluation: **Date: 12/26/12 Initials:** RG

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 7/16/09	Date of Application 7/15/09	Date Acceptable for Filing 10/19/09
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#:** (b) (4) (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: 4/25/12* ☐ 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) 12/28/12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 11/28/12 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 11/30/12 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: 12/26/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 12/26/12

☒ 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: 12/27/2012**

Chief, Reg. Support Branch **Initials:** IM for 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:11/18/2011 Is applicant eligible for 180 day No	
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:BOS = NDA 20-702 (Lipitor) ANDA submission 7/16/2009 to the 10 mg, 20 mg, 40 mg and 80 mg strengths with PIII to the '893, '995 and '667 patents and PIV certification to the '104, '156 and '971 patents. ACK LO 10/19/2009. Patent amendment dated 11/3/2009 with PIV RR sent 10/22/2009 to Pfizer (IRE, NY, CT) and Warner-Lambert (NJ) and rc'd 10/27, 10/23, 10/23 and 10/23/2009, respectively. Patent amendment dated 12/11/2009 with notice of litigation filed 12/3/2009 in USDC of Del, CA# 1:09-cv-00924, for infringement of the '156 patent only. Patent amendment dated 11/22/2011 notifying the agency Kudco had reached a settlement with Pfizer and a copy of the Order of Dismissal without prejudice dated 11/18/2011. Ranbaxy, ANDA 76-477, was awarded 180-day exclusivity for all four strengths. This exclusivity expired 5/29/2012. As there are no blocking regulatory issues, this application is eligible for immediate Full Approval.	

2. ***Labeling Endorsement***

Reviewer, Betty Turner:
Date12/26/12
InitialsBT

Labeling Team Leader, Lisa Kwok for Ruby Wu:
Date12/26/12
InitialsLK

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Turner, Betty
Sent: Wednesday, March 27, 2013 1:49 PM
To: Gaines, Robert; Wu, Ruby (Chi-Ann)
Subject: FW: ANDA 91624 full approval - EES now AC

Hi Bob,

This is to confirm that the labeling for ANDA 091624 remains adequate.

Thanks,

Betty

From: Gaines, Robert
Sent: Wednesday, March 27, 2013 11:49 AM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 91624 full approval - EES now AC

Good morning Betty and Ruby.

This one has been sitting since December waiting for EES. It is now ready for full approval. Please confirm that the labeling remains adequate.

Thanks

Bob

<< File: 91624 label rev.pdf >> << File: 91624.apltr.DOC >>

From: Kwok, Lisa
Sent: Wednesday, December 26, 2012 11:42 AM
To: Turner, Betty; Gaines, Robert; Wu, Ruby (Chi-Ann)
Cc: Nguyen, Sarah
Subject: RE: ANDA 91624 APPROVAL - EXPEDITED REVIEW

I concur.

Sarah/Bob - Please change the signature authority to Dr. Geba.

Thanks,
Lisa

From: Turner, Betty
Sent: Wednesday, December 26, 2012 10:56 AM
To: Gaines, Robert; Wu, Ruby (Chi-Ann); Kwok, Lisa
Cc: Nguyen, Sarah
Subject: RE: ANDA 91624 APPROVAL - EXPEDITED REVIEW

Good morning Bob,

I have checked Drugs@FDA, USP, MedWatch, OB and DARRTS for updates. No changes were found. The labeling is current.

Thanks,

Betty

From: Gaines, Robert
Sent: Wednesday, December 26, 2012 10:29 AM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Cc: Nguyen, Sarah
Subject: ANDA 91624 APPROVAL - EXPEDITED REVIEW

Good morning Betty and Ruby.

This one is ready for approval. Please provide labeling endorsement. Sarah is covering for me this week so I've cc'd her on the email.

Thank you.

Bob

<< File: 91624 label rev.pdf >> << File: 91624.apltr.DOC >>

Robert Gaines, PharmD

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 12/27/12**
OGD Regulatory Counsel **Initials SL**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes saved to the v drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 12/28/12**
Chemistry Div. **III (Sayeed)** **Initials VAS**
Comments:cmc satisfactory.

CMC recommendation for approval remains unchanged (e-mail from PM). RLWest 4/5/13.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 4/5/13**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

OGD Office Management Evaluation

6. Peter Rickman **Date 4/5/13**
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 to the 10 mg, 20 mg and 40 mg strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable OSI inspection histories. Office-level bio endorsed 4/19/11, 7/25/11, 11/30/11 and 5/22/12.

Final-prinnted labeling (FPL) found acceptable for approval 11/30/12, as endorsed 3/27/13. No REMS is required.

CMC found acceptable for approval (Chemistry Review #6) 12/28/12.

AND/OR

7. Robert L. West **Date 4/5/13**
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 3/27/13 (Verified 4/5/13). No "OAI" Alerts noted.

The applicant, Kudco Ireland Ltd., provided paragraph IV certifications to the '104, '156 and '971 patents, and was only sued within the 45-day period on the '156 patent. The litigation involving the '156 patent was subsequently dismissed. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Kathleen Uhl, M.D., Acting director, Office of Generic Drugs 4/5/13.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 4/5/13
Initials SN for BG

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/

SARAH K NGUYEN
04/05/2013

From: Turner, Betty
Sent: Tuesday, December 04, 2012 9:37 AM
To: 'Kurt.Zimmer@ucb.com'
Subject: ANDA 091624 Atorvastatin Calcium Tablets

Attachments: emfinfo.txt
Good morning Mr. Zimmer,

The following are requested revisions from the review of your amendment dated November 21, 2012 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg. The revisions are "POST-APPROVAL" revisions and may be submitted in the next annual report.

1. CONTAINER: 10 mg and 20 mg, (1000's)
As agreed upon in the email correspondence from Mr. Kurt Zimmer to Betty Turner, dated 11/30/12, please make the following revisions:

- (b) (4)
- Revise the "Distributed by" statement to read:
  Distributed by:
  Kremers Urban
  Pharmaceuticals Inc.
  Princeton, NJ 08540, USA

In addition, please make the following revisions.

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

2. INSERT

FULL PRESCRIBING INFORMATION

A. 2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors-
   - Revise the fourth sentence to read "In patients taking the HIV protease inhibitor nelfinavir…"

B. 7.1 Strong Inhibitors of CYP 3A4
   Combination of Protease Inhibitors
   - Revise the first sentence to read "Atorvastatin AUC was significantly…..protease inhibitors, as well as with the hepatitis C protease …"
   - Revise the second sentence to read "Therefore, in patients taking the "HIV protease inhibitor tipranavir plus…"

Submit your revised labeling in the next annual report with all changes described in full.

Regards,
Betty

Betty Turner, Pharm.D.
Labeling Reviewer
Office of Generic Drugs

Food and Drug Administration
7520 Standish Place
Rockville, MD 20855
tel: 240-276-8728
betty.turner@fda.hhs.gov

From: Kurt.Zimmer@ucb.com [mailto:Kurt.Zimmer@ucb.com]
Sent: Friday, November 30, 2012 2:32 PM
To: Turner, Betty
Subject: RE: ANDA 091624

Hi Betty,

Yes, the labels submitted in the amendment dated 3/4/10 are the true color, size, and clarity. Please let me know if you need anything else. Have a wonderful weekend!

Best regards,
Kurt

From: Turner, Betty [mailto:Betty.Turner@fda.hhs.gov]
Sent: Friday, November 30, 2012 2:20 PM
To: Zimmer Kurt
Subject: RE: ANDA 091624

Good afternoon Mr. Zimmer,

Thanks for your quick response! The labels for the 1000s count were submitted in the amendment dated 3/4/10. Can you confirm that the labels are true to color, size and clarity?

Thanks,

Betty

From: Kurt.Zimmer@ucb.com [mailto:Kurt.Zimmer@ucb.com]
Sent: Friday, November 30, 2012 1:50 PM
To: Turner, Betty
Subject: ANDA 091624

Good afternoon Ms. Turner,

I received your message. You are correct that in Sequence 0011, a statement that the 1000-count bottles were not going to be marketed at the time of launch was included in 1.14.2. Very recently, based on information obtained from our marketing and sales group, the decision was made by the applicant to launch with the 1000-count bottles for the 10 mg and 20 mg strengths. Draft labeling was submitted for these two configurations and the only differences between the current Final Container Label and the Draft Container Label is the name change from Kremers Urban, LLC to Kremers Urban Pharmaceuticals Inc. and the removal of the (b) (4) Is

it acceptable to submit the 10 mg and 20 mg 1000-count Final Container Labels along with the SPL within 14 days post-approval? If you would like to discuss over the phone, feel free to call me at 812.523.5539.

Best regards,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.
1101 C Ave West
Seymour, IN 47274
Tel: 812.523.5539
Fax: 812.523.6889
Email: kurt.zimmer@ucb.com

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
12/04/2012

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 091624 APPLICANT: Kudco Ireland Limited
DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg DATE OF SUBMISSION:7/15/09

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☐	RG 11/30/12
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
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☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☒ Deny☐	RLW/RG for 11/30/12

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: Team 34
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE 11/30/12
Paste Email Copy Below:

From: West, Robert L
Sent: Friday, November 30, 2012 2:36 PM
To: Gaines, Robert
Subject: RE: ANDA 091624 - Atorvastatin Tablets - Kremers --ANDA 91-226s/001 Mylan
Yes.

Bob

From: Gaines, Robert
Sent: Friday, November 30, 2012 2:35 PM
To: West, Robert L; Greenberg, Harvey A; Sears, Leigh Ann
Cc: Rickman, William P
Subject: RE: ANDA 091624 - Atorvastatin Tablets - Kremers --ANDA 91-226s/001 Mylan
Last question: Do we categorize it as drug shortage expedite? I'm asking because the points difference is significant.

Thanks

Bob

From: West, Robert L
Sent: Friday, November 30, 2012 2:34 PM
To: Greenberg, Harvey A; Gaines, Robert; Sears, Leigh Ann
Cc: Rickman, William P
Subject: RE: ANDA 091624 - Atorvastatin Tablets - Kremers --ANDA 91-226s/001 Mylan
Absolutely. Bob - Please do the paperwork for both and forward to me early next week. Repeat for any other Atorvastatin ANDAs or supplements discovered by Harvey.

Bob

From: Greenberg, Harvey A
Sent: Friday, November 30, 2012 2:30 PM
To: West, Robert L; Gaines, Robert; Sears, Leigh Ann
Cc: Rickman, William P
Subject: RE: ANDA 091624 - Atorvastatin Tablets - Kremers --ANDA 91-226s/001 Mylan
Hello everyone,
Couple things, this is going to be a very big recall and does have the potential of a large shortage which we really do not want or need at this time. In addition, again Ranbaxy gives generics a bad name. I believe we need to expedite the pending ANDA 91-624 by Kremer Urban to prevent the potential shortage. Plus I have another firm requesting an expedite of their supplemental application 91-226/s-001 by Mylan to provide a bigger supply. Plus I believe we will have more companies requesting help. So at this time--Bob West do you concur that we expedite the current ANDA 91-624 and ANDA 91-226/S-001--Thanks Harvey

From: West, Robert L
Sent: Friday, November 30, 2012 12:20 PM

To: Gaines, Robert; Sears, Leigh Ann
Cc: Greenberg, Harvey A; Rickman, William P
Subject: FW: ANDA 091624 - Atorvastatin Tablets - Kremers -
Bob:

I'm forwarding this message to you for follow up. I'll be out of the office next week. I've also included Harvey on this message for potential drug shortage input.

Thanks,

Bob

From: Kurt.Zimmer@ucb.com [mailto:Kurt.Zimmer@ucb.com]
Sent: Friday, November 30, 2012 8:51 AM
To: West, Robert L
Subject: ANDA 091624
Good morning Bob,

I have left a couple messages for Bob Gaines but have not heard back to date and I believe he works from home on Fridays. I realize it has only been a few days since the initial message, but as you can imagine, this is extremely high on the Kremers Urban priority list. The content of the messages were to inquire about an approximate review/approval timeline and confirmation of expedited review for ANDA 091624, Atorvastatin Calcium Tablets.

A brief background, Kremers Urban (KU) submitted electronically November 21 the responses to the Complete Response letter. KU was notified the DMF holder, (b) (4) (b) (4), responded November 27 to a deficiency they had received.

As a result of the recent Ranbaxy recall, Kremers Urban believes a shortage of product will occur as early as end of business today, as Ranbaxy has approximately (b) (4) of the market share. If there is any additional information and/or review timeline you can provide, it would be greatly appreciated. If you have any questions, my contact information is below. Thank you for your time.

Best regards,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.
1101 C Ave West
Seymour, IN 47274
Tel: 812.523.5539
Fax: 812.523.6889
Email: kurt.zimmer@ucb.com

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/s/

ROBERT T GAINES
12/03/2012

KREMERS URBAN PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Gregory Geba, Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

November 21, 2012

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg

0015: RESUBMISSION / AFTER ACTION – MINOR AMENDMENT
COMPLETE RESPONSE AMENDMENT

Dear Dr. Geba:

Reference is made to ANDA 091624, which was submitted through the ESG on July 16, 2009. Reference is also made to *Complete Response* dated November 9, 2012. A copy of the letter is included for reference (complete-response-letter). On behalf of Kudco Ireland Limited, Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this full and complete response to the Complete Response (response-to-complete-response-0015). Please note this application has been granted priority review following a February 1, 2012 telephone call with Martin Shimer as a settlement agreement has been reached and was submitted to the application in Amendment 0009.

The following review disciplines have been addressed in this response:

- **Chemistry** – Responses to deficiencies, including updated sections where appropriate.
- **Labeling** – Acknowledgment and updated labeling based on recent RLD changes.
- **Bioequivalence** – Acknowledgment of dissolution testing as recommended by FDA.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 30 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 20.2.0.19 (Virus Definition Date: 11/21/2012).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Gregory Geba, Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

September 7, 2012

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg

0014: Quality Minor Amendment – Response to Information Request

Dear Dr. Geba:

Reference is made to ANDA 091624, which was submitted through the ESG on July 16, 2009. Reference is also made to *Quality Deficiency – Minor* dated June 8, 2012. A copy of the deficiency is included for reference (quality-deficiency-minor-06-08-2012). On behalf of Kudco Ireland Limited, Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this full and complete response to the Quality Deficiency (minor-deficiency-response-0014). Please note this application has been granted priority review following a February 1, 2012 telephone call with Martin Shimer as a settlement agreement has been reached and was submitted to the application in Amendment 0009.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 38 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 19.8.14.0 (Virus Definition Date: 9/7/2012).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA See Attached

Date: 8/20/2012

Attention:
Department of Regulatory Affairs
KUDCO IRELAND C/O KREMERS URBAN LLC
1101 C AVE WEST
SEYMOUR, IN 47274

RE: Request to Withdraw Applications from the Generic Drug Backlog to Avoid Incurring Backlog Fee

Dear Sir or Madam:

This letter is in reference to your Abbreviated New Drug Applications (ANDAs), included in the attached list, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), enacted on July 9, 2012, establish a one-time backlog fee for any ANDA that is pending at the US Food and Drug Administration (FDA) on October 1, 2012 and has not received a tentative approval.

FDA is issuing this letter to encourage applicants who have pending ANDAs for which the applicants no longer wish to seek approval to notify FDA of the request to withdraw those ANDAs (see Federal Register Notice Docket Number FDA-2012-N-0879). **Requests for withdrawal should be submitted in writing individually for each ANDA as a "Request for Withdrawal" to the affected ANDA**. A decision to withdraw the ANDA is without prejudice to refiling.

Any ANDA that is not withdrawn by September 28, 2012 will incur the obligation to pay the backlog fee. Payment of backlog fees will be due no later than 30 calendar days after publication in the Federal Register of a notice (to be issued by October 31, 2012) announcing the amount of the backlog fee. Applicants with original ANDAs that fail to pay the backlog fee by the due date will be placed on a publicly available arrears list, and FDA will not receive new ANDAs or supplements submitted by those applicants, or any affiliates of those applicants, until the outstanding fee is paid.

To avoid incurring the backlog fee for an application, you, the applicant, must submit a request to withdraw the application and that request must be received by the FDA on or before **September 28, 2012**. However, to expedite this process, you are encouraged to submit the request by **September 15, 2012**.

You should submit the request to withdraw your applications by standard application submission methods. If an application was submitted via the FDA electronic gateway, a request for withdrawal should be submitted to the application via the gateway. Alternatively, you should send written notification to the ANDA archival file at the following address: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Document Control Room, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

In addition, please provide electronic confirmation of all ANDAs you wish to withdraw by sending an email to OGDGDUFA@fda.hhs.gov within the timeframe specified above**.**

For your convenience, a list of pending ANDAs for which we have identified you as the applicant is attached. **However, this list may be incomplete. Therefore, it is important to note that the absence of an ANDA from this list does not exempt that ANDA from incurring a backlog fee. Please verify the list for completeness of all ANDAs you have submitted. Discrepancies should be reported to the email address noted above.**

The GDUFA statute exempts only generic Positron Emission Tomography (PET) products from the user fees. There are no additional exemptions or waivers for GDUFA fees beyond those in the statute.

If you have questions regarding this communication, contact Thomas Hinchliffe at OGDGDUFA@fda.hhs.gov.

Please direct general GDUFA questions to ASKGDUFA@fda.hhs.gov.

Sincerely,

{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

CC: Attached List of ANDAs

PENDING ANDAs
(List produced as of 8/20/2012)

ANDA #	Drug Name
91624	ATORVASTATIN CALCIUM
91695	METHYLPHENIDATE HYDROCHLORIDE

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/s/

WILLIAM P RICKMAN
08/21/2012

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll-Free)
(812) 523-1887 (Fax)

Office of Generic Drugs and Kremers Urban T-CON
June 18, 2012

Subject: ANDA 091624, Atorvastatin Calcium Tablets
Quality Deficiency letter dated June 8, 2012

Attendees:

Office of Generic Drugs (OGD)
- Dr. Vilayat Sayeed, Director Division of Chemistry III
- Dr. Dave Gill, Deputy Director Division of Chemistry III
- Laxma Nagavelli, Team Leader Division of Chemistry III
- Haitao Li, Reviewer Division of Chemistry III

Kremers Urban Pharmaceuticals Inc. (KU)
- Jeff Siefert, Vice-President Manufacturing
- Xiu Xiu Cheng, Vice-President Research and Development
- Holly Kleman, Director Quality Control/Laboratory
- Mary Freeman, Manager Quality Control/Laboratory
- Brian Reckers, Supervisor Quality Control/Laboratory
- Elaine Siefert, Director Regulatory Affairs
- Kurt Zimmer, Manager Regulatory Affairs

KU initiated the conversation by thanking OGD for participating in the T-CON. The following points were discussed:

Deficiency Point 1:

(b) (4)

(b) (4)

Deficiency Point 2:

(b) (4)

(b) (4)

Deficiency Point 3:

(b) (4)

OGD does not require compliance with pending USP monographs, but it is in the best interest of the applicant to try these methods and correspond with USP regarding any issues.

The drug substance DMF review may require further clarification from (b) (4) regarding the purity of their (b) (4) but it is most likely not a request that will hold up the approval.

Dr. Sayeed stated to contact Laxma Nagavelli if KU had additional questions. KU thanked the team from OGD for taking the time to discuss and assist with understanding what is requested of KU.

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

/s/

HAITAO LI
06/26/2012

LAXMA R NAGAVELLI
06/26/2012

QUALITY DEFICIENCY - MINOR

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: KUDCO Ireland Limited

TEL: 812-523-5539

ATTN: Elaine Siefert

FAX: 812-523-6889

FROM: Leigh Ann Sears

FDA CONTACT PHONE: (240) 276-8453

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 15, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated June 4, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091624 APPLICANT: KUDCO Ireland Limited

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

A. The deficiencies presented below represent Minor deficiencies:

4. Please submit a complete response with all the requested information. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been adequately addressed.

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
06/08/2012

LAXMA R NAGAVELLI
06/08/2012
signed for Vilayat A Sayeed, PhD

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

June 4, 2012

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg

0013: Quality Minor Amendment – Response to Information Request

Dear Dr. Webber:

Reference is made to ANDA 091624, which was submitted through the ESG on July 16, 2009. Reference is also made to *Quality Deficiency – Minor* dated May 31, 2012. A copy of the deficiency is included for reference (quality-deficiency-minor-05-31-2012). On behalf of Kudco Ireland Limited, Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this full and complete response to the Quality Deficiency (minor-deficiency-response). Please note this application has been granted priority review following a February 1, 2012 telephone call with Martin Shimer as a settlement agreement has been reached and was submitted to the application in Amendment 0009.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 6 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 19.7.1.5 (Virus Definition Date: 6/4/2012).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

QUALITY DEFICIENCY - MINOR

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Kremers Urban LLC
AGENT FOR: KUDCO Ireland Limited

TEL: (812) 523-5539

FAX: (812) 523-6889

ATTN: Kurt Zimmer

FDA CONTACT PHONE: (240) 276-8453

FROM: Leigh Ann Sears

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 15, 2009, 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.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091624 APPLICANT: KUDCO Ireland Limited

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

A. The deficiencies presented below represent Minor deficiencies:

4. Please provide all available long term stability data.

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

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/s/

LEIGH A SEARS
05/31/2012

LAXMA R NAGAVELLI
05/31/2012
Signed for Vilayat A Sayeed, PhD

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 091624 APPLICANT: Kudco Ireland Ltd.
DRUG: Atorvastatin DATE OF SUBMISSION:7/15/09

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☐	RG 5/23/12
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
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☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☒ Deny☐	RLW 5/23/12

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: Team 34
a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS DATE 5/23/12
Paste Email Copy Below:

From: West, Robert L
Sent: Wednesday, May 23, 2012 1:21 PM
To: Gaines, Robert; Li, Haitao
Cc: Nagavelli, Laxma; Sears, Leigh Ann
Subject: RE: UPDATE: ATORVASTATIN - KUDCO 91-624
Importance: High

With this e-mail, please consider Kudco's ANDA 91-624 to have "expedited review" status. Under the current circumstances, we should try to get it approved next Tuesday if possible.

Bob or Leigh Ann will forward the formal request to me in DARRTS and I will sign it. For now, consider this e-mail the authorization.

Thank you,

Bob

From: Gaines, Robert
Sent: Wednesday, May 23, 2012 11:53 AM
To: West, Robert L
Subject: FW: UPDATE: ATORVASTATIN
Importance: High

Hi Bob.

Is there any chance we can make this expedited? Please see below email.

Thanks

Bob G

From: Li, Haitao
Sent: Tuesday, May 22, 2012 2:00 PM
To: Gaines, Robert; Nagavelli, Laxma
Cc: Sears, Leigh Ann
Subject: RE: UPDATE: ATORVASTATIN

If this DP is not expedited, there is no way I can do it, because I have other DP that have higher score.

If it is expedited, it's another story.

From: Gaines, Robert
Sent: Tuesday, May 22, 2012 1:57 PM
To: Nagavelli, Laxma; Li, Haitao
Cc: Sears, Leigh Ann
Subject: UPDATE: ATORVASTATIN
Importance: High

Haitao and Laxma,

I hate to do this but the OSI inspection for Bio just came back and the bio just became adequate for this application today. I think I previously was not expecting this one to be on pace for approval. But if at all possible, could

this one be looked at? I really apologize for this last minute but DBE was not in touch with me at all about this.

Thanks

Bob

From: Nagavelli, Laxma
Sent: Wednesday, May 16, 2012 7:41 AM
To: Li, Haitao; Gaines, Robert
Subject: RE: ATORVASTATIN

Haitao,

If ANDA 91624 looks like an approval product, then please do review it to get it done by 5/29/2012.

For ANDA 78773, please include the AM info in the addendum. There is no need to create a cycle.

Thanks,
Laxma

From: Li, Haitao
Sent: Tuesday, May 15, 2012 8:42 AM
To: Gaines, Robert
Cc: Nagavelli, Laxma
Subject: RE: ATORVASTATIN

Bob,

What's the status of 91624? If this application is not going to be expedited, I can not work on it because of its low score in my queue.

ANDA 78773 has an AM that need to be reviewed, it should be OK. This ANDA has been TA-ed, when I review this new AM, should I open a new cycle, or just create an addendum?

ANDA 91226 has been TA-ed and I did not see any AM. So I guess it will be Ok.

Hope this helps.

Haitao

From: Gaines, Robert
Sent: Tuesday, May 15, 2012 8:36 AM
To: Sears, Leigh Ann; Nagavelli, Laxma; Patankar, Suhas; Samy, Raghu; Vera, Matthew; Li, Haitao
Cc: Sayeed, Vilayat A
Subject: ATORVASTATIN
Importance: High

Good morning review team.

Please provide updates on the review status of all Atorvastin CMC and DMF reviews. Also please indicate whether they appear to be adequate or will be deficient. I am creating approval packets and approval letters for all

applications. The approval date for this product is 5/29/12 and it would be desirable to have the CMC wrapped up as soon as possible. You can reply directly to me with any updates you may have regarding any of the projects. I've attached a spreadsheet with the ANDA numbers and their current review status. Those highlighted in green are the ones that are most likely to make the deadline.

Thank you.

Bob

<< File: Atorvastatin.xls >>

Robert Gaines, PharmD
LCDR, United States Public Health Service
Product Quality Regulatory Project Manager
Office of Generic Drugs
Food and Drug Administration
7500 Standish Place Room E145
Rockville, MD 20855
Phone: 240-276-8495
Fax: 240-276-8474

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/s/

ROBERT T GAINES
05/23/2012

ROBERT L WEST
05/23/2012
Deputy Director, Office of Generic Drugs

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
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(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

May 9, 2012

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg

0012: Quality Minor Amendment – Response to Information Request

Dear Dr. Webber:

Reference is made to ANDA 091624, which was submitted through the ESG on July 16, 2009. Reference is also made to *Quality Deficiency – Minor* dated April 24, 2012. A copy of the deficiency is included for reference (quality-deficiency-minor-04-24-2012.pdf). On behalf of Kudco Ireland Limited, Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this amendment in response to the Quality Deficiency. Please note this application has been granted priority review following a February 1, 2012 telephone call with Martin Shimer as a settlement agreement has been reached and was submitted to the application in Amendment 0009.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 3.0 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 19.7.0.9 (Virus Definition Date: 5/9/2012).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

April 24, 2012

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg

0011: Response to Labeling Comments

Dear Dr. Webber:

Reference is made to ANDA 091624, which was submitted through the ESG on July 16, 2009. Reference is also made to *Labeling Comments* dated April 16, 2012. A copy of the labeling comments is included for reference (labeling-comments-04-2012.pdf). On behalf of Kudco Ireland Limited, Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this amendment in response to the Labeling Comments. Please note this application has been granted priority review following a February 1, 2012 telephone call with Martin Shimer as a settlement agreement has been reached and was submitted to the application in Amendment 0009.

The applicant commits to submitting labeling in SPL format within 14 business days of approval of the application.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 9 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 19.6.2.10 (Virus Definition Date: 4/24/2012).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

QUALITY DEFICIENCY - MINOR

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: KUDCO Ireland Limited
U.S. Agent: Kremers Urban LLC

ATTN: Kurt Zimmer

FROM: Leigh Ann Sears

TEL: (812) 523-5539

FAX: (812) 523-6889

FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 15, 2009, 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 January 12, and August 18, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091624 APPLICANT: KUDCO Ireland Limited

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.

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
04/24/2012

LAXMA R NAGAVELLI
04/24/2012
Signed for Vilayat A Sayeed, PhD

Please send an email to the labeling reviewer (betty.turner@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8728)

TO: Kudco Ireland Limited

TEL: (812) 523-5539

ATTN: Kurt Zimmer

FAX: (812) 523-6889

FROM: Betty Turner

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg.

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

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

ANDA Number: 091624 Date of Submission: March 26, 2012

Applicant's Name: KUDCO Ireland Limited

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

---

Labeling Deficiencies:

A. CONTAINER:

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

B. INSERT:

1. HIGHLIGHTS, WARNINGS AND PRECAUTIONS: second paragraph, revise the second sentence to read "Check liver enzyme tests before initiating therapy……"

2. FULL PRESCRIBING INFORMATION: CONTENTS*:

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

      2.1 Hyperlipidemia
      2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

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

   iii. Revise subtitles 14.1, 14.2 and 14.3 to read as follows:

      14.1 Prevention of Cardiovascular Disease
      14.2 Hyperlipidemia and Mixed Dyslipidemia
      14.3 Hypertriglyceridemia

3. FULL PRESCRIBING INFORMATION:

   i. GENERAL COMMENT- Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.

   ii. 4 CONTRAINDICATIONS
      a. Revise 4.1 to read as follows.

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

      b. Revise 4.2 to read as follows.

         4.2 Hypersensitivity to any component of this medication

   iii. 16 HOW SUPPLIED
      Add "Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin."

Submit revised insert labeling electronically.

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

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

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

CHI-ANN Y WU
04/16/2012
For Wm. Peter Rickman

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

March 26, 2012

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg

0010: Gratuitous Amendment - Labeling Update to Match RLD Changes

Dear Dr. Webber:

Reference is made to ANDA 091624, which was submitted through the ESG on July 16, 2009. On behalf of Kudco Ireland Limited, Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this amendment to match recent updates to the RLD labeling as discussed in a March 5, 2012 telephone call with Leigh Ann Sears, Project Manager, OGD. Please note this application has been granted priority review following a February 1, 2012 telephone call with Martin Shimer II as a settlement agreement has been reached and was submitted to the application in Amendment 0009.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 11 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 19.6.2.10 (Virus Definition Date: 3/26/2012).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 "C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

November 22, 2011

RE: ANDA 091624
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

0009: PATENT AMENDMENT

Dear Dr. Webber:

Reference is made to the ANDA 091624, which was submitted through the ESG on July 16, 2009. On behalf of Kudco Ireland Limited (Kudco), Kremers Urban Pharmaceuticals Inc. (KU), the U.S. Agent, submits this patent amendment to notify the Agency of a Settlement Agreement between the common parties of Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner-Lambert Company LLC, and the common parties of Kremers Urban LLC., Kudco Ireland LTD., and Kremers Urban Pharmaceuticals Inc. A copy of the agreement is supplied for reference. Additionally, a copy of the Order of Dismissal is included herein.

All of the information contained herein is privileged and confidential. Under no condition is the disclosure of any portion of the attached materials to any person or entity other than the Food and Drug Administration authorized without prior consent of the applicant.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 2 MB. The applicant certifies that this submission is virus free as tested by Norton's Internet Security version 19.2.0.10 (Virus Definition Date: 11/22/2011).

If there are any questions regarding this submission, please contact Kurt Zimmer, Regulatory Affairs Manager, KU, who may be contacted at 812-523-5539 (phone), 812-523-6889 (fax), or by email at kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Regulatory Affairs Manager
Kremers Urban Pharmaceuticals Inc.

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 " C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

October 31, 2011

ANDA 091624: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Amendment 0008: BIOEQUIVALENCE RESPONSE TO INFORMATION REQUEST

Dear Dr. Webber:

Reference is made to ANDA 091624 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg submitted July 16, 2009. Reference is also made to a facsimile entitled Bioequivalence Amendment, received from Nam Chun on July 28, 2011 (dated July 27, 2011) containing bioequivalency deficiencies identified during the review of Amendment 0006, dated June 27, 2011. Kremers Urban Pharmaceuticals Inc., on behalf of the applicant, herein provides full and complete responses to the Deficiency Letter.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 12 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus; the virus signature database and virus definition files are updated on a daily basis.

If there are any questions regarding this submission, please contact Kurt Zimmer, Manager, Regulatory Affairs, Kremers Urban Pharmaceuticals Inc., by phone (812.523.5539), fax (812.523.6889), or email (kurt.zimmer@ucb.com).

Sincerely,

Zimmer Kurt

Digitally signed by Zimmer Kurt
DN: cn=Zimmer Kurt, email=Kurt.Zimmer@ucb.com
Reason: I am the author of this document
Date: 2011.10.26 14:40:32 -04'00'

Kurt Zimmer
Manager, Regulatory Affairs

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 " C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

August 18, 2011

ANDA 091624: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Amendment 0007: QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST

Dear Dr. Webber:

Reference is made to ANDA 091624 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg submitted July 15, 2009. Reference is also made to a facsimile entitled Quality Deficiency – Minor, received from Leigh Ann Bradford on November 3, 2010 containing CMC Deficiencies identified during the review. Kremers Urban Pharmaceuticals Inc., on behalf of the applicant, herein provides full and complete responses to the Deficiency Letter.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 18 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus; the virus signature database and virus definition files are updated on a daily basis.

If there are any questions regarding this submission, please contact Kurt Zimmer, Manager, Regulatory Affairs, Kremers Urban Pharmaceuticals Inc., by phone (812.523.5539), fax (812.523.6889), or email (kurt.zimmer@ucb.com).

Sincerely,

Kurt Zimmer
Manager, Regulatory Affairs

BIOEQUIVALENCE AMENDMENT

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: KUDCO Ireland Limited

TEL: (812) 523-5544

ATTN: Elaine Siefert

FAX: (812) 523-6889

FROM: Nam J. Chun

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 15, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated June 27, 2011.

The Division of Bioequivalence 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.

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 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

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Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
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 identified the following deficiencies:

On 27 June 2011, you submitted an amendment to address the deficiencies communicated in the DBE letter dated 25 April 2011. Regarding the objectionable finding identified by the Division of Scientific Investigations (DSI) related to the analytical site's manual reintegration practice, you provided justification for the manual reintegration of the study samples in your bioequivalence studies. The DBE has reviewed your response and found that it is not adequate for the following reason:

You stated that *"To evaluate the impact between the initial integration and the modified integration, the difference in peak area and percent difference of the change were included in the tables. The percent change in peak area should be equivalent to the change in calculated concentration since the internal standard response did not change between the initial integration and the reintegration of the samples listed"*, and that *"In order to evaluate the impact of the samples for which manual reintegration was performed, analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t and Cmax PK parameters for atorvastatin, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin for both studies under fed (AA77268) and fasted conditions (AA77267) for exploratory purposes, to determine if setting the manually integrated samples to missing had an effect on the PK conclusions. Excluding the manually reintegrated samples did not significantly impact the results nor alter the conclusion of either study. Specifically, the bioequivalence criteria were still met for the assessed parameters in both the fed and fasted studies."*

However, you have not demonstrated that ***including*** the original results of these reintegrated samples (results prior to reintegration) in the statistical analysis of both

the fed and fasted studies did not change the study outcome. In addition, you did not provide all the original assay results (prior to reintegration) to the DBE for verification.

Therefore, we ask that you submit the following additional information/data:

- Electronic SAS Transport data files (.xpt) for **individual concentration and PK parameter data that are based on original integration results (i.e., obtained before reintegration)** for your fasting (AA77267) and fed (AA77268) studies. These bioequivalence data to be submitted in the two usual separate files as described below:

  a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf KE_FIRSTKE_LAST (where KE_FIRST and KE_LAST are the beginning and ending time points selected for calculation of the elimination constant KE, and expressed in the order of the time points, e.g., KE_FIRST=12 means the 12th time point.)

  b. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn T1 T2 T3 .... Tn Each field should be separated with a blank space, and missing values should be indicated with a period (.).

- The summary of your study results, based on the data of the original integration (**before** reintegration), in the following tabular format:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr-1)	
Study #	Fasting study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol.# p.#
Study #	Fed study Title	Randomized single-dose crossover	Test product strength Tab./Cap./Susp p.o. [Batch #] Ref. product strength Tab./Cap./Susp p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M (%CV) M (%CV)	Median (Range)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	M (%CV) M (%CV)	Vol. # p. #

Drug name Dose Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No.				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr *ng/ml)				
AUC_{∞} (hr *ng/ml)				
C_{max} (ng/ml)				

- You also stated in the current amendment that *"Initial chromatograms, for all manually modified chromatography for each study, were saved as word document files for each batch (AA77267 Manual Edited Chromatography and AA77268 Manual Edited Chromatography). Complete sets of chromatograms for all batches with at least one manual reintegration have been saved as pdf files (AA77267 Accepted Batch Chromatography and AA77268 Accepted Batch Chromatography). Refer to Global SOP GL-BIO-10610, "Chromatographic Peak Identification, Review, and Acceptance".* For verification, please submit all aforementioned initial chromatograms for each manually modified chromatography from both studies, together with legible raw numerical data associated with these chromatograms.

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 P CONNER
07/27/2011

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 " C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

June 27, 2011

ANDA 091624: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Amendment 0006: BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT / BIOEQUIVLENCE RESPONSE TO INFORMATION REQUEST

Dear Dr. Webber:

Reference is made to ANDA 091624 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg accepted for filing July 16, 2009. Reference is also made to a facsimile from Nam Chun entitled *Bioequivalence Amendment,* dated April 25, 2011 containing Bioequivalence Deficiencies identified during the review. Responses to the deficiency letter are herein provided.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 290 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus, the virus signature database and virus definition files are updated on a daily basis.

If there are any questions regarding this submission, please contact Kurt Zimmer, Manager, Regulatory Affairs, by phone (812) 523-5539, fax (812) 523-6889, or email kurt.zimmer@ucb.com.

Sincerely,

Jeff Engle
Manager, Regulatory Affairs
Kremers Urban Pharmaceuticals Inc.

BIOEQUIVALENCE AMENDMENT

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: KUDCO Ireland Limited TEL: (812) 523-5544

ATTN: Elaine Siefert FAX: (812) 523-6889

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 15, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated January 12, 2011.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement **Bioequivalence Response to Information Request**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

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Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

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Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
DRUG PRODUCT:	Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

The Division of Bioequivalence (DBE) has completed its review of the submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your dissolution testing data using your newly revised dissolution method is acceptable but your proposed specification (NLT (b) (4)% (Q) in 30 minutes) is not acceptable. Based on your dissolution testing data, the DBE recommends a more appropriate specification for your test product. Please acknowledge your acceptance of the following dissolution method and specification:

   The dissolution testing should be conducted in 900 mL of 0.3% Polysorbate 80 in 0.05 M Phosphate Buffer, pH 6.8 using USP apparatus II (Paddle) at 75 rpm. The test products should meet the following specification:

   Not less than (b) (4)% (Q) of the labeled amount of drug in the dosage form is dissolved in 30 minutes.

2. During February 2008, the Division of Scientific Investigation (DSI) inspected the analytical sites of (b) (4) for another application. This is the same site where the subject samples from the fasting (AA77267) and fed (AA77268) bioequivalence (BE) studies for your application were also analyzed. Following the inspection, a Form FDA-483 was issued for each site. Subsequently, the analytical sites provided its responses to Form 483 observations and these responses were included in the final evaluation by DSI, which recommended that the inspected studies be considered questionable based on the DSI's original findings and the sites' responses.

   For considering the impact of similar objectionable study conduct and site practices by the same analytical facility on the BE studies submitted in your application,

the DBE reviewed the above DSI inspection report and found that the following objectionable finding by the DSI at the analytical site could potentially compromise the integrity of the studies of ANDA 091624 as well:

- Analytical results, specifically chromatogram peak integrations, were modified. These modifications were made by manually picking the baseline or changing integrations parameters.

Please address the above specific finding by the DSI with respect to its impact on the BE studies of the current ANDA, providing any necessary supporting documents in your response, including but not limited to:

- Confirmation of the existence of any manual reintegration/manual baseline adjustment in any chromatograms of the BE studies, if any.
- If such manual modification of chromatograms was indeed carried out for certain chromatograms, please submit:
  - all chromatograms of the affected runs for comparison.
  - In addition, for chromatograms manually modified for reintegration, please also submit the same chromatograms prior to modification, for comparison, and
  - the peak height/area response counts before and after modification, together with the resulting calculated concentration values associated with the unmodified and modified chromatograms.
  - Standard Operating Procedure (SOP) for chromatography integration/reintegration.

3. According to your standard operating procedure (SOP) for repeat analysis (SOP# GL-BIO-10601-01), "if an analytical reason for reassay can be assigned to a sample, the original result is not reported." For future submissions, please revise your SOP to include the procedure of reporting the original results of all reassays, including the analytical related reassays, if applicable.

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 P CONNER
04/25/2011

KREMERS URBAN
PHARMACEUTICALS

Kremers Urban Pharmaceuticals Inc.
1101 " C" Avenue West
Seymour, Indiana 47274
(812) 523-3457 (Telephone)
(800) 457-9856 (Toll Free)
(812) 523-1887 (Fax)

Dr. Keith Webber, Acting Director
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

January 12, 2011

ANDA 091624: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

Amendment 0005: BIOEQUIVALENCE RESPONSE TO INFORMATION REQUEST

NAME CHANGE: US Agent, Manufacturing / Analytical Test Site / Packaging Site

Dear Dr. Webber:

Reference is made to ANDA 091624 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg accepted for filing July 16, 2009. Reference is also made to a facsimile from Nam Chun entitled *Bioequivalence Amendment,* dated August 16, 2010 containing Bioequivalence Deficiencies identified during the review. Responses to the deficiency letter are herein provided.

In addition, this letter serves as notice that, effective immediately, the name of the U.S. Agent has been changed to Kremers Urban Pharmaceuticals Inc. and the name of the manufacturing, analytical testing and packaging site has been changed from Schwarz Pharma Manufacturing, Inc. to Kremers Urban Pharmaceuticals Inc. The establishment number for the manufacturing, testing and packaging site, 1819171, has not changed. The 356h Attachment 1 which accompanies this submission has been updated with this new information. Please note that the site address remains the same, as well as the applicant's regulatory contact information, which is listed below.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 6 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus, the virus signature database and virus definition files are updated on a daily basis.

If there are any questions regarding this submission, please contact Kurt Zimmer, Manager, Regulatory Affairs, by phone (812) 523-5539, fax (812) 523-6889, or email kurt.zimmer@ucb.com.

Sincerely,

Kurt Zimmer
Manager, Regulatory Affairs
Kremers Urban Pharmaceuticals Inc.

QUALITY DEFICIENCY - MINOR

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: KUDCO Ireland Limited

TEL: (812) 523-5544

ATTN: Elaine Siefert

FAX: (812) 523-6889

FROM: Leigh Ann Bradford

FDA CONTACT PHONE: (240) 276-8453

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 15, 2009, 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.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **6** 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/

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091624 APPLICANT: KUDCO Ireland Limited

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. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

3. Please be advised that the use of in-house analytical methods does not relieve you from meeting the compendial

standards. In the event of a dispute, the official USP methods will prevail.

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/

LAXMA R NAGAVELLI
11/02/2010
Signed for Vilayat A. Sayeed, PhD

BIOEQUIVALENCE AMENDMENT

ANDA 091624

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: KUDCO Ireland Limited TEL: (812) 523-5544

ATTN: Elaine Siefert FAX: (812) 523-6889

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on July 15, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to your amendment dated February 26, 2010.

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 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.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	091624
APPLICANT:	KUDCO Ireland Limited
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 repeat analysis of fasting BE study (study # AA77267), there was a discrepancy in your summary tables (Table 9, Section 5.3.1.4.1 of the electronic submission) and the full analytical report (Section 5.3.1.4 of the electronic submission): The summary table reported a total of **25** reassays for non-analytical reasons; the full analytical report indicated a total of **34** reassays for non-analytical reasons. Please explain this discrepancy.

2. For repeat analysis of both fasting and fed studies (study # AA77267 and AA77268, respectively), you only submitted the original concentrations of the samples reanalyzed due to non-analytical reasons. Please provide complete tables containing the original concentrations and repeated concentrations for **all** reanalyzed study samples, where possible.

3. Please specify the salt form of the Ethylenediaminetetraacetic Acid, (EDTA), i.e., K_2EDTA, K_3EDTA or NaEDTA, used in your pre-study method validation, bioanalytical studies and clinical studies.

4. The dissolution data based on your proposed dissolution method [900 mL of 0.05 M Phosphate Buffer, pH 6.8 using USP Apparatus II (Paddle) at 75 rpm] indicated that this method was not sufficiently discriminative: For all strengths of your test product, more than (b)(4)% of the drug was released within 5 minutes. Please develop a new dissolution method or modify your current method for more gradual dissolution profiles by reducing the paddle speed and/or reducing the concentration of the surfactant in the medium, etc.

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-91624	ORIG-1	KUDCO IRELAND 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
08/16/2010

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

March 4, 2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 091624:
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg
LABELING AMENDMENT

Dear Sir/Madam:

Reference is made to ANDA 091624 submitted by KUDCO Ireland, Ltd. on July 16, 2009. Reference is also made to the labeling deficiency letter dated January 20, 2010. Further reference is made to a telephone conversation with Ann Vu, Division of Labeling and Program Support on February 1, 2010.

In the telephone conversation dated February 1, 2010, the Agency clarified that the side-by-side labeling comparisons requested in the deficiency letter should include the applicant's revised insert labeling with the reference listed drug, Lipitor® (NDA 20702/ S056 approved 6/17/2009) with all differences annotated and explained. In addition, the side-by-side label comparisons should include the applicant's revised container labels with the container labels submitted in the original ANDA.

In accordance with 21 CFR 314.96, Kremers-Urban on behalf of KUDCO Ireland, Ltd. hereby submits this labeling amendment in response to the deficiency letter dated January 20, 2010. The response to the labeling deficiency letter is provided in MS Word and PDF file formats.

In accordance with 21 CFR § 314.94(1), the applicant has submitted a completed and signed application form that contains the information described under 314.50(a)(1), (a)(3), (a)(4), and (a)(5).

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274

The labeling amendment also provides for the following:

- A copy of the prescribing information (PI) and patient information sheet labeling for the reference listed drug, Lipitor® (NDA 20702/S056 approved 6/17/2009).

- The revised insert labeling and patient information sheet in MS Word and structured product labeling (SPL) file format. Please note the content of labeling in SPL format is identical to the enclosed labeling text.

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 13.1 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus, version of virus signature database 4890, updated on 02/23/2010 or later.

If there are any questions regarding this submission, please contact Jasen Wallace, Manager, Regulatory Affairs by telephone at (812) 523-5413, by fax at (812) 523-6889, or by email at jasen.wallace@ucb.com.

Sincerely,

Jasen Wallace
Manager, Regulatory Affairs

KUDCO Ireland, Ltd.
Shannon, County Clare, Republic of Ireland
SCHWARZ PHARMA Manufacturing, Inc.
Seymour, IN 47274
Kremers Urban, LLC
301 Carnegie Center Suite 300
Princeton, NJ 08540

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

February 26, 2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 091624:
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg

BIOEQUIVALENCE AMENDMENT:
Bioequivalence Response to Information Request

Dear Sir/Madam:

Reference is made to ANDA 091624 submitted on July 16, 2009 by KUDCO Ireland, Ltd. Further reference is made to the bioequivalence deficiency letter dated January 12, 2010 and received January 15, 2010 by Kremers Urban.

In accordance with 21 CFR § 314.96, Kremers Urban on behalf of KUDCO Ireland, Ltd. hereby submits this bioequivalence amendment in response to information requested by the Division of Bioequivalence in the deficiency letter dated January 12, 2010. The responses to the bioequivalence deficiency letter are provided in MS Word and PDF file formats.

In accordance with 21 CFR § 314.94(1), the applicant has submitted a completed and signed application form that contains the information described under 314.50(a)(1), (a)(3), (a)(4), and (a)(5).

This submission is being sent in electronic format via the FDA Electronic Submissions Gateway. The size of this submission is approximately 2.29 MB. All files were checked and verified to be free of viruses using ESET NOD32 Antivirus, version of virus signature database 4890, updated on 02/23/2010 or later.

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274

If there are any questions regarding this submission, please contact Jasen Wallace, Manager, Regulatory Affairs by telephone at (812) 523-5413, by fax at (812) 523-6889, or by email at jasen.wallace@ucb.com.

Sincerely,

Jasen Wallace
Manager, Regulatory Affairs

KUDCO Ireland, Ltd.
Shannon, County Clare, Republic of Ireland
SCHWARZ PHARMA Manufacturing, Inc.
Seymour, IN 47274
Kremers Urban, LLC
301 Carnegie Center Suite 300
Princeton, NJ 08540

Telephone Fax

ANDA 91624

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: Kremers Urban LLC
U.S. Agent for Kudco Ireland Ltd.

TEL: 812-523-5544

FAX: 812-523-6889

ATTN: Elaine Siefert

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: 091624 Date of Submission: July 15, 2009

Applicant's Name: Kudco Ireland Ltd.

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

---

Labeling Deficiencies:

1. CONTAINER (10 mg and 20 mg= bottles of 90s, 1000s and 5000s
   40 mg and 80 mg= bottles of 90s, 500s and 2500s):

   a. Revise “DOSAGE AND USE” to “USUAL DOSAGE”.

   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

   Due to changes in the insert labeling for the reference listed drug, Lipitor (20702/S-056, approved 6/17/2009), please revise your labeling to be in accord with RLD. The RLD labeling may be accessed at the Drugs@FDA website.

3. PATIENT INFORMATION SHEET:

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

Submit labels and labeling electronically.

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

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

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND 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/

JOHN F GRACE
01/20/2010
for Wm Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 091624

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: KUDCO Ireland Limited TEL: (812) 523-5413

ATTN: Jansen Wallace FAX: 856-424-1461

FROM: Teresa Vu FDA CONTACT PHONE: (240) 276-8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalence data submitted on July 15, 2009, 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.

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 Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 091624

APPLICANT: KUDCO Ireland Ltd.

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

The Division of Bioequivalence (DBE) has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the fasting and fed studies along with the waiver requests will be conducted at a later date. The following deficiencies have been identified:

1. Your dissolution testing is incomplete. You stated in your submission that '*The dissolution was originally based on the method published by the Office of Generic Drugs (OGD). However, during execution of the validation protocol, it was determined that the dissolution media was not suitable for the tablet formulation due to the low dissolution rate. The media was changed to* (b) (4) *% Tween 80 in* (b) (4) *It should be noted that the RLD contains Polysorbate 80, which is also known as Tween 80, so the need for the addition of the surfactant to the OGD-recommended dissolution media is not immediately apparent.*' However, you did not conduct dissolution using the appropriate FDA-recommended dissolution method. Therefore, please conduct and submit comparative dissolution testing on all strengths of the test and reference products (12 dosage units each) using the following FDA-recommended method and sampling times:

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed of Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Sampling Times	5, 10, 15 and 30 minutes until (b) (4) % of the labeled amounts of atorvastatin is dissolved.

The dissolution method is currently available in the dissolution database in the FDA website: http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.

2. In addition, please provide dissolution testing data on 12 dosage units of the 10 mg, 20 mg, and 40 mg strengths of the

reference product, Pfizer Pharmaceutical's Lipitor® (Atorvastatin Calcium) Tablets using your proposed dissolution method.

When you submit the additional dissolution data requested above, the DBE will compare the data from the FDA-recommended method with those from your proposed method, and determine which dissolution method is more suitable for your test product.

For all dissolution testing data, please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, % coefficient of variation (%CV) at each time point for the 12 tablets tested and dates of dissolution testing. The dissolution testing data summary tables should be submitted in the DBE-recommended Electronic Common Technical Document (eCTD) format.

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-91624	ORIG-1	KUDCO IRELAND 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
01/12/2010

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

December 11, 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 091624:
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg

PATENT AMENDMENT:
Notice of Summons by Holder of Approved Application for
Lipitor® (atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg)

Dear Sir/Madam:

Reference is made to the above-cited ANDA submitted by KUDCO Ireland, Ltd. on July 16, 2009. Reference is made to the Agency's October 19, 2009 acknowledgement letter regarding the ANDA's acceptance for filing. Further reference is made to the Patent Amendment submitted November 3, 2009 certifying that the required notice of certification, in accordance with Section 505(j)(2)(B)(iv) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.95, was provided to:

Pfizer Ireland Pharmaceuticals as holder of approved New Drug Application No. 20-702 for Lipitor® (atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg) according to the records of the U.S. Food and Drug Administration ("FDA");

Pfizer Inc. as U.S. representative for Pfizer Ireland Pharmaceuticals according to the records of the FDA;

Ursula Campbell of Pfizer Inc. as representative of Pfizer Inc. according to the records of FDA;

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274

Warner-Lambert Company as owner of U.S. Patent Nos. 5,686,104, 5,969,156 and 6,126,971 according to the records of the U.S. Patent and Trademark Office;

Francis J. Tinney of Warner-Lambert Company and Pfizer Inc. as agents for Warner-Lambert Company. An attempt was made to serve notice for U.S. Patent Nos. 5,686,104; 5,969,156 and 6,126,971 to Francis J. Tinney of Warner-Lambert Company, 2800 Plymouth Road Ann Arbor, MI 48105. This address was listed with the United States Patent Office as the correspondence address for United States Patent No. 5,969,156. The package was undeliverable because the facility at 2800 Plymouth Road, Ann Arbor, MI has been closed. Therefore, an additional copy of the notice was provided to Pfizer Inc., U.S. representative for Pfizer Ireland Pharmaceuticals, according to the records of the FDA as the current owner of Warner-Lambert and its assets.

KUDCO Ireland, Ltd. hereby submits this Patent Amendment notifying the Agency that the organization was served a Summons by Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, and Warner-Lambert Company LLC in the United States District Court for the District of Delaware for patent infringement of U.S. Patent No. 5,969,156 and its Reexamination Certificate. Please refer to **Attachment 1** for a copy of the Summons.

The size of the submission is approximately 5 MB. All files were checked and verified to be free of viruses using Computer Associates eTrust Antivirus, program 8.1.660.0, signature version 35.1.7164.0, with a release date of 8 December 2009, or later.

If there are any questions regarding this submission, please contact Jasen Wallace, Manager, Regulatory Affairs by telephone at (812) 523-5413, by fax at (812) 523-6889, or by email at jasen.wallace@ucb.com.

Sincerely,

Jasen Wallace
Manager, Regulatory Affairs

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

November 3, 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 091624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg

PATENT AMENDMENT
Notice to Holder of U.S. Patents and Holder of Approved Application for Lipitor®(atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg)

Dear Sir/Madam:

Reference is made to the above-cited ANDA submitted by KUDCO Ireland, Ltd. on July 16, 2009. Reference is made to the Agency's October 19, 2009, acknowledgment letter regarding the ANDA's acceptance for filing. Further reference is made to the electronic correspondence received October 5, 2009 from Ms. Saundra T. Middleton granting permission to use Federal Express in lieu of the U.S. Postal service for the purpose of providing notice to the NDA holder; the U.S. agent for the NDA holder; and to the patent owner and/or assignees. Please refer to **Attachment 1** for more information.

In accordance with Section 505(j)(2)(B)(iv) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.95, this statement certifies that Notice of Certification ("notice") has been provided to:

> **Pfizer Ireland Pharmaceuticals** as holder of approved New Drug Application ("NDA") No. 20-702 for LIPITOR® (atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg) according to the records of the U.S. Food and Drug Administration ("FDA");

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

Pfizer Inc. as U.S. representative for Pfizer Ireland Pharmaceuticals according to the records of the FDA;

Ursula Campbell of Pfizer Inc. as representative of Pfizer Inc. according to the records of FDA;

Warner-Lambert Company as owner of U.S. Patent Nos. 5,686,104 ("the '104 patent"), 5,969,156 ("the '156 patent") and 6,126,971 ("the '971 patent") according to the records of the U.S. Patent and Trademark Office ("USPTO");

Francis J. Tinney of Warner-Lambert Company and **Pfizer Inc.** as agents for Warner-Lambert Company

The notice met the requirements under 21 CFR §314.95(c). Please refer to **Attachment 2** for the Federal Express proof-of-delivery signatures documenting receipt.

An attempt was made to serve notice for U.S. Patent Nos. 5,686,104; 5,969,156 and 6,126,971 to **Francis J. Tinney** of Warner-Lambert Company, 2800 Plymouth Road Ann Arbor, MI 48105. This address was listed with the United States Patent Office as the correspondence address for United States Patent No. 5,969,156. The package was undeliverable because the facility at 2800 Plymouth Road, Ann Arbor, MI has been closed. Therefore, an additional copy of the notice was provided to **Pfizer Inc.**, U.S. representative for Pfizer Ireland Pharmaceuticals, according to the records of the FDA as the current owner of Warner-Lambert and its assets. Please refer to **Attachment 3** for the Federal Express proof-of-delivery signature documenting receipt of the redirected notice.

In accordance with 21 CFR §314.52, the day following the date of receipt of notice by the patent owner or its representative and by the approved application holder is the first day of the 45-day period provided for in section 505(c)(3)(C) of the act.

This submission has been prepared in electronic format and is approximately 2.0 MB in size. All files were checked and verified to be free of viruses using Computer Associates eTrust Antivirus Agent; Program 8.1.660.0; Antivirus Engine Version 35.1.0.0; Signature Version 35.1.7088.0. The last signature update was 10/28/2009.

KREMERS URBAN

Kremers Urban Development Company
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

If there are any questions regarding this submission, please contact Jasen Wallace, Manager, Regulatory Affairs by telephone at (812) 523-5413, by fax at (812) 523-6889, or by email at jasen.wallace@ucb.com.

Sincerely,

Jasen Wallace
Manager, Regulatory Affairs

KUDCO Ireland, Ltd.
Shannon, County Clare, Republic of Ireland
SCHWARZ PHARMA Manufacturing, Inc.
Seymour, IN 47274
Kremers Urban, LLC
301 Carnegie Center Suite 300
Princeton, NJ 08540

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 #: 91-624 **FIRM NAME**: KUDCO IRELAND LIMITED

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM
DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Review Team: (Bolded/Italicized Lines indicate Assignment or DARRTS designation)

Quality Team: DC3 Team 12	***Bio Team 8: Bing Li***
ANDA/Quality RPM: Jeanne Skanchy	Bio PM: Nam J. Chun (Esther)
Quality Team Leader: Iser, Robert	☐ ***Clinical Endpoint Team Assignment: (No)***
Labeling Reviewer: Thuyanh (Ann) Vu	☐ ***Micro Review (No)***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: JULY 15, 2009 **Received Date**: JULY 16, 2009

Comments: **EC - 4 YES** **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: YES SENTT 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 Shannon Hill **Date October 8, 2009**	**Recommendation:** **M FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date: ____**

ADDITIONAL COMMENTS REGARDING THE ANDA:

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: JULY 15, 2009	☒
1.2.1	**Form FDA 3674** **(PDF)** YES	☒
*	**Table of Contents (paper submission only)** N/A	☒
1.3.2	**Field Copy Certification (original signature)** N/A **(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) YES	☒
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) – 4684893, 5273995, RE40667
   (PIV) – 5686104, 5969156, 6126971
2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☒
   PIV ☒ (Statement of Notification) ☒
3. Expiration of Patent(s): 1/8/2017
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES; will not market prior to exp of I-523 exclusivity

Patent and Exclusivity Search Results from query on Appl No 020702 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020702	001	4681893	Sep 24, 2009	Y	Y	U-161
020702	001	4681893*PED	Mar 24, 2010			U-161
020702	001	5273995	Dec 28, 2010	Y	Y	U-162
020702	001	5273995*PED	Jun 28, 2011			U-162
020702	001	5686104	Nov 11, 2014		Y	U-213
020702	001	5686104*PED	May 11, 2015			U-213
020702	001	5969156	Jul 8, 2016	Y		
020702	001	5969156*PED	Jan 8, 2017			
020702	001	6126971	Jan 19, 2013		Y	
020702	001	6126971*PED	Jul 19, 2013			
020702	001	RE40667	Dec 28, 2010	Y	Y	U-162
020702	001	RE40667*PED	Jun 28, 2011			

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 Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020702	001	I-471	Sep 21, 2008
020702	001	I-523	Mar 2, 2010

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 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; (b) (4) Type II DMF No. N/A b. Type III DMF authorization letter(s) for container closure YES; (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES (b) (4)	☒
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 SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒

1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 10 MG, 20 MG AND 40 MG	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **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.) **HOW SUPPLIED:** Atorvastatin Calcium Tablets are supplied as white, round, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin. **10 mg tablets:** debossed with "1" on one side and plain on the other. NDC 62175-890-46 bottles of 90 NDC 62175-890-43 bottles of 1000 NDC 62175-890-45 bottles of 5000 **20 mg tablets:** debossed with "2" on one side and plain on the other. NDC 62175-891-46 bottles of 90 NDC 62175-891-43 bottles of 1000 NDC 62175-891-45 bottles of 5000 **40 mg tablets:** debossed with "40" on one side and plain on the other. NDC 62175-892-46 bottles of 90 NDC 62175-892-41 bottles of 500 NDC 62175-892-44 bottles of 2500 **80 mg tablets:** debossed with "80" on one side and plain on the other. NDC 62175-897-46 bottles of 90 NDC 62175-897-41 bottles of 500 NDC 62175-897-44 bottles of 2500	☒
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: (b) (4) 4. CFN or FEI numbers N/A **3.2.S.2.1 Manufacturer**	☒
3.2.S.3	**Characterization** refer to DMF # (b) (4)	☒

Manufacturer	Responsibility
(b) (4)	
Schwarz Pharma Manufacturing, Inc. 1101 C Avenue West Seymour, IN 47274 USA Drug Establishment Registration Number: 1819171 Date of last FDA Inspection: January, 2008 Contact Person: Chad Kurdziel Email: chad.kurdziel@ucb.com Phone: 812.523.5396 Fax: 812.523.6889	• Analytical testing of drug substance • Final release of drug substance

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: DID NOT LOCATE a. Drug Substance b. Same lot number(s) **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** YES	☒
3.2.S.6	**Container Closure Systems** refer to DMF # (b) (4)	☒
3.2.S.7	**Stability** refer to DMF # (b) (4)	☒

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

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

Facility for the Manufacturing, Packaging, and Testing

Manufacturer	Responsibilities
Schwarz Pharma Manufacturing, Inc. (SPMI) 1101 C Avenue West Seymour, Indiana 47274 Drug Establishment Registration Number: 1819171 Date of last FDA Inspection: January, 2008 Contact person: Chad Kurdziel Director, Quality Assurance Email: chad.kurdziel@ucb.com Phone: 812.523.5396 Fax: 812.523.6889	• Control of materials • Raw material testing • Packaging component testing • Manufacturing of bulk product • Process controls • Packaging of bulk / finished product • Labeling of packaged product • Release testing of bulk product • Final release of finished product • Finished product stability testing

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)
3. If sterile product: Aseptic fill / Terminal sterilization N/A
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 N/A
2. Filter validation (if aseptic fill) N/A

PROPOSED COMMERCIAL BATCH SIZE:

10 mg: (b) (4)
20 mg: (b) (4)
40 mg: (b) (4)
80 mg: (b) (4)
ANDA BATCH SIZE: (b) (4)

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 YES	☒

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: DID NOT LOCATE 1. Finished Dosage Form 2. Same lot numbers **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 24 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 10 mg: P803503, 20 mg: P803603, 40 mg: P803703, 80 mg: P803401	☒

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)** N/A **3.2.R.2.S Comparability Protocols** N/A **3.2.R.3.S Methods Validation Package** YES 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

Table 23 – Lot Reconciliation (Final Dosage)

Strength	Input	Output[1]	Actual Yield	Lot Accountability	Reconciliation Limit[2]
	(b) (4)				
10 mg (Lot P80350)					
20 mg (Lot P80360)					
40 mg (Lot P80370)					
80 mg (Lot P80340)					
10 mg (Lot P80350)					
20 mg (Lot P80360)					
40 mg (Lot P80370)					
80 mg (Lot P80340)					
10 mg (Lot P80350)					
20 mg (Lot P80360)					
40 mg (Lot P80370)					
80 mg (Lot P80340)					
10 mg					
20 mg					
40 mg					
80 mg					
10 mg					
20 mg					
40 mg					
80 mg					
	(b) (4)				

Table 24 – Packaging Reconciliation

Strength	Bottle Count	Number of Bottles Packaged	Lot Number	Input (tablets)	Output[1] (tablets)	Actual Yield	Lot Accountability	Reconciliation Limit[2]
								(b) (4)
10 mg								
20 mg								
40 mg								
80 mg								
				(b) (4)				

3.2.R.1.P.2 Information on Components YES; see 3.2.P.4.1 & 3.2.P.7.1

3.2.R.2.P Comparability Protocols N/A

3.2.R.3.P Methods Validation Package NO

Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)

(Required for Non-USP drugs)

MODULE 5

CLINICAL STUDY REPORTS ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1 (complete study data)

Bioavailability/Bioequivalence ☒

1. Formulation data same?

a. Comparison of all Strengths (check proportionality of multiple strengths)

PROPORTIONAL

b. Parenterals, Ophthalmics, Otics and Topicals

per 21 CFR 314.94 (a)(9)(iii)-(v) N/A

2. Lot Numbers of Products used in BE Study(ies): ANDA: P803401 RLD: 08107V

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

Table 3 Statistical Summary of the Comparative Bioavailability Data

Atorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	129.431	134.182	96.5	92.2% - 100.9%
AUC∞	135.101	139.138	97.1	93.2% - 101.2%
Cmax	28.55709	32.66828	87.4	80.8% - 94.6%
Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	158.900	158.192	100.4	96.3% - 104.8%
AUC∞	163.145	162.584	100.3	96.3% - 104.6%
Cmax	37.24821	40.19861	92.7	82.8% - 103.7%

Ortho-hydroxyatorvastatin Dose (1 x 80 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (Study No. AA77267)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	144.582	151.099	95.7	90.6% - 101.1%
AUC∞	151.868	156.919	96.8	91.9% - 102.0%
Cmax	23.08675	25.63698	90.1	82.1% - 98.8%
Fed Bioequivalence Study (Study No. AA77268)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t	147.082	147.054	100.0	96.3% - 103.9%
AUC∞	153.242	152.363	100.6	96.8% - 104.4%
Cmax	21.27159	22.41062	94.9	87.3% - 103.3%

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) FASTING AND FED ON 80 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: YES	☐
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	☐

Table 5 - Summary of In Vitro Dissolution Studies

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	(b)% Tween 80 in(b l (proposed test product media)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b)% (Q) of the labeled amount is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Schwarz Pharma Manufacturing, Inc. 1101 C Avenue West – Seymour, IN 47274	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 5 min	10 min	15 min	30 min	Study Report Location
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	86	90	93	96	Table 5.2
					Range	(b) (4)				
					%CV	1.6	1.8	2.2	2.1	
Study Report[1]	6/12/09	Atorvastatin Calcium Tablets 20mg / P80360 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	89	93	95	99	Table 5.3
					Range	(b) (4)				
					%CV	2.3	1.7	2.0	1.8	
Study Report[1]	6/14/09	Atorvastatin Calcium Tablets 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	87	91	93	97	Table 5.4
					Range	(b) (4)				
					%CV	1.9	1.8	1.7	1.7	
Study Report[1]	6/14/09	Atorvastatin Calcium Tablets 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	89	93	95	99	Table 5.5
					Range	(b) (4)				
					%CV	1.4	1.0	1.4	1.5	
Study Report[1]	6/16/09	Lipitor Tablets, 80mg / 08107v (Expires: 04 / 2009)	80 mg Tablets	12	Mean	72	85	90	95	Table 5.5
					Range	(b) (4)				
					%CV	1.5	0.9	1.4	1.4	

[1]Report number is not applicable as individual results can be found in the Study Report Location noted above.

Table 5 - Summary of In Vitro Dissolution Studies (continued)

Dissolution Conditions	**Apparatus:**	USP Apparatus 2 (Paddles)
	Speed of Rotation:	75 rpm
	Medium:	(b) (4) (OGD recommended media)
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	NLT (b), (Q) of the labeled amount is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Schwarz Pharma Manufacturing, Inc. 1101 C Avenue West – Seymour, IN 47274	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 5 min	10 min	15 min	30 min	Study Report Location
Study Report[1]	5/13/09	Atorvastatin Calcium Tablets 10mg / P80350 (manufactured: 12 / 2008)	10 mg Tablets	12	Mean	70	73	75	77	Table 5.6
					Range	(b) (4)				
					%CV	1.7	1.7	1.9	1.8	
Study Report[1]	5/11/09	Atorvastatin Calcium Tablets 20mg / P80350 (manufactured: 12 / 2008)	20 mg Tablets	12	Mean	71	74	75	78	Table 5.7
					Range	(b) (4)				
					%CV	1.7	1.4	1.7	1.6	
Study Report[1]	6/27/09	Atorvastatin Calcium Tablets 40mg / P80370 (manufactured: 12 / 2008)	40 mg Tablets	12	Mean	69	72	74	75	Table 5.8
					Range	(b) (4)				
					%CV	3.0	2.2	2.1	1.7	
Study Report[1]	5/12/09	Atorvastatin Calcium Tablets 80mg / P80340 (manufactured: 12 / 2008)	80 mg Tablets	12	Mean	70	73	74	76	Table 5.9
					Range	(b) (4)				
					%CV	1.9	1.0	1.1	1.6	
Study Report[1]	5/12/09	Lipitor Tablets, 80mg / 08107v (Expires: 04 / 2009)	80 mg Tablets	12	Mean	35	39	42	46	Table 5.9
					Range	(b) (4)				
					%CV	3.9	1.7	2.3	2.8	

[1]Report number is not applicable as individual results can be found in the Study Report Location noted above.

Table 6 Formulation Data

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

Ingredient	Amount (%) / Tablet	Amount (mg) / Tablet			
		10 mg	20 mg	40 mg	80 mg
(b) (4) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)

For additional information concerning the composition of the (b) (4) [redacted], refer to 3.2.P.1.2.

JUSTIFICATION OF INACTIVE INGREDIENTS:

CROSCARMELLOSE SODIUM	(b) (4) [redacted]
METHACRYLIC ACID COPOLYMER	[redacted]
LACTOSE MONOHYDRATE	[redacted]
SODIUM STEARYL FUMARATE	[redacted]
SILICON DIOXIDE, COLLOIDAL	[redacted]

(b) (4) [redacted]

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

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/s/

SHANNON L HILL
10/14/2009

MARTIN H Shimer
10/19/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-624

Kremers Urban LLC
U.S. Agent for KUDCO Ireland Limited
Attention: Elaine Siefert
1101 C. Ave W
Seymour, IN 47274

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

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

DATE OF APPLICATION: July 15, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 16, 2009

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND LTD	ATORVASTATIN CALCIUM

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/s/

MARTIN H Shimer
10/19/2009
Signing for Wm Peter Rickman

Request for Permission to FedEx Notice of Para. IV CertificationsFrom: Middleton , Saundra T

Sent: Monday, October 05, 2009 2:54 PM

To: 'Beaver, Nathan A.'

Cc: Rosen, David L.

Subject: RE: Request for Permission to FedEx Notice of Para. IV Certifications 9 1-624

Dear Mr. Beaver,

It is permissible to use Federal Express in lieu of the US Postal service for th e purpose of providing notice to the NDA holder and any patent assignees associa ted with PIV certifications contained within ANDA 91-624.

Regards,

Saundra T. Middleton

From: Beaver, Nathan A. [mailto:NBeaver@foley.com]

Sent: Monday, October 05, 2009 2:30 PM

To: Middleton, Saundra T

Cc: Rosen, David L.

Subject: Request for Permission to FedEx Notice of Para. IV Certifications

Dear Ms. Middleton.

On behalf of Kremers-Urban, LLC we are seeking permission to send the Notice of Paragraph IV certifications via Federal Express to the NDA holder; the U.S. agen t for the NDA holder; and to the patent owner, with respect to ANDA # 91-624 for Kremers-Urban for atorvastatin calcium tablets 10 mg, 20 mg, 40 mg and 80 mg.

If you need any other information, or have any questions, please contact me.

Thank you.

Nathan

Nathan A. Beaver

Partner

Foley & Lardner LLP

3000 K St. NW, Ste 500

Washington, DC 20007

(p) 202-295-4039

(f) 202-672-5399

nbeaver@foley.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91624	ORIG-1	KUDCO IRELAND 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/

SAUNDRA T MIDDLETON
10/05/2009

KREMERS URBAN

Kremers Urban, LLC
1101 "C" Avenue West
Seymour, IN 47274
T: (812) 523-3457
F: (812) 523-1887

July 15, 2009

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation & Research, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Original Abbreviated New Drug Application 91-624
Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg, and 80 mg

Dear Mr. Buehler:

Pursuant to 21 CFR §314.94, KUDCO Ireland, Limited ("KUDCO") herein submits original Abbreviated New Drug Application 91-624 for a generic version of Pfizer's Lipitor® Tablets, NDA 20-702. The 10 mg, 20 mg, and 40 mg strength tablets were approved on December 17, 1996, and the 80 mg strength was approved on April 7, 2000.

The sponsor of this application is KUDCO Ireland, Limited. The US agent for KUDCO is Kremers Urban, LLC, an affiliated company. Schwarz Pharma Manufacturing, Inc. (SPMI), an affiliate of the applicant located in Seymour, IN, is the proposed manufacturing, packaging, and analytical release and stability test site for this product.

The patents listed in the Orange Book for the Reference Listed Drug (RLD) are located in 1.3.5.1. Paragraph III and Paragraph IV certifications are included in Module 1.

To assist in the review of this application, KUDCO has prepared a list of abbreviations that are used throughout the document. The list is placed immediately following this cover letter.

KUDCO Ireland, Ltd.
Shannon, County Clare, Republic of Ireland
SCHWARZ PHARMA Manufacturing, Inc.
Seymour, IN 47274
Kremers Urban, LLC
301 Carnegie Center Suite 301
Princeton, NJ 08540

This application is supported by two pivotal studies which demonstrate the bioequivalence of the proposed generic drug product to the RLD, consistent with the March 2003 guidance *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*:

- Study AA77267 – A Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fasting Conditions,

  and

- Study AA77268 – A Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Kremers Urban and Parke-Davis (Lipitor®) 80 mg Atorvastatin Tablets (as Atorvastatin Calcium) in Healthy Adult Volunteers under Fed Conditions.

It should be noted that Parke-Davis is the distributor, whereas Pfizer is the owner of the application.

This is an electronic submission organized using the *ANDA Checklist for CTD or eCTD Format for Completeness and Acceptability of an Application for Filing* updated May 28, 2008. This submission has been prepared in eCTD format and is approximately 850 MB in size. All files were checked and verified to be free of viruses using Computer Associates eTrust Antivirus, program 8.1.660.0, and signature version is 31.6.6602.0, with a release date of July 15, 2009 or later.

If there are any regulatory or technical questions regarding this submission, please contact Kurt Zimmer, Manager of Regulatory Affairs, at 812-523-5539 (phone), 812-523-6889 (fax), or email kurt.zimmer@ucb.com.

Sincerely,

Jeffery W. Siefert
Director, KUDCO Ireland, Ltd.

KUDCO Ireland, Ltd.
Shannon, County Clare, Republic of Ireland
SCHWARZ PHARMA Manufacturing, Inc.
Seymour, IN 47274
Kremers Urban, LLC
301 Carnegie Center Suite 301
Princeton, NJ 08540