CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 202357

Name: Atorvastatin Calcium Tablets, 80 mg (base)

Sponsor: Dr. Reddy's Laboratories Limited

Approval Date: July 17, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202357

Dr. Reddy's Laboratories Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
Attention: Kimberly Ernst
Director Regulatory Affairs
200 Somerset Corporate Blvd. 7th Floor
Bridgewater, NJ 08807

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 27, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 80 mg (base).

Reference is also made to your amendments dated February 21, March 18, and March 31, 2011; and May 17, June 25, 27, and 29, 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, 80 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lipitor Tablets 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 expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

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

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, 80 mg (base), under this ANDA. You notified the agency that Dr. Reddy's Laboratories Limited (DRL) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '156 patent was brought against DRL 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. Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories Inc., Civil Action No. 1:10-cv-01135-LPS]. You notified the agency that the case has been dismissed.

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(s) directly to:

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

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

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

Sincerely yours,

{See appended electronic signature page}

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/

ROBERT L WEST

07/17/2012

Deputy Director, Office of Generic Drugs
for Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

LABELING

Atorvastatin Calcium Tablets, 80 mg
Rx only
I 0312
55111-124-02

55111-124-02
Rx only
I 0312
Atorvastatin Calcium Tablets, 80 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Atorvastatin Calcium Tablets for oral administration

Initial U.S. Approval: 1996

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

Drug Interactions (7) 02/2012

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

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

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

Limitations of Use

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

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

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

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

80 mg tablets (3).

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

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

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

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

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

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories Inc., at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: [03/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Prevention of Cardiovascular Disease

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

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

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

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

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

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

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

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

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

2.3 Homozygous Familial Hypercholesterolemia

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

2.4 Concomitant Lipid-Lowering Therapy

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

2.5 Dosage in Patients with Renal Impairment

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

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

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

3 DOSAGE FORMS AND STRENGTHS

Atorvastatin calcium tablets of 80 mg are white to off-white, oval shaped, biconvex, film coated tablets debossed 'RDY'on one side and '124' on other side.

4 CONTRAINDICATIONS

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

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin calcium use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM 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 should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see **Use in Specific Populations (8.1)**].

4.4 Nursing mothers

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

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

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

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

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

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

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

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

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

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

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

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

5.2 Liver Dysfunction

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

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

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

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

5.3 Endocrine Function

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

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

5.4 CNS Toxicity

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

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

5.5 Use in Patients with Recent Stroke or TIA

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

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

Rhabdomyolysis and myopathy [see **Warnings and Precautions (5.1)**]

Liver enzyme abnormalities [see **Warnings and Precautions (5.2)**]

6.1 Clinical Trial Adverse Experiences

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

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

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

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

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

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

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

Other adverse reactions reported in placebo-controlled studies include:

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

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

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

Collaborative Atorvastatin Diabetes Study (CARDS)

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

Treating to New Targets Study (TNT)

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

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

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

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

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

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

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

6.2 Postmarketing Experience

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

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

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

6.3 Pediatric Patients (ages 10-17 years)

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

7 DRUG INTERACTIONS

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

7.1 Strong Inhibitors of CYP 3A4:

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

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

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

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

7.2 Grapefruit Juice:

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

7.3 Cyclosporine:

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

7.4 Gemfibrozil:

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

7.5 Other Fibrates:

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

7.6 Niacin:

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

7.7 Rifampin or other Inducers of Cytochrome P450 3A4:

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

7.8 Digoxin:

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

7.9 Oral Contraceptives:

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

7.10 Warfarin:

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

7.11 Colchicine:

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

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

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin calcium had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population**. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see **Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10-17 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 therapy [see **Contraindications, Pregnancy (4.3)** and **Use in Specific Populations, Pregnancy (8.1)**]. **Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

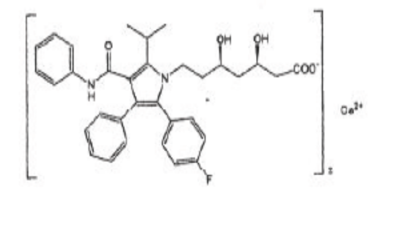
10 OVERDOSAGE

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

11 DESCRIPTION

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

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of atorvastatin calcium is $C_{66}H_{68}CaF_2N_4O_{10}$ and its molecular weight is 1155.36. Its structural formula is:



PHARMACIST - DETACH FROM HERE

PATIENT INFORMATION
Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium 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, ask your doctor or pharmacist.

What is Atorvastatin Calcium?

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

Atorvastatin calcium 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 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 starts 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?

Do not take atorvastatin calcium if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium and call your doctor right away.
- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium 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.

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

Before you start Atorvastatin Calcium

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. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium 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?

- Take atorvastatin calcium exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium. Your dose of atorvastatin calcium may be changed based on these blood test results.
- Take atorvastatin calcium each day at any time of day at about the same time each day. Atorvastatin calcium 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. Stay on this low-fat diet when you take atorvastatin calcium.
- If you miss a dose of atorvastatin calcium, take it as soon as you remember. Do not take atorvastatin calcium 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 at the same time.
- If you take too much atorvastatin calcium or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

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What should I avoid while taking Atorvastatin Calcium?

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

What are the possible side effects of Atorvastatin Calcium?

Atorvastatin calcium 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 is stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium 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.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium and if you have symptoms of liver problems while you take atorvastatin calcium. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

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

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium: 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: 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. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

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

General information about Atorvastatin Calcium

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium for a condition for which it was not prescribed. Do not give atorvastatin calcium 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. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

To reorder additional Patient Information Sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Issued: 0312 DR.REDDY'S

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Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in dimethyl sulphoxide, slightly soluble in alcohol, very slightly soluble in water, in pH 7.4 phosphate buffer and in acetonitrile and practically insoluble in aqueous solutions of pH 4 and below.

Atorvastatin calcium tablets for oral administration contain 80 mg atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

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

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

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

Specific Populations

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

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

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

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

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

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

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

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

& Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).
\# See Sections 5.1 and 7 for clinical significance.
* Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with 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 reduction in atorvastatin plasma concentrations.
‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

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

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

\# See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

14 CLINICAL STUDIES

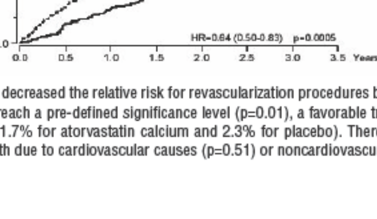
14.1 Prevention of Cardiovascular Disease

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

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

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

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



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

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

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

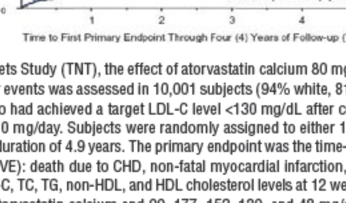
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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

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

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

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



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

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

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

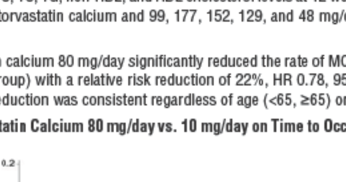


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg
b Component of other secondary endpoints
* Secondary endpoints not included in primary endpoint HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

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

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

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin calcium and 105, 179, 142, 47, and 132 mg/dL during treatment with 20–40 mg of simvastatin.

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

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

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

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

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

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

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

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

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

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin calcium 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

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

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

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin Calcium 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin Calcium 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin Calcium 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

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

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

14.3 Hypertriglyceridemia (*Fredrickson* Type IV)

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

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

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

14.4 Dysbetalipoproteinemia (*Fredrickson* Type III)

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

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

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Atorvastatin Calcium 10 mg	Atorvastatin Calcium 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

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

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to atorvastatin calcium (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin calcium group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

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

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

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

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the atorvastatin calcium group compared 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 children. The long-term efficacy of atorvastatin calcium therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin calcium tablets of 80 mg are white to off-white, oval shaped, biconvex, film coated tablets debossed 'RDY' on one side and '124' on other side and are supplied in bottles of 30's, 60's, 90's and 500's.

Bottles of 30	NDC 55111-124-30
Bottles of 60	NDC 55111-124-60
Bottles of 90	NDC 55111-124-90
Bottles of 500	NDC 55111-124-05

Storage

Store atorvastatin calcium tablets at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

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

17.1 Muscle Pain

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

17.2 Liver Enzymes

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

17.3 Pregnancy

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

17.4 Breastfeeding

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

PATIENT INFORMATION
Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium 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, ask your doctor or pharmacist.

What is Atorvastatin Calcium?

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

Do not take atorvastatin calcium if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium and call your doctor right away.
- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium 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.

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

Before you start Atorvastatin Calcium

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. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium 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?

- Take atorvastatin calcium exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium. Your dose of atorvastatin calcium may be changed based on these blood test results.
- Take atorvastatin calcium each day at any time of day at about the same time each day. Atorvastatin calcium 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. Stay on this low-fat diet when you take atorvastatin calcium.
- If you miss a dose of atorvastatin calcium, take it as soon as you remember. Do not take atorvastatin calcium 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 at the same time.
- If you take too much atorvastatin calcium 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?

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

What are the possible side effects of Atorvastatin Calcium?

Atorvastatin calcium 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 is stopped. These serious side effects include:

- **Muscle problems**. Atorvastatin calcium 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.
- **Liver problems**. Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium and if you have symptoms of liver problems while you take atorvastatin calcium. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

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

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium: 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: 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. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

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

General information about Atorvastatin Calcium

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium for a condition for which it was not prescribed. Do not give atorvastatin calcium 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. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium
Inactive Ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

To reorder additional Patient Information Sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Issued: 0312 DR.REDDY'S

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PATIENT INFORMATION

Atorvastatin Calcium Tablets

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

Atorvastatin calcium 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 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 starts to work in about 2 weeks.

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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?

Do not take atorvastatin calcium if you:

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- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium 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.

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

Before you start Atorvastatin Calcium

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. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

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- Take atorvastatin calcium each day at any time of day at about the same time each day. Atorvastatin calcium can be taken with or without food.

  Don't break atorvastatin calcium tablets before taking.
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- If you take too much atorvastatin calcium or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

(Continued on other side)

(Continued from previous side)

What should I avoid while taking Atorvastatin Calcium?

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- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium right away and call your doctor.

What are the possible side effects of Atorvastatin Calcium?

Atorvastatin calcium 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 is stopped. These serious side effects include:

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  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
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Call your doctor right away if you have:

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

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium: 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: 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. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

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

General information about Atorvastatin Calcium

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What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

To reorder additional Patient Information Sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Issued: 0312

DR.REDDY'S

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

LABELING REVIEWS

*****This AP Summary supersedes review dated 5/15/2012*****

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

ANDA Number: 202357

Date of Submission: March 5, 2012 and May 17, 2012

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

REMS required?

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

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

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

Do you have 12 Final Printed Labels and Labeling? Electronic submission.

CONTAINER LABELS: (30s, 60s, 90s and 500s): Final Printed Labels acceptable in 3/5/12 e-submission

PROFESSIONAL PACKAGE INSERT LABELING: Final Printed Labeling acceptable in the 3/5/12 e-submission

PATIENT INFORMATION SHEET: Final Printed Labels acceptable in 3/5/12 e-submission

Revisions needed post-approval: Yes

1. CONTAINER:

Revise the "*Each tablet contains…" statement to read "*Each film-coated tablet contains Atorvastatin calcium equivalent to __X__ mg atorvastatin".

2. INSERT:

FULL PRESCRIBING INFORMATION: CONTENTS*

i. 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)

ii. Revise subheading “6.2 Postintorduction Reports” to read “6.2 Postmarketing Experience”.

iii. 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)

iv. Revise the subheading 7.1 to read “7.1 Strong Inhibitors of CYP 3A4”.

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

In the cover letter dated May 17, 2012, the firm acknowledges the agency’s comments, and commits to revise the labeling as recommended by the agency and submit the revised labeling post approval. The revisions requested as stated above, were communicated to the firm in the deficiency letter dated May 15, 2012, to Jaya Ayyagari of the firm at 908-203-4977.

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 02/28/2012.

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

From: Rickman, William P
Sent: Wednesday, May 16, 2012 2:20 PM
To: Turner, Betty
Subject: FW: Atorvastatin Calcium Tablets, 10 mg, 20 mg, and 40 mg ANDA 091650 and Atorvastatin Calcium Tablets, 80 mg ANDA 202357 Labeling review status request
Betty I'm going to allow them to make this change post approval and at next printing.

Peter

From: Sayeed, Vilayat A
Sent: Wednesday, May 16, 2012 2:09 PM
To: Nagavelli, Laxma; Gaines, Robert

Cc: Gill, Devinder
Subject: RE: Atorvastatin Calcium Tablets, 10 mg, 20 mg, and 40 mg ANDA 091650 and Atorvastatin Calcium Tablets, 80 mg ANDA 202357 Labeling review status request

Folks

As the sponsor is committing to revise the label in the next printing, I think we can let it go with a commitment as this has been done in the past. We can discuss more when I am back in office tomorrow

Thanks

Vilayat

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD
7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV

From: Nagavelli, Laxma
Sent: Wednesday, May 16, 2012 1:49 PM
To: Gaines, Robert
Cc: Gill, Devinder; Sayeed, Vilayat A
Subject: RE: Atorvastatin Calcium Tablets, 10 mg, 20 mg, and 40 mg ANDA 091650 and Atorvastatin Calcium Tablets, 80 mg ANDA 202357 Labeling review status request

Bob,

What the firm saying about the CMC and labeling letters about the description of the drug substance in the drug product label is correct based on no official monograph available for the drug substance at that time. But now, with official monograph in place, the firm is requested to comply with the monograph for the drug substance labeling. I completely understand firm's point of view as well and it is for the labeling to make a call.

Thanks,
Laxma

From: Turner, Betty
Sent: Wednesday, May 16, 2012 12:28 PM
To: Gaines, Robert; Nagavelli, Laxma
Subject: FW: Atorvastatin Calcium Tablets, 10 mg, 20 mg, and 40 mg ANDA 091650 and Atorvastatin Calcium Tablets, 80 mg ANDA 202357 Labeling review status request
Importance: High

Hi Bob,

I wanted to let you know my communication with the firm regarding the container labels for ANDA 091650 and 202357 ATORVASTATIN CALCIUM. I have been very firm with them that they should revise their labels prior to approval, but they are still pushing for their labels to be approved as is.

Thanks,

Betty

From: jayalakshmia@drreddys.com [mailto:jayalakshmia@drreddys.com]
Sent: Wednesday, May 16, 2012 11:35 AM
To: Turner, Betty
Cc: kernst@drreddys.com
Subject: RE: Atorvastatin Calcium Tablets, 10 mg, 20 mg, and 40 mg ANDA 091650 and Atorvastatin Calcium Tablets, 80 mg ANDA 202357 Labeling review status request
Importance: High

Dear Ms Turner

The revision to the labels was made based on the specific request received from Chemistry division in chemistry deficiency letter dated April 29,2011 and subsequently this revision was made and submitted in our response dated May 13,2011 for ANDA 091650.

A copy of the cover letter stating the same is attached for your quick reference .The revision was confirmed as acceptable for approval by Ms Ann Vu on September 21,2011 .Based on this confirmation we had packed the launch quantities per the last approved labels

However we acknowledge the comment and commit to make the revision in the next printing since the launch quantities are already packed.If needed we could send you the revised labels along with the response with a commitment to implement the revision from the next printing. Since the launch quantities are already packed , a revision to the container labels would necessitate a huge rework.

In view of the possible approval on May 29th we request you to kindly consider our request and make an exception to use the existing labels for the launch quantities .We commit to implement the revised labels from the next printing .

I lefty you a voice mail as well. Please discuss and respond as soon possible. Thank you very much for you timely follow up on this matter.

Best Regards,

Jaya Ayyagari
Senior Manager,Regulatory Affairs
Dr Reddy's Laboratories Inc
200 Somerset Corporate Blvd, Floor 7
Bridgewater NJ 08807
Ph: 908-203-4977
cell : 704-930-3630
Fax : 908-203-4980
jayalakshmia@drreddys.com

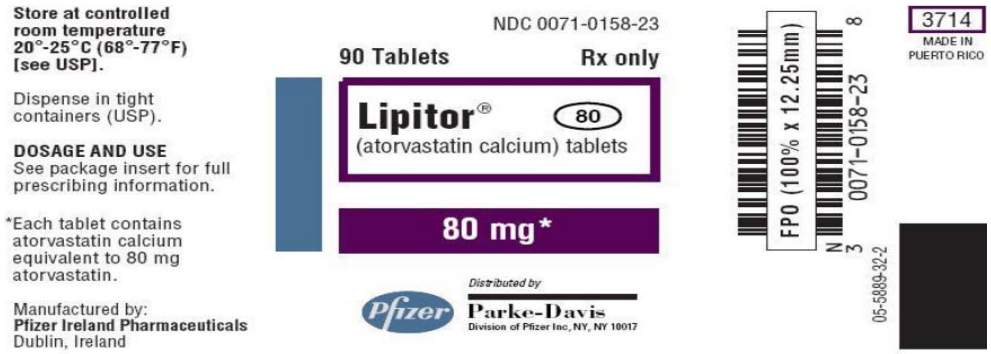
FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 12/8//2011 and 5/15/2012 in DARRTS.

1. MODEL LABELING: This review was based on the labeling of the RLD, Lipitor®, NDA 020702/S-060, approved 2/28/2012.

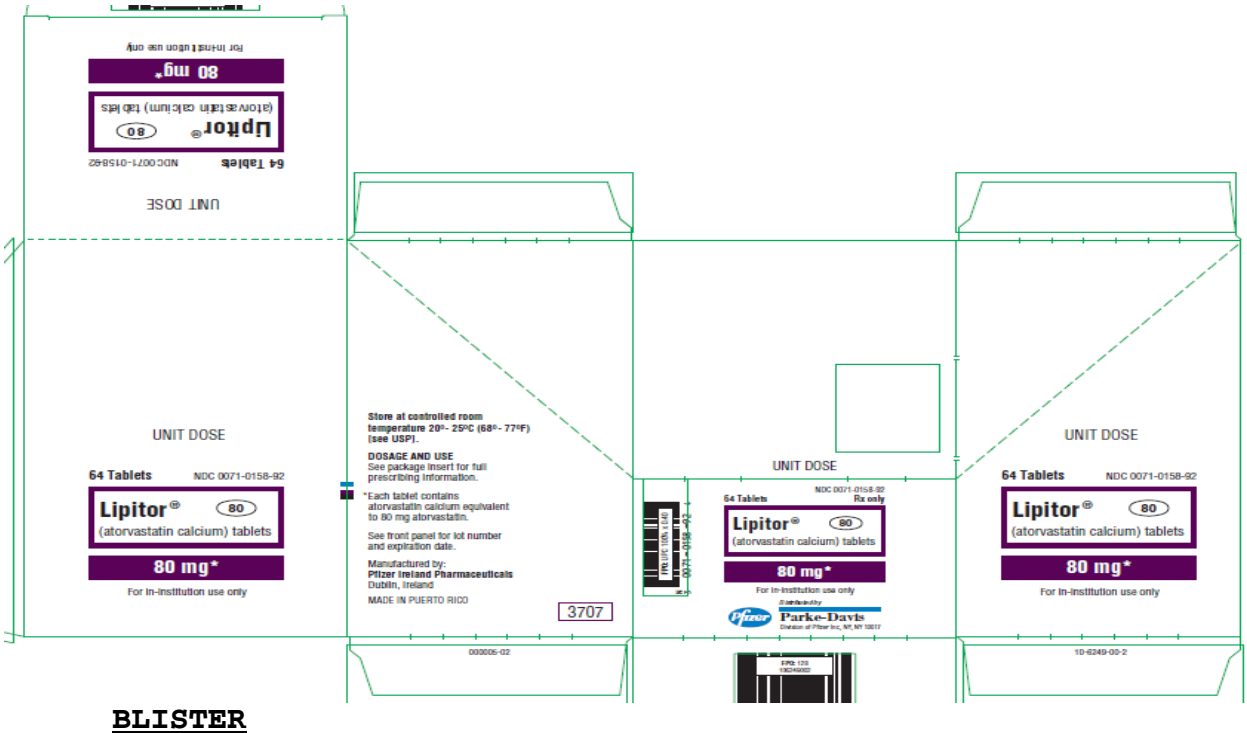
   Supplement 056 was approved June 17, 2009, and provided for labeling in PLR format.

   Note that the DS is the [redacted] (b) (4) form, the RLD DS has 3 H_2O molecules attached.

CONTAINER



CARTON



BLISTER

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL: 020702

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

			HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA		

PATENT AMENDMENT: Update on Paragraph IV certification submitted 4/27/2012

The original ANDA submission for Atorvastatin Calcium Tablets, 80 mg dated September 27,2010 included a paragraph IV certification for Patents 5,686,104 ; 5,969,156 and 6,126,971 . A copy of the return receipt acknowledging the receipt of Paragraph IV notification by the Patent /NDA holder is provided as **Exhibit # 1** to the cover letter.

We would like to confirm that patent infringement actions were brought against Dr. Reddy's Laboratories (Case no 10-01135-LPS) for Patent 5,969,156 within the stipulated time. The case has been dismissed with Dr. Reddy's maintaining all of its paragraph IV certifications and having the right to launch prior to expiration of these patents. A copy of the stipulation of dismissal is attached as **Exhibit # 2.**

Dr Reddy's was not sued for the patents 5,686,104 and 6,126,971.

Based on the above information, Dr Reddy's Laboratories request the approval of the application upon the expiry of the 180 day exclusivity associated with the first generic applicant.

Patent and Exclusivity Data from Orange Book checked May 14, 2012
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	Delist Requested
N020702	001	5686104	Nov 11, 2014		Y	U - 213	
N020702	001	5686104*PED	May 11, 2015			U - 213	
N020702	001	5969156	Jul 8, 2016	Y			
N020702	001	5969156*PED	Jan 8, 2017				
N020702	001	6126971	Jan 19, 2013		Y		
N020702	001	6126971*PED	Jul 19, 2013				

Exclusivity Data
There is no unexpired exclusivity for this product.

[1.3.5.2-original submission]

3. 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. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains (b) (4) (b) (4) polyvinyl alcohol, talc, titanium dioxide, lecithin and xanthan gum.

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.3-original submission]

Dr. Reddy's Laboratories Limited (Generics)
Located at Bachepalli – 502 325
INDIA

5. FINISHED DOSAGE FORM

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

ANDA:

80 mg: White to Off- white, oval shaped , biconvex , film coated tablets debossed 'RDY' on one side and '124'on other side

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

Package Size	Configuration
30's	• 30 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • (b) (4) •
60's	• 60 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) •
90's	• 90 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) •
500's	• 500 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) •

(b) (4)

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature (DS is compendial, not DP)
RLD: Store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

8. DISPENSING STATEMENTS COMPARISON

USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature (DS is compendial, not DP)
RLD: Dispense in tight containers (USP)
ANDA: Same as above.

9. BIOAVAILABILITY/BIOEQUIVALENCE: As of March 3, 2011, Dissolution is inadequate per DBE.

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

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

ANDA: 30's, 60's, 90's, 500s (b) (4)

(b) (4) were withdrawn by the firm in the amendment dated February 7, 2012.

12. REMS:
REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

13. SPL Data Elements:
RLD:
80 mg tablet: No score, 19 mm size

ANDA:
80 mg tablet: No score, 19mm size

Firm provided labeling in SPL format in the amendment dated 3/5/12 [redacted] (b) (4) are not listed in the data elements section of the SPL.

In the amendment submitted February 7, 2012 (cover letter dated 2/7/12) information on [redacted] (b) (4)

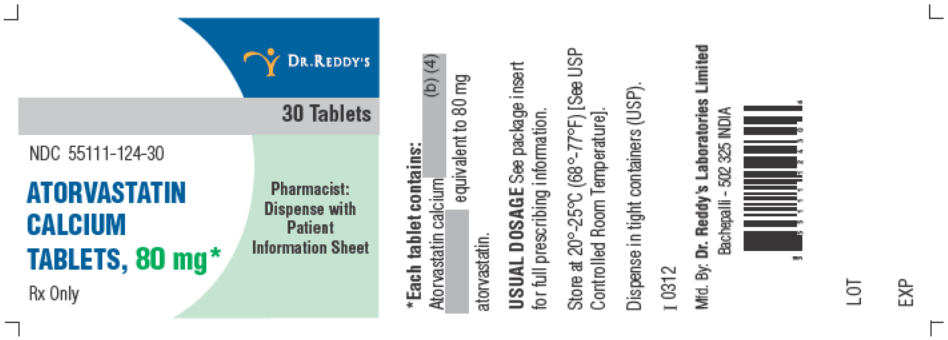
We would like to inform to the Agency that, we have reviewed the 24 months stability data of [redacted] (b) (4) and as the data is not meeting the above proposed specification, Dr. Reddy's would like to withdraw the [redacted] (b) (4) from the ANDA.

Date of Review: May 18, 2012 Date of Submission: March 5, 2012 and May 17, 2012

Primary Reviewer: Betty Turner

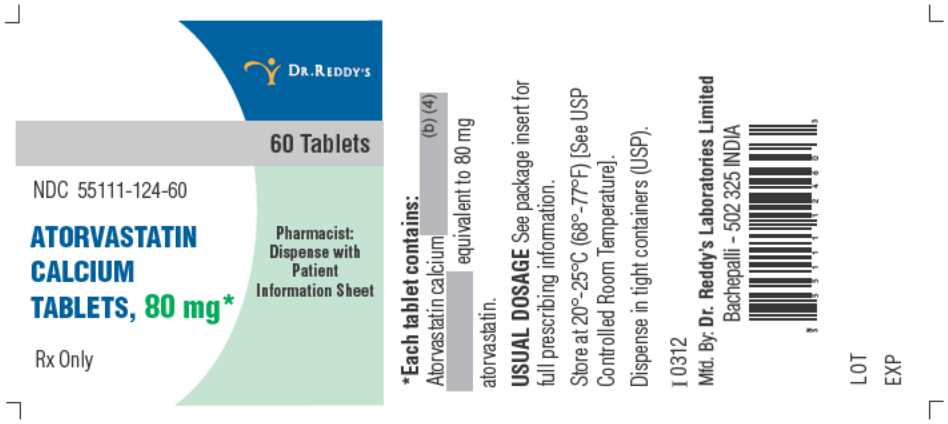
Team Leader: Ruby (Chi-Ann) Wu

Final Container Label for Atorvastatin Calcium Tablets, 80 mg
80 mg - 30's Count
Label Size: [redacted]



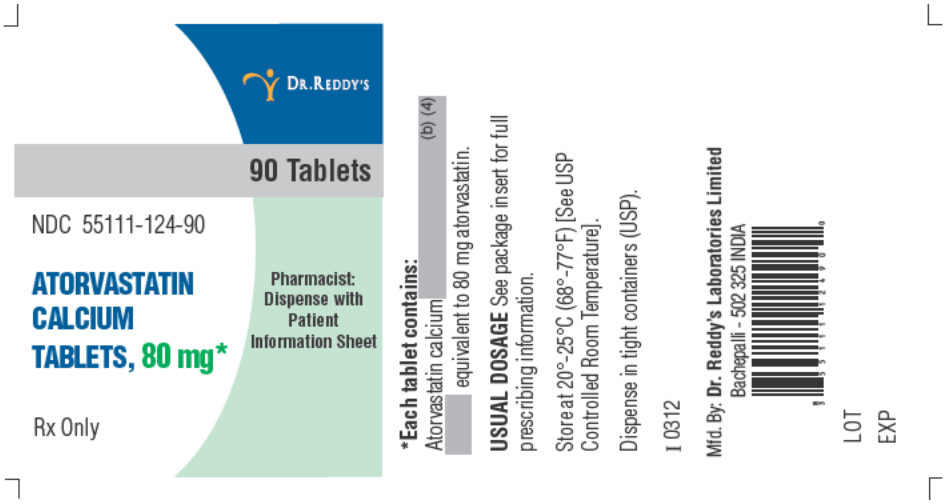
[redacted]

Final Container Label for Atorvastatin Calcium Tablets, 80 mg
80 mg - 60's Count
Label Size: (b) (4)



(b) (4)

Final Container Label for Atorvastatin Calcium Tablets, 80 mg
80 mg - 90's Count
Label Size: (b) (4)



(b) (4)

Final Container Label for Atorvastatin Calcium Tablets, 80 mg
80 mg - 500's Count
Label Size: (b) (4)

DR. REDDY'S

500 Tablets

NDC 55111-124-05

ATORVASTATIN CALCIUM TABLETS, 80 mg*

Rx Only

Pharmacist: Dispense with Patient Information Sheet

***Each tablet contains:** Atorvastatin calcium (b) (4) equivalent to 80 mg atorvastatin.

USUAL DOSAGE See package insert for full prescribing information.

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

Dispense in tight containers (USP).

I 0312

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

LOT

EXP

(b) (4)

Atorvastatin Calcium Tablets, 80 mg
Rx only
I 0312
55111-124-02

55111-124-02
Rx only
I 0312
Atorvastatin Calcium Tablets, 80 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Atorvastatin Calcium Tablets for oral administration

Initial U.S. Approval: 1996

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

Drug Interactions (7) 02/2012

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

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

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

Limitations of Use

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

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

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

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

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

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

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

80 mg tablets (3).

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

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

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

Nursing mothers (4.4).

Hypersensitivity to any component of this medication (4.2).

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

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

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

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories Inc., at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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

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

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

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

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

See **17 for PATIENT COUNSELING INFORMATION**

Revised: [03/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Prevention of Cardiovascular Disease

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

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

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

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

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

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

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

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

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

2.3 Homozygous Familial Hypercholesterolemia

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

2.4 Concomitant Lipid-Lowering Therapy

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

2.5 Dosage in Patients with Renal Impairment

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

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

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

3 DOSAGE FORMS AND STRENGTHS

Atorvastatin calcium tablets of 80 mg are white to off-white, oval shaped, biconvex, film coated tablets debossed 'RDY'on one side and '124' on other side.

4 CONTRAINDICATIONS

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

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of atorvastatin calcium use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM 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 should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see **Use in Specific Populations (8.1)**].

4.4 Nursing mothers

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

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

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

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

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

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

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

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

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

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

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

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

5.2 Liver Dysfunction

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

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

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

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

5.3 Endocrine Function

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

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

5.4 CNS Toxicity

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

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

5.5 Use in Patients with Recent Stroke or TIA

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

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

Rhabdomyolysis and myopathy [see **Warnings and Precautions (5.1)**]

Liver enzyme abnormalities [see **Warnings and Precautions (5.2)**]

6.1 Clinical Trial Adverse Experiences

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

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

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

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

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

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

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

Other adverse reactions reported in placebo-controlled studies include:

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

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

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

Collaborative Atorvastatin Diabetes Study (CARDS)

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

Treating to New Targets Study (TNT)

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

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

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

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

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

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

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

6.2 Postmarketing Experience

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

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

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

6.3 Pediatric Patients (ages 10-17 years)

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

7 DRUG INTERACTIONS

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

7.1 Strong Inhibitors of CYP 3A4:

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

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

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

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

7.2 Grapefruit Juice:

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

7.3 Cyclosporine:

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

7.4 Gemfibrozil:

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

7.5 Other Fibrates:

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

7.6 Niacin:

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

7.7 Rifampin or other Inducers of Cytochrome P450 3A4:

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

7.8 Digoxin:

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

7.9 Oral Contraceptives:

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

7.10 Warfarin:

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

7.11 Colchicine:

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

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

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin calcium had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see **Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10-17 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 therapy [see **Contraindications, Pregnancy (4.3)** and **Use in Specific Populations, Pregnancy (8.1)**]. **Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

10 OVERDOSAGE

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

11 DESCRIPTION

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

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of atorvastatin calcium is $C_{66}H_{68}CaF_2N_4O_{10}$ and its molecular weight is 1155.36. Its structural formula is:

PHARMACIST - DETACH FROM HERE

PATIENT INFORMATION
Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium 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, ask your doctor or pharmacist.

What is Atorvastatin Calcium?

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

Atorvastatin calcium 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 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 starts 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?

Do not take atorvastatin calcium if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium and call your doctor right away.
- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium 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.

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

Before you start Atorvastatin Calcium

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. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium 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?

- Take atorvastatin calcium exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium. Your dose of atorvastatin calcium may be changed based on these blood test results.
- Take atorvastatin calcium each day at any time of day at about the same time each day. Atorvastatin calcium 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. Stay on this low-fat diet when you take atorvastatin calcium.
- If you miss a dose of atorvastatin calcium, take it as soon as you remember. Do not take atorvastatin calcium 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 at the same time.
- If you take too much atorvastatin calcium or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

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What should I avoid while taking Atorvastatin Calcium?

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

What are the possible side effects of Atorvastatin Calcium?

Atorvastatin calcium 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 is stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium 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.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium and if you have symptoms of liver problems while you take atorvastatin calcium. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

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

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium: 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: 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. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

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

General information about Atorvastatin Calcium

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium for a condition for which it was not prescribed. Do not give atorvastatin calcium 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. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

To reorder additional Patient Information Sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Issued: 0312

PHARMACIST - DETACH FROM HERE

Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in dimethyl sulphoxide, slightly soluble in alcohol, very slightly soluble in water, in pH 7.4 phosphate buffer and in acetonitrile and practically insoluble in aqueous solutions of pH 4 and below.

Atorvastatin calcium tablets for oral administration contain 80 mg atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

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

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

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

Specific Populations

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

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

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

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

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

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

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

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

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

\# See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with 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 reduction in atorvastatin plasma concentrations.

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

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

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

\# See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

14 CLINICAL STUDIES

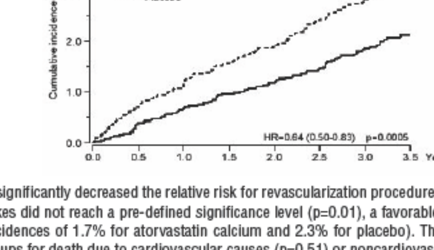
14.1 Prevention of Cardiovascular Disease

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

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

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

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



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

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

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

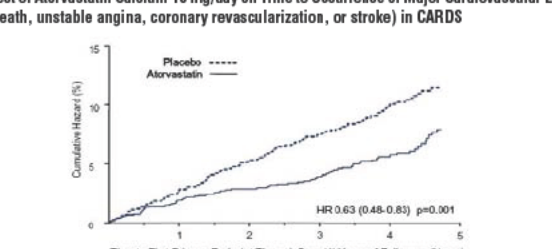
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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

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

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

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



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

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

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

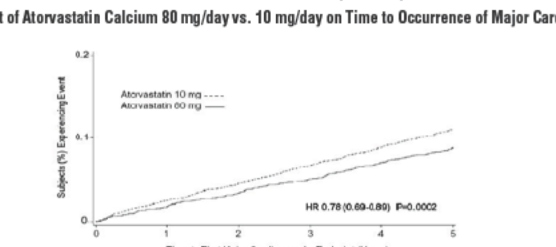


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HRa (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedureb	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpointb	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg

b Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft

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

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

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

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin calcium and 105, 179, 142, 47, and 132 mg/dL during treatment with 20–40 mg of simvastatin.

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

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

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

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

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

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

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

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

a Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin calcium 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

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

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

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin Calcium 10 mg	707	-27a	-36a	-28a	-17a	+7	-37a
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff1		-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 10 mg	222	-25b	-35b	-27b	-17b	+6	-36b
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff1		-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 10 mg	132	-29c	-37c	-34c	-23c	+7	-39c
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff1		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

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

a Significantly different from lovastatin, ANCOVA, p ≤0.05

b Significantly different from pravastatin, ANCOVA, p ≤0.05

c Significantly different from simvastatin, ANCOVA, p ≤0.05

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

14.3 Hypertriglyceridemia (*Fredrickson* Type IV)

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

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

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

14.4 Dysbetalipoproteinemia (*Fredrickson* Type III)

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

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

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Atorvastatin Calcium 10 mg	Median % Change (min, max) Atorvastatin Calcium 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

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

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to atorvastatin calcium (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin calcium group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

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

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

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

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the atorvastatin calcium group compared 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 children. The long-term efficacy of atorvastatin calcium therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin calcium tablets of 80 mg are white to off-white, oval shaped, biconvex, film coated tablets debossed 'RDY' on one side and '124' on other side and are supplied in bottles of 30's, 60's, 90's and 500's.

Bottles of 30	NDC 55111-124-30
Bottles of 60	NDC 55111-124-60
Bottles of 90	NDC 55111-124-90
Bottles of 500	NDC 55111-124-05

Storage

Store atorvastatin calcium tablets at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

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

17.1 Muscle Pain

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

17.2 Liver Enzymes

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

17.3 Pregnancy

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

17.4 Breastfeeding

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

PATIENT INFORMATION

Atorvastatin Calcium Tablets

Read the Patient Information that comes with atorvastatin calcium 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, ask your doctor or pharmacist.

What is Atorvastatin Calcium?

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

Atorvastatin calcium 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 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 starts 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?

Do not take atorvastatin calcium if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium and call your doctor right away.
- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium 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.

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

Before you start Atorvastatin Calcium

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. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium 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?

- Take atorvastatin calcium exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium. Your dose of atorvastatin calcium may be changed based on these blood test results.
- Take atorvastatin calcium each day at any time of day at about the same time each day. Atorvastatin calcium 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. Stay on this low-fat diet when you take atorvastatin calcium.
- If you miss a dose of atorvastatin calcium, take it as soon as you remember. Do not take atorvastatin calcium 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 at the same time.
- If you take too much atorvastatin calcium 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?

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

What are the possible side effects of Atorvastatin Calcium?

Atorvastatin calcium 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 is stopped. These serious side effects include:

- **Muscle problems**. Atorvastatin calcium 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.
- **Liver problems**. Your doctor should do blood tests to check your liver before you start taking atorvastatin calcium and if you have symptoms of liver problems while you take atorvastatin calcium. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

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

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium: 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: 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. Ask your doctor or pharmacist for a complete list.

How do I store Atorvastatin Calcium Tablets

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

General information about Atorvastatin Calcium

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium for a condition for which it was not prescribed. Do not give atorvastatin calcium 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. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

To reorder additional Patient Information Sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Issued: 0312

[redacted] (b) (4)

55111-124-02

PATIENT INFORMATION

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Atorvastatin calcium 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 starts to work in about 2 weeks.

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- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium and call your doctor right away.
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- have muscle aches or weakness
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- have diabetes
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- have kidney problems

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  Don't break atorvastatin calcium tablets before taking.
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- If you take too much atorvastatin calcium or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

(Continued on other side)

(Continued from previous side)

What should I avoid while taking Atorvastatin Calcium?

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- nausea and vomiting.
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- you feel more tired than usual
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General information about Atorvastatin Calcium

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Active Ingredient: atorvastatin calcium

Inactive Ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

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Issued: 0312

DR.REDDY'S

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
05/18/2012

CHI-ANN Y WU
05/18/2012
For Wm. Peter Rickman

Supersedes AP summary dated 12/8/2011
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202357 Date of Submission: March 5, 2012

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

LABELING DEFICIENCIES:

1. CONTAINER:

Revise the "*Each tablet contains…" statement to read "*Each film-coated tablet contains Atorvastatin calcium equivalent to __X__ mg atorvastatin".

2. (b) (4)

3. INSERT:

FULL PRESCRIBING INFORMATION: CONTENTS*

i. 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)

ii. Revise subheading "6.2 Postintorduction Reports" to read "6.2 Postmarketing Experience".

iii. 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)

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

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

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 02/28/2012.

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

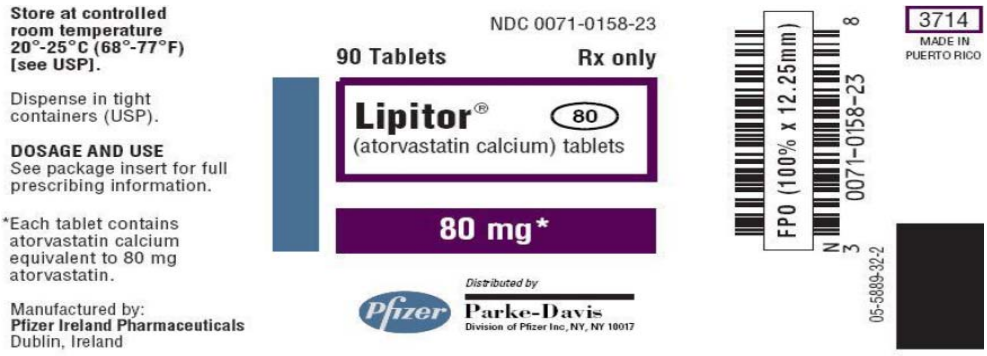
FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 12/8//2011 in DARRTS.

1. MODEL LABELING: This review was based on the labeling of the RLD, Lipitor®, NDA 020702/S-060, approved 2/28/2012.

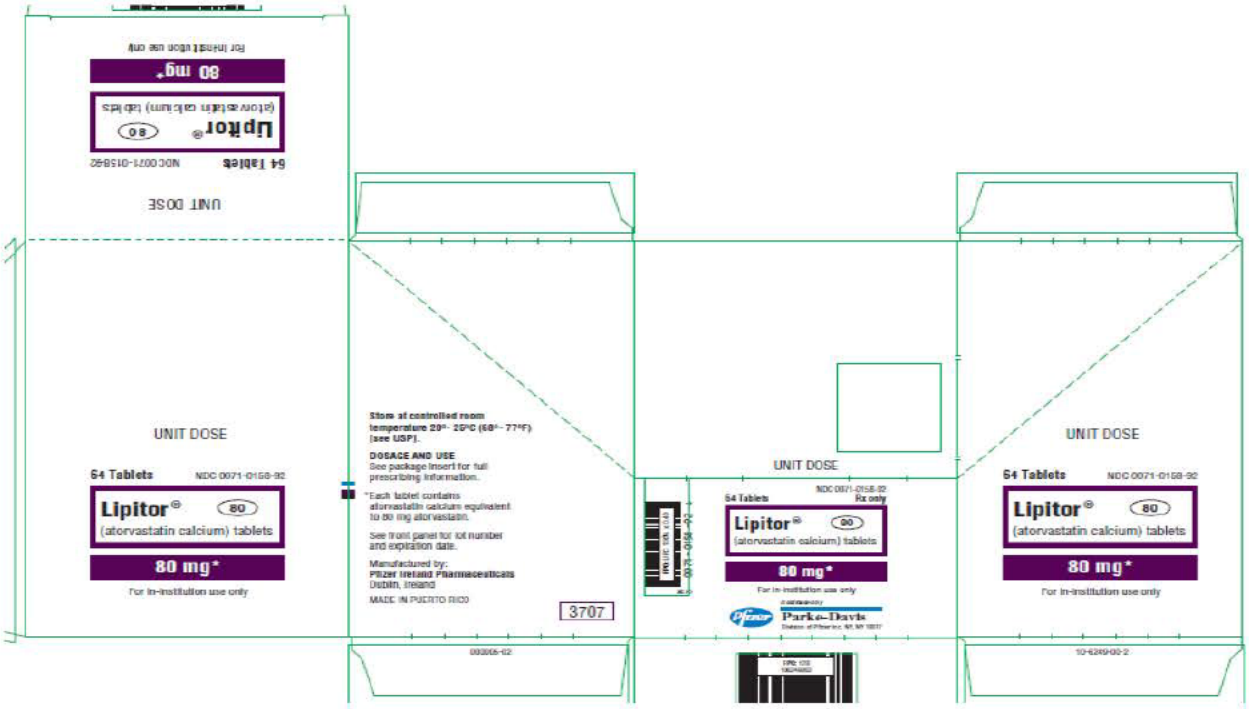
   Supplement 056 was approved June 17, 2009, and provided for labeling in PLR format.

   Note that the DS is the [redacted] (b) (4) form, the RLD DS has 3 H_2O molecules attached.

   CONTAINER



CARTON



BLISTER

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL: 020702

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

PATENT AMENDMENT: Update on Paragraph IV certification submitted 4/27/2012

The original ANDA submission for Atorvastatin Calcium Tablets, 80 mg dated September 27,2010 included a paragraph IV certification for Patents 5,686,104 ; 5,969,156 and 6,126,971 . A copy of the return receipt acknowledging the receipt of Paragraph IV notification by the Patent /NDA holder is provided as **Exhibit # 1** to the cover letter.

We would like to confirm that patent infringement actions were brought against Dr. Reddy's Laboratories (Case no 10-01135-LPS) for Patent 5,969,156 within the stipulated time. The case has been dismissed with Dr. Reddy's maintaining all of its paragraph IV certifications and having the right to launch prior to expiration of these patents. A copy of the stipulation of dismissal is attached as **Exhibit # 2.**

Dr Reddy's was not sued for the patents 5,686,104 and 6,126,971.

Based on the above information, Dr Reddy's Laboratories request the approval of the application upon the expiry of the 180 day exclusivity associated with the first generic applicant.

Patent and Exclusivity Data from Orange Book checked May 14, 2012
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	Delist Requested
N020702	001	5686104	Nov 11, 2014		Y	U - 213	
N020702	001	5686104*PED	May 11, 2015			U - 213	
N020702	001	5969156	Jul 8, 2016	Y			
N020702	001	5969156*PED	Jan 8, 2017				
N020702	001	6126971	Jan 19, 2013		Y		
N020702	001	6126971*PED	Jul 19, 2013				

Exclusivity Data
There is no unexpired exclusivity for this product.

[1.3.5.2-original submission]

3. 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. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains (b) (4), (b) (4) polyvinyl alcohol, talc, titanium dioxide, lecithin and xanthan gum.

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.3-original submission]

Dr. Reddy's Laboratories Limited (Generics)
Located at Bachepalli – 502 325
INDIA

5. FINISHED DOSAGE FORM

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

ANDA:

80 mg: White to Off- white, oval shaped , biconvex , film coated tablets debossed 'RDY' on one side and '124'on other side

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

Package Size	Configuration
30's	• 30 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • (b) (4) • (b) (4)
60's	• 60 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • (b) (4) • (b) (4)
90's	• 90 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • (b) (4) • (b) (4)
500's	• 500 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • (b) (4) • (b) (4)

(b) (4)

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature (DS is compendial, not DP)
RLD: store at CRT (20-25°C (68-77°F) [see USP].
ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

8. DISPENSING STATEMENTS COMPARISON

USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature (DS is compendial, not DP)
RLD: Dispense in tight containers (USP)
ANDA: Same as above.

9. BIOAVAILABILITY/BIOEQUIVALENCE: As of March 3, 2011, Dissolution is inadequate per DBE.

10. SCORING

RLD: Not scored
ANDA: Not scored

11. PACKAGE CONFIGURATION

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

ANDA: 30's, 60's, 90's, 500s (b) (4)

12. REMS:
REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

13. SPL Data Elements:
RLD:
80 mg tablet: No score, 19 mm size

ANDA:
80 mg tablet: No score, 19mm size

Firm provided labeling in SPL format in the amendment dated 3/5/12 [redacted] (b) (4) are not listed in the data elements section of the SPL.

Date of Review: May 15, 2012 Date of Submission: March 5, 2012

Primary Reviewer: Betty Turner

Team Leader: Ruby (Chi-Ann) Wu

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
05/15/2012

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

ANDA Number: 202357 Date of Submission: March 31, 2011

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

REMS required? NO

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

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

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (30s, 60s, 90s and 500s): Final Printed Labels acceptable submitted on 3/31/2011

(b) (4)

Professional Package Insert Labeling: 3/31/2011 e-submission

Patient Information Sheet: 3/31/2011 e-submission

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. S-056 provides for changes in the format of the PI and PPI in response to the PLR.

   Note that the DS is the [redacted] (b) (4) form, the RLD DS has 3 H_2O molecules attached.

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

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

6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As
RE40667* PED	Jun 28, 2011	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIII	Same As

No exclusivities remaining

[1.3.5.2-original submission]

3. 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. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains (b) (4), (b) (4) polyvinyl alcohol, talc, titanium dioxide, lecithin and xanthan gum.

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.3-original submission]

Dr. Reddy's Laboratories Limited (Generics)
Located at Bachepalli – 502 325
INDIA

5. FINISHED DOSAGE FORM

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

ANDA:

80 mg: White to Off- white, oval shaped , biconvex , film coated tablets debossed 'RDY' on one side and '124'on other side

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

Package Size	Configuration
30's	• 30 Tablets in [redacted] High Density Polyethylene container • [redacted] • Desiccant: [redacted]
60's	• 60 Tablets in [redacted] High Density Polyethylene container • [redacted] • Desiccant: [redacted]
90's	• 90 Tablets in [redacted] High Density Polyethylene container • [redacted] • Desiccant: [redacted]
500's	• 500 Tablets in [redacted] High Density Polyethylene container • [redacted] • Desiccant: [redacted]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature(DS is compendial, not DP)
   RLD: store at CRT (20-25°C (68-77°F) [see USP].
   ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

8. DISPENSING STATEMENTS COMPARISON

   USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature(DS is compendial, not DP)
   RLD: Dispense in tight containers (USP)
   ANDA: Same as above.

9. BIOAVAILABILITY/BIOEQUIVALENCE: As of March 3, 2011, Dissolution is inadequate per DBE.

10. SCORING

    RLD: Not scored
    ANDA: Not scored

11. PACKAGE CONFIGURATION

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

    ANDA: 30's, 60's, 90's, 500s (b) (4)

Date of Review: December 8, 2011 Date of Submission: March 31, 2011

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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/s/

THUYANH VU
12/08/2011

JOHN F GRACE
12/08/2011

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

ANDA Number: 202357 Date of Submission: September 27, 2010

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

Labeling Deficiencies:

1. CONTAINER (30s, 60s, 90s, and 500s)

   Acceptable in final print.

[redacted] (b) (4)

4. INSERT

   11 DESCRIPTION: You may delete [redacted] (b) (4) and just state the composition of the [redacted] (b) (4).

3. PATIENT INFORMATION SHEET:

   Please refer to INSERT comment.

Submit label and labeling electronically.

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

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

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 (30s, 60s, 90s and 500s): Final Printed Labels acceptable submitted on 9/27/10 e-submission

(b) (4)

Professional Package Insert Labeling: See comment

Patient Information Sheet: See comment

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. S-056 provides for changes in the format of the PI and PPI in response to the PLR.

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
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RE40667* PED	Jun 28, 2011	U-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIII	Same As

No exclusivities remaining

[1.3.5.2-original submission]

3. 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. [Vol. A1.1 pg. 106 and Vol. A1.2 pg. 532.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: Basic butylated methacrylate copolymer, crospovidone, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, methanol, microcrystalline cellulose, sodium bicarbonate and sodium lauryl sulphate. The tablet coating contains (b) (4) (b) (4) polyvinyl alcohol, talc, titanium dioxide, lecithin and xanthan gum.

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.3-original submission]

Dr. Reddy's Laboratories Limited (Generics)
Located at Bachepalli – 502 325
INDIA

5. FINISHED DOSAGE FORM

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

ANDA:

80 mg: White to Off- white, oval shaped , biconvex , film coated tablets debossed ‘RDY’ on one side and ‘124’on other side

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Package Size	Configuration
30’s	• 30 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • •
60’s	• 60 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • •
90’s	• 90 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • •
500’s	• 500 Tablets in (b) (4) High Density Polyethylene container (b) (4) • (b) (4) • Desiccant: (b) (4) • (b) (4) • •

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature(DS is compendial, not DP)
   RLD: store at CRT (20-25°C (68-77°F) [see USP].
   ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

8. DISPENSING STATEMENTS COMPARISON

   USP: Packaging and Storage: Preserve in well-closed containers, and store at room temperature(DS is compendial, not DP)
   RLD: Dispense in tight containers (USP)
   ANDA: Same as above.

9. BIOAVAILABILITY/BIOEQUIVALENCE: As of March 3, 2011, Dissolution is inadequate per DBE.

10. SCORING

    RLD: Not scored
    ANDA: Not scored

11. PACKAGE CONFIGURATION

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

    ANDA: 30's, 60's, 90's, 500s (b) (4)

12. CONTAINER LABELS

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

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

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/s/

THUYANH VU
03/10/2011

JOHN F GRACE
03/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

CHEMISTRY REVIEWS

ANDA 202357

Addendum #1 to Review #2

Atorvastatin Calcium Tablets, 80 mg

Dr. Reddy's Laboratories, Inc.

Matthew D. Vera, Ph.D.
Team 34
Division of Chemistry III
Office of Generic Drugs

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Background:

When review #2 of ANDA 202357 was finalized on June 29, 2012, Type II DMFs 21125 and (b) (4) had been reviewed and found Adequate with additional information requested. In addition, the Bioequivalence review had an Inadequate status. A subsequent Bioequivalence review was entered in DARRTS on July 5, 2012 showing Adequate status.

The DMF holder has also provided responses which were reviewed and found adequate on 10-July-2012.

The purposes of this review addendum are:

- to reflect the current status of DMF 21125 and (b) (4) as fully adequate;
- to update the bioequivalence review status as adequate;

Updated replacement tables for Items 17 and 19 in Review #2 are shown below.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)							
21125	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium	1	Adequate	10-July-2012	M. Vera
(b) (4)	II	(b) (4)		1	Adequate	10-July-2012	M. Vera
	III			4	N/A		
	III			4	N/A		
							(b) (4)
	III			4	N/A		
	III			4	N/A		

CHEMISTRY REVIEW

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)
	III			4	N/A		
							(b) (4)
	III			4	N/A		
	t						
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	25-Apr-2012	
Methods Validation	Not Applicable		
Labeling	Adequate	18-May-2012	B. Turner
Bioequivalence	Adequate	05-July-2012	J. Walters
EA	Categorical exclusion requested	26-Aug-2010	K. Khan
Radiopharmaceutical	Not Applicable		
Pharm/Tox (2012-0668)	Adequate – per email to pharm/tox team dated 6/22/2012	29-May-2012	I. Antonipillai

III. List Of Deficiencies To Be Communicated: None

ADMINISTRATIVE

Endorsement Block

HFD-630/M. Vera/ 7/11/2012
HFD-630/V. Sayeed/

File Name and Path:

C:\Documents and Settings\veram\My Documents\Reviews in progress\ANDA 202357 Atorvastatin calcium\rev1_202357R02_Addendum1.doc

TYPE OF LETTER: Approvable

Appears this way on the original

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/s/

MATTHEW D VERA
07/13/2012

VILAYAT A SAYEED
07/13/2012

ANDA 202357

Atorvastatin Calcium Tablets, 80 mg

Dr. Reddy's Laboratories, Inc.

Matthew D. Vera, Ph.D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. ANDA 202357

2. REVIEW #: 02

3. REVIEW DATE: 05/25/2012

4. REVIEWER: Matthew D. Vera, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original	27-Sept-2010
Amendment	20-Oct-2010
Amendment	18-Mar-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD# 6, eCTD seq 0005)	2-Dec-2011
Amendment (SD# 7, eCTD seq 0006)	07-Feb-2012
Amendment (SD# 9, eCTD seq 0008)	26-Mar-2012
Amendment (SD #10, eCTD seq 0009)	11-Apr-2012
Amendment (SD #13, eCTD seq 0012)	23-May-2012
Amendment (SD #14, eCTD seq 0013	14-Jun-2012
Amendment (SD #15, eCTD seq 0014)	25-Jun-2012
Amendment (SD #16, eCTD seq 0015)	27-Jun-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Dr. Reddy's Laboratories Ltd.
Address:	Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad – 500 072, India Contact person: Zoher T. Sihorwala Head-Global Regulatory Affairs & Compliance (India Operations) Tel. No. (040) 2304 4971 Fax No. (040) 2304 5238 CFN: 9613925 FEI: 3005466224

Kimberly Ernst, Director of Regulatory Affairs
US Representative: Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd., 7th Fl., Bridgewater, NJ 08807

Telephone: 908-203-7022

Fax: 908-203-4937

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets, 80 mg
Code Name/# (ONDC only): N/A
Chem. Type/Submission Priority (ONDC only): N/A

- Chem. Type: N/A
- Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Lipitor Tablets, NDA #: 20702

Paragraph III Patent Certification re: U.S. Patent No. 4,681,893; 5,273,995 and RE40667

In accordance with Section 505(j)(2)(A)(vii)(III) and 21 CFR §314.94(a)(12)(i)(A)(3), Dr. Reddy's Laboratories Limited ("Dr. Reddy's") certifies that the following patents listed for LIPITOR® Tablet 80 mg will expire on the dates indicated below:

- US Patent No 4,681,893 – Expiry Date: Sep 24, 2009 [PED Expiry Date: Mar 24, 2010]
- US Patent No. 5,273,995 – Expiry Date: Dec 28, 2010 [PED Expiry Date: Jun 28, 2011]
- US Patent No. RE40667 – Expiry Date: Dec 28, 2010 [PED Expiry Date: Jun 28, 2011]

Dr. Reddy's will not market its Atorvastatin Calcium tablets for which this application is submitted prior to expiration of US Patent Nos. 4,681,893; 5,273,995 and RE40667

3.2 EXCLUSIVITY STATEMENT

In accordance with 21 CFR §314.94(a)(3)(ii), Dr. Reddy's Laboratories Limited is submitting this statement regarding marketing exclusivities to which the reference listed drug is entitled. Information published in "Approved Drug Products with Therapeutic Equivalence Evaluations," Electronic Version current as of August 2010, lists the following exclusivities to which the referenced listed drug is entitled:

- I-523: Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure – Expiry Date: Mar 2, 2010

Based upon the preceding statement, Dr. Reddy's Laboratories, Ltd. certifies that it has included the referenced indication in its proposed labeling and intends to launch its Atorvastatin Calcium tablets upon approval of this application, but not prior to the expiration of the PED attached to US Patent Nos. 4,681,893; 5,273,995 and RE40667.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

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

__X___Not a NANO product

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

This information is covered in detail in section 2.3.S.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
							(b) (4)
21125	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium	1	Adequate-IR	25-May-2012	M. Vera
(b) (4)	II		(b) (4)	1	Adequate-IR	27-May-2012	M. Vera
	III			4	N/A		
	III			4	N/A		
							(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)
	III			4	N/A		
							(b) (4)
	III			4	N/A		
							(b) (4)
	III			4	N/A		
	III			4	N/A		

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(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

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	25-Apr-2012	
Methods Validation	Not Applicable		
Labeling	Adequate	18-May-2012	B. Turner
Bioequivalence	Inadequate	07-June-2012	J. Walters
EA	Categorical exclusion requested	26-Aug-2010	K. Khan
Radiopharmaceutical	Not Applicable		
Pharm/Tox (2012-0668)	Adequate – per email to pharm/tox team dated 6/22/2012	29-May-2012	I. Antonipillai

19. ORDER OF REVIEW

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

Executive Summary Section

=

Chemistry Review for ANDA 202357

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Approvable

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

II. Summary of Chemistry Assessments

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

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. The 80 mg tablets are white to off- white, oval shaped , biconvex , film coated tablets debossed 'RDY' on one side and '124'on other side.

The DP is manufactured by (b) (4) The unit operations are (b) (4)

Critical Attributes of the Formulation: The manufacturing process is (b) (4) (b) (4). The DS is about (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite) are present. Mechanism of Drug Release: The dosage form consists of (b) (4)% of (b) (4), Crospovidone. The dosage form disintegrates and releases the drug simultaneously.

Drug Substance: The DS is atorvastatin calcium (b) (4) The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The (b) (4) material is not compendial, however, there is an official USP monograph for crystalline Atorvastatin Calcium.

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

The DP is intended for long term use. Thus, it is packaged in bottles, with [redacted], in 30's, 60's, 90's, 500's count, and [redacted] in bulk package of [redacted] for pharmacy. Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions

Note in Review #2: The Applicant has withdrawn [redacted].

The MDD for adults is 80 mg.

ICH Q3A: IT: 0.10%, QT: 0.15%.

ICH Q3B: IT: 0.2%, QT: [redacted]%.

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.

Note: Currently all other disciplines are acceptable/adequate except the Bio.

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

/s/

MATTHEW D VERA
06/29/2012

LAXMA R NAGAVELLI
06/29/2012
CMC Approvable at the Team Level

LEIGH A SEARS
06/29/2012

ANDA 202357

Atorvastatin Calcium Tablets, 80 mg

Dr. Reddy's Laboratories, Inc.

Khalid M. Khan
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. **ANDA 202357**

2. **REVIEW #: 01**

3. **REVIEW DATE: 08/17/2011: 09/28/2011**

4. **REVIEWER: Khalid M. Khan**

5. **PREVIOUS DOCUMENTS:**

Previous Document(s)	Document Date
None	N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	27-Sept-2010
Amendment	20-Oct-2010
Amendment	18-Mar-2011

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Dr. Reddy's Laboratories Ltd.
Address:	Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad – 500 072, India Contact person: Zoher T. Sihorwala Head-Global Regulatory Affairs & Compliance (India Operations) Tel. No. (040) 2304 4971 Fax No. (040) 2304 5238 CFN: 9613925 FEI: 3005466224
US Representative:	Kumara Sekar Dr. Reddy's Laboratories, Inc. 200 Somerset Corporate Blvd., 7th Fl., Bridgewater, NJ 08807
Telephone:	908-203-4900
Fax:	908-203-4937

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets, 80 mg
Code Name/# (ONDC only): N/A
Chem. Type/Submission Priority (ONDC only): N/A

- Chem. Type: N/A
- Submission Priority: N/A

9. LEGAL BASIS FOR SUBMISSION:

Lipitor Tablets, NDA #: 20702

Paragraph III Patent Certification re: U.S. Patent No. 4,681,893; 5,273,995 and RE40667

In accordance with Section 505(j)(2)(A)(vii)(III) and 21 CFR §314.94(a)(12)(i)(A)(3), Dr. Reddy's Laboratories Limited ("Dr. Reddy's") certifies that the following patents listed for LIPITOR® Tablet 80 mg will expire on the dates indicated below:

- US Patent No 4,681,893 – Expiry Date: Sep 24, 2009 [PED Expiry Date: Mar 24, 2010]
- US Patent No. 5,273,995 – Expiry Date: Dec 28, 2010 [PED Expiry Date: Jun 28, 2011]
- US Patent No. RE40667 – Expiry Date: Dec 28, 2010 [PED Expiry Date: Jun 28, 2011]

Dr. Reddy's will not market its Atorvastatin Calcium tablets for which this application is submitted prior to expiration of US Patent Nos. 4,681,893; 5,273,995 and RE40667

3.2 EXCLUSIVITY STATEMENT

In accordance with 21 CFR §314.94(a)(3)(ii), Dr. Reddy's Laboratories Limited is submitting this statement regarding marketing exclusivities to which the reference listed drug is entitled. Information published in "Approved Drug Products with Therapeutic Equivalence Evaluations," Electronic Version current as of August 2010, lists the following exclusivities to which the referenced listed drug is entitled:

- I-523: Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure – Expiry Date: Mar 2, 2010

Based upon the preceding statement, Dr. Reddy's Laboratories, Ltd. certifies that it has included the referenced indication in its proposed labeling and intends to launch its Atorvastatin Calcium tablets upon approval of this application, but not prior to the expiration of the PED attached to US Patent Nos. 4,681,893; 5,273,995 and RE40667.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: **Tablets**

12. STRENGTH/POTENCY: **80 mg**

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: **__X_Rx** **___OTC**

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

_____SPOTS product – Form Completed

___X___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

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

___X___Not a NANO product

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

This information is covered in detail in section 2.3.S.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
							(b) (4)
21125	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium Tablets	1	Inadequate	29-Sep-2011	by K. Khan
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
							(b) (4)
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
							(b) (4)
(b) ( )	III		(b) ( )	4	N/A		
							(b) (4)
. . . .			. . . .				
							(b) (4)
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
							(b) (4)

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(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 (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	28-Apr-2010	E. Johnson
Methods Validation	Not Applicable		
Labeling	Inadequate	14-Mar-2011	T. Vu
Bioequivalence	Pending		
EA	Categorical exclusion requested	26-Aug-2010	K. Khan
Radiopharmaceutical	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:

Executive Summary Section

=

Chemistry Review for ANDA 202357

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NA-Minor deficiencies (Review #1)

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

II. Summary of Chemistry Assessments

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

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. The 80 mg tablets are white to off- white, oval shaped , biconvex , film coated tablets debossed 'RDY' on one side and '124'on other side.

The DP is manufactured by [redacted] (b) (4). The unit operations [redacted] (b) (4) [redacted].

Critical Attributes of the Formulation: The manufacturing process is a [redacted] (b) (4) [redacted] (b) (4). The DS is about [redacted] (b) (4)% w/w of the dosage form. The PSD of the DS may be critical since this DS is "low soluble" (Class II BCS definition). The DS has large number of both synthetic and degradation impurities. Notably, the epoxide impurities and lactone impurity (which is also a metabolite) are present. Mechanism of Drug Release: The dosage form consists of [redacted] (b) (4)% of [redacted], Crospovidone. The dosage form disintegrates and releases the drug simultaneously.

Drug Substance: The DS is atorvastatin calcium [redacted] (b) (4) The DS is "low soluble" in water and the solubility decreases with increase in acidity. It is a chiral molecule with two chiral centers. The [redacted] (b) (4) material is not compendial, however, there is an official USP monograph for crystalline Atorvastatin Calcium.

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

The DP is intended for long term use. Thus, it is packaged in bottles, with [redacted] in 30's, 60's, 90's, 500's count, and [redacted], [redacted] in bulk package of [redacted] for pharmacy. Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions

The MDD for adults is 80 mg.
ICH Q3A: IT: 0.10%, QT: 0.15%.
ICH Q3B: IT: 0.2%, QT: [redacted]%.

Basis for Approvability or Not-Approval Recommendation

The application is not approvable 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/

KHALID M KHAN
10/07/2011
ANDA 202357R01 NA-Minor

LEIGH A SEARS
10/11/2011

LAXMA R NAGAVELLI
10/12/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202357		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	80 mg		
Applicant Name	Dr. Reddy's Laboratories Limited		
Applicant Address	Mailing Address: Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad - 500 072, India Factory Address: Bachepalli 502 325, India		
US Agent Name and the mailing address	Dr. Reddy's Laboratories, Inc. 200 Somerset Corporate Boulevard 7th Floor, Bridgewater, NJ 08807		
US agent's Telephone Number	Tel: 908-203-4937		
US Agent's Fax Number	Fax: 908-203-4980		
Original Submission Date(s)	27 September 2010 22 February 2011		
Submission Date(s) of Amendment(s) Under Review	29 June 2012 (current)		
First Generic (Yes or No)	No		
Reviewer	Johnetta F. Walters, Ph.D.		
Study Number (s)	10-VIN-095	09-VIN-105	
Study Type (s)	Fasting	Fed	
Strength (s)	80 mg	80 mg	
Clinical Site	**Veeda clinical research Pvt. Ltd.**	Nuvisan GmbH	
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India.	Wegenerstraße 13 89231 Neu-Ulm Germany Tel: +49 731 – 9840 151 Fax: +49 731 – 9840 355	
Analytical Site	(b) (4)		
Analytical Site Address			
OSI Status	**ADEQUATE**		
REVIEW RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Fasting**	**80 mg**	**ADEQUATE**
1	**Fed**	**80mg**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of previously submitted fasting (10-VIN-095) and fed (09-VIN-105) bioequivalence (BE) studies comparing the test product, Dr. Reddy's Atorvastatin Calcium Tablet, 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 subjects. **Both BE studies were incomplete due to four deficiencies** (1) pending OSI action, 2) low AUC values (T and R) in fasting BE study 3) no potency (assay) data on the RLD and 4) a routine DBI advice on a non-standard high-fat vegetarian breakfast in your fed study. The pharmacokinetic results of the fasting and fed studies are summarized below:

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 10-VIN-095, N=77 (Male=38, Female=39) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	120.89	109.02	1.11	104.56	117.61
AUC∞ (ng·hr/mL)	146.97	134.04	1.10	100.97	119.06
Cmax (ng/mL)	36.37	33.41	1.09	99.04	119.68

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. 09-VIN-105, N=72 (Male=72) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	260.85	294.38	0.89	85.35	91.99
AUC∞ (ng·hr/mL)	263.82	297.41	0.89	85.48	92.06
Cmax (ng/mL)	49.11	54.39	0.90	84.57	96.41

In the current submission, the firm has submitted adequate responses to each of the deficiencies.

The application is **acceptable**.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Atorvastatin Calcium Tablets, EQ. 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	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:

[1] Electronic Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last accessed: 16 April 2010.

	• Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina • **(2) Hypercholesterolemia** LIPITOR® is indicated: • as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb); • as an adjunct to diet for the treatment of patients with elevated serum TG levels*(Fredrickson* Type IV); • for the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet; • to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments (eg, LDL apheresis) or if such treatments are unavailable. • as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL or b. LDL-C remains ≥ 160 mg/dL and: - there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient

3.2 PK/PD Information[2]

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

[2] Drugs at FDA: http://www.accessdata fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 15 March 2011.

	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[3]

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:	Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to

[3] Draft Guidance on Atorvastatin Calcium: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082580.pdf. Recommended May 2008; Revised October 2010.

		the Individual Product Bioequivalence Recommendations Guidance on Progesterone Capsules

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:	Please see additional comments above
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:		Draft Guidance on Atorvastatin (Recommended May 2008; Revised Oct 2010)
Summary of OGD or DBE History		There is currently one approved generic drug product. ANDA 076477 (Ranbaxy Labs) The DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets[5]: ANDA 078773 (Teva) ANDA 077575 (Sandoz) ANDA 091226 (Matrix Labs) ANDA 090548 (Apotex) ANDA 091624 (Kudco) ANDA 091650 (Dr. Reddy's – 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	--

[4] The ortho- and parahydroxylated metabolites of atorvastatin are formed by ***presystemic metabolism*** and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

[5] DARRTS Search: Submission Search Results: http://darrts.fda.gov:7777/darrts/submissionSearch.do.

Failed Studies	No	--
Amendments	Yes	1

3.5 Formulation

Location in appendix	See earlier review in DARRTS at WALTERS, JOHNETTA F 06/07/2012 N/A 06/07/2012 REV-BIOEQ-01(General Review) Original-1 Archive for ANDA 202357
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

Location of DBE Dissolution Review	See DARRTS for ANDA 202357 at ZHANG, HONGLING 03/02/2011 N/A 03/02/2011 REV-BIOEQ-02(Dissolution Review) Original-1 Archive
Submitted Method (USP, FDA, or Firm)	FDA
Recommended Method (details below)	
Medium	0.05 M Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Specifications	NLT (b)(4)% (Q) in 30 minutes
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	S1
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 drug product
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.7 Waiver Request(s) For Immediate Release Dosage Forms

N/A - No waiver request was submitted for this ANDA.

3.8 Firm's Response to the Deficiency Comments

Deficiency Comment #1 (letter date: 15 June 2012): You have not provided the potency (assay) data of the reference listed drug (RLD) lot 04568V (80 mg). Please provide the Certificate of Analysis (COA) of the RLD lot number 04568V.

Firm's Response to Deficiency Comment #1 (No new Data): *We would like to inform the Agency that, the Certificate of Analysis (COA) for the RLD lot number 04568V was already provided in the original ANDA submission in Section 16.1.6, page 271 of fed study report and in Section 16.1.6, page 274 of fasting study report. However, a copy of the same is provided in Module 5.3.1.2 for quick reference.*

Reviewer's Comments for Deficiency Comment #1: The firm has submitted its Certificate of Analysis (COA) of the RLD lot number 04568V. The potency assay data of the RLD is within the acceptable range. Please see below. **The firm's response to this deficiency is adequate**.

Formulations
Generics

DR.REDDY'S

CERTIFICATE OF ANALYSIS
For Innovator Product

Name of the Product : Lipitor® 80 (Atorvastatin Calcium Tablets 80 mg)	
Batch No. : 04568V	Batch Size : Not Applicable
AR No. : BO01258	Ref. Specification No.: FS1224-00
Date of Manufacturing: Not Applicable	Date of Expiry : 03/2011
Date of analysis : 25 July, 2009	Page No. : 1 of 3

Sr.No.	Test	Specifications	Results
1.			(b) (4)
2			
3			
4			

Prepared by :	Checked by :	Authorised Signatory :
Date : 03-08-2009	Date : 03-08-2009	Date : 03-08-2009

Factory Address : Generics, Survey No. 41, Bachepalli 502325, Andhra Pradesh, India
Mailing Address : P.B. No. 15, Kukatpally, Hyderabad 500 072, Andhra Pradesh, India
Regd. Office : 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India
Factory : 91-40-2304 5206, Regd. Office : 91-40-23731946

FORMAT NO. : FTGQC050/F01-00

Deficiency Comment #2 (letter date: 15 June 2012): As shown in the table below, the atorvastatin CMAX and AUC values for both test and reference treatments in your current fed bioequivalence (BE) study No. 10-VIN-105 on the 80 mg tablet strength, using the dosage of 1x80 mg, were approximately two times (or greater) those determined for the fed BE study on the 40 mg strength (ANDA 091650) of both test and reference treatments (using the dosage of 1x40 mg), as expected. However, the atorvastatin CMAX and AUC values for both test and reference treatments in your current fasting BE study No. 10-VIN-095 on the 80 mg tablet strength, using the dosage of 1x80 mg, were comparable with those determined for the fasting BE study on the 40mg strength (ANDA 091650) (using the dosage of only 1x40 mg). Please explain this observed inconsistency in the pharmacokinetic (PK) results for these BE studies.

		FASTING (D=1x40 mg)	**FASTING (D=1x40 mg)**	**FED (D=1x40 mg)**	**FED (D=1x40 mg)**
91650	**REDDY**	**T**	**R**	**T**	**R**
40mg	AUCT (hr ng/mL)	125.94	130.62	107.03	113.44
Atorvastatin	AUCI (hr ng/mL)	129.25	135.96	110.65	116.6
	CMAX (ng/mL)	28.71	30.24	13.89	15.17
		FASTING (D=1x80 mg)	**FASTING (D=1x80 mg)**	**FED (D=1x80 mg)**	**FED (D=1x80 mg)**
202357	**REDDY**	**T**	**R**	**T**	**R**
80mg	AUCT (hr ng/mL)	120.89	109.02	260.85	294.38
Atorvastatin	AUCI (hr ng/mL)	125.28	113.82	263.82	297.41
	CMAX (ng/mL)	36.37	33.41	49.11	54.39

D: Dose

Firm's Response to Deficiency Comment #2 (New Data)*: We acknowledge the agency's concern on the differences observed in the pharmacokinetic results in the Bioequivalence studies conducted by DRL.*

As per US-FDA draft guidance [1] on the bioequivalence studies for atorvastatin to support ANDA for generic products stipulates the requirement to assess bioequivalence of atorvastatin under fasting and fed conditions and to provide supportive PK analysis of ortho and para hydroxy atorvastatin in general population. Dr Reddy's Laboratories Ltd. has conducted both the studies as per the IRB approved study protocol and in accordance with the applicable GCP and GLP principles.

The 90% confidence intervals for pharmacokinetic parameters i.e. Cmax, AUCo-t and AUCo-inf were evaluated for plasma Atorvastatin and are within the regulatory acceptance interval of 80.00-125.00% and the test product is bioequivalent to the reference product, the complete details of the studies are provided in ***Table-L***

As per the information available in summary basis of approval (SBOA) for the innovator product "Lipitor", the administration of Atorvastatin is associated with large variability as evidenced by percent relative standard deviation (%RSD) values for pharmacokinetic parameters ranging from 30-50%. In a study conducted to assess intra-subject and inter-subject variability, intra-subject variability accounted for 66.1% of the variability in Cmax[2].

The high inter-subject variability in pharmacokinetic parameters for atorvastatin has also been observed in subjects without renal disease. Age, gender, food intake, and level of CYP3A4 expression and activity all influence the body's handling of Atorvastatin, an important characteristic of CYP3A4 is the large inter-individual variability in activity (about 5fold), which reflects genetic polymorphism combined with modulation by environmental factors. CYP3A5 genotype has minimal effects on the pharmacokinetic parameters of atorvastatin[3]. Food decreases Cmax and AUC by 25% and 9% respectively.

The pharmacokinetic parameter values for Atorvastatin are evaluated and the details (Study no Fast# 10-VIN-095, Fed# 09-VIN-105) are presented below:

Study type		Fasting		Fed	
Study No.		10-VIN-095		09-VIN-105	
		Clinical	Bioanalytical	(b) (4)	Bioanalytical
Study Sites		Nuvisan GmbH, Germany	(b) (4)		(b) (4)
No. of Subjects		80 (77 subjects completed the study)		80 (72 subjects completed the study)	
Race		Caucasian: 77		Asian: 72	
Pharmacokinetic Parameters of Test Vs Reference					
		Test	Reference	Test	Reference
Cmax (ng/mL)	Geo.mean	36.646	33.417	49.111	54.387
	Min-Max	10.06-124.37	12.32-87.49	26.70-119.00	22.10-115.0
	CV%	61.31	42.92	39.43	38.82
AUC0-t (ng.hr/mL)	Geo.mean	120.887	109.008	260.848	294.379
	Min-Max	48.71-401.83	32.57-298.80	145.50-764.85	137.74-725.60
	CV%	49.06	48.14	38.48	35.18
AUC0-Inf (ng.hr/mL)	Geo.mean	124.713	112.920	263.997	298.056
	~~Min-Max~~	~~51.79-416.56~~	~~34.55-301.90~~	~~146.72-768.96~~	~~140.05-731.84~~
	CV%	48.47	47.32	38.20	34.86
Ratio (90% Confidence Interval)					
Cmax		109.14% (99.85 -119.28)%		90.30% (84.57- 96.41)%	
AUC0-t		111.13% (105.58- 116.96)%		88.61% (85.35-- 91.99)%	
AUC0-Inf		110.66% (105.26- 116.34)%		88.57% (85.33%- 91.93)%	

The test and reference lots used in the BE studies were of same lot numbers and the % difference in the potency of the test and reference lots was found to be (b) (4) % and (b) (4) %respectively, which is less than (b) (4) % of regulatory acceptance limit. The lot numbers of test and reference products used is tabulated below as Table-H.

Study No	Fast: 10-VIN-095 Fed: 09-VIN-105	
Product	Test (Atorvastatin)	Reference (Lipitor)
Batch/Lot No	EC9156	04568V
Potency%	(b) (4)	

*The clinical sites where the fasting and fed studies for 80 mg strength were conducted are at different locations. The number of subjects dosed in study# **10-VIN-095** was 80 (77 subjects completed the study) that included male and female subjects belonging to ethnic race of Caucasians. The number of subjects dosed in study **09-VIN-105** was 80 (72 subjects completed the study) and included only male volunteers belonging to the ethnic race of Asians. The demographics of the subjects from all the studies are provided in **Table -III.***

Table-III: Demographic Table for Atorvastatin 80mg Tablets

Strength	80mg			
	Fasting		Fed	
Study No	10-VIN-095		09-VIN-105	
Study Sites	Clinic	Bioanalytical	(b) (4)	Bioanalytical
	Nuvisan GmbH	(b) (4)		(b) (4)
Number of Subjects	80 (77 subjects completed the study)		80 (72 subjects completed the study)	
Race	Caucasian: 77		Asian: 72	
Demographics	Age: Mean (Range)	37.73 (19-54)	Age: Mean (Range)	29.32 (18-43)
	Weight Mean (Range)	70.97 (52.50-93.90)	Weight Mean (Range)	59.76 (50.40- 79.10)
	BMI: Mean (Range)	24.02 (18.79 to 29.89)	BMI: Mean (Range)	21.50 (19.02 to 24.80)
	Sex	Male:38 Female: 39	Sex	Male: 72 Female: 0

- *Dosing compliance was checked by the trained personnel as per the approved study protocol. There are no significant protocol deviations observed during the conduct of the study which would have an impact on the overall outcome of the study.*

- *The plasma samples were analyzed using validated bioanalytical methods for quantifying plasma Atorvastatin, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin.*

- *The intersubject and intra subject variability was observed very high in both the studies, approximately greater than 30%.*

- *We would like to bring to agency note that Dr Reddy's laboratories Limited had also conducted few other, two-way crossover bioequivalence studies under fasting*

state only at [redacted] *(Clinical Site- Clinical Hospital of the Ministry of Health, Moldavia) for Atorvastatin 80mg tablets respectively against Canadian and European Union reference products. These studies were conducted as per GCP and GLP requirements and met the bioequivalence requirements as per the applicable regulatory guidelines, the pharmacokinetic data was evaluated is presented below for your reference as* ***Table-IV.***

Table-IV

Study type		80 mg Fasting		80 mg Fasting	
Market		Canada		Europe	
Study No.		ATV-BESD-15-RDL/11		ATV-BESD-10-RDL/09	
		Clinical	Bioanalytical	Clinical	Bioanalytical
Study Sites		Clinical Hospital of the Ministry of Health, Moldavia	[redacted]	Clinical Hospital of the Ministry of Health, Moldavia	[redacted]
Number of Subjects		80 (80 subjects completed the study)		80 (79 subjects completed the study)	
Race		Caucasian: 80		Caucasian: 80	
Pharmacokinetic Parameters of Test Vs Reference					
		Test	Reference	Test	Reference
$Cm_{,,}$(ng/mL)	Geo.mean	59.520	55.587	49.157	49.277
	Min-Max	14.132-302.160	11.124-374.652	16.28- 596.776	19.739-244.832
	CV%	73.048	87.778	116.374	64.372
AUCo-t (ng.hr/mL)	Geo.mean	238.377	229.984	188.315	183.990
	Min-Max	77.462-808.621	66.250-1098.729	77.92 -1592.449	51.681 -665.620
	CV%	52.787	74.424	85.179	58.499
AUCo.tnr (ng.hr/mL)	Geo.mean	244.762	236.882	195.270	191.528
	Min-Max	80.989-814.589	71.925-1102.821	83.57- 1597.926	56.776 -674.067
	CV%	51.781	72.896	82.958	56.822
Ratio (90% Confidence Interval)					
$Cm_{,,}$		107.07% (94.41 - 121.44)%		99.84% (89.91 – 110.86)	
AUCo.t		103.65% (95.96 – 111.96)%		102.30 % (96.27 – 108.72)	
AUCo.tnr		103.33% (95.84 – 111.40)%		101.91 %(96.00 – 108.18)	

- *A cross study comparison of the pharrnacokinetic parameters evaluated from the studies conducted by Dr Reddy's laboratories Ltd against marketed reference products in US (study No.* ***10-VIN-095)*** ***Europe (study no ATV-BESD-10-RDL/09) and Canada (Study no ATV-BESD-15-RDL/11)*** *were provided along with the available published literature information for the PK parameters of Atorvastatin in the below mentioned table as* ***Table-V.***

It was observed the geometric means for atorvastatin when reference product was administered in study no 10-VIN-095, are comparable with the reported literature data.

Table-V

		tudies Conducted by Dr Reddy's Laboratories limited			Published literature data			
C eo.Mean omparison C		Study No. ATV-BESD-15-RDL/11 (80 mg) Canada	Study No 10-VIN-095 (80mg) US	Study No ATV-BESD-10-RDL/09 (80mg) Europe	Literature Data(EU Innovatort 80mg Fast	Literature data (EU Innovator)[5] 80mg Fast	Literaturedata (Clinicaltrials.gov)' BE Study 80mg Fast Pfizer US	Literature data (EU Innovator}' 80mgFast T-2x40 mg R-80mg Geo.Mean
Cmu (lllfmL)	Test GeoMean ±SD	59.520 ±54.230	36.346 ±26.222	49.157 ±75.544	55.55 ±22.06	40.70 ±19.36	43.17 ±31.70	29.24
	Ref GeoMean ±SD	55.587 ±62.339	33.417± 15.722	49.277 ±36.149	60.52 ±22.19	39.69 ±18.06	43.05 ±36.47	28.85
AUCo.t (nlbr/mL)	Test GeoMean ±SD	238.377 ±142.708	120.887 ±66.027	188.315 ±188.787	194.82 ±67.37	161.08 ±70.25	162.50 ±100.56	127.49
	Ref GeoMean ±SD	229.984 ±208.695	109.008 ±58.310	183.990 ±122.483	173.44 ±59.34	155.0 ±70.53	170.47 ±119.70	120.79
AUCo.oo (nlbr/mL)	Test GeoMean ±SD	244.762 ±142.999	124.713 ±67.059	195.270 ±189.239	198.12 ±67.43	166.47 ±70.37	168.13 ±100.77	131.13
	Ref GeoMean ±SD	236.882 ±208.740	112.920 ±59.152	191.528 ±122.944	177.23 ±59.48	162.85 ±68.88	176.17 ±120.18	124.03

- *The metabolite data (Ortho and Para hydroxy atorvastatin) measured in the BE study of 10- VIN-095 were also compared with the literature data which is comparable, please refer to the below mentioned table (Table VI) for reference*

Table-VI : Ortho Hydroxy and Para Hydroxy Atorvastatin Pharmacokinetic data

		Studies Conducted by Dr Reddy's Laboratories limited		Literature Data				
		Ortho-hydroxy Atorvastatin	Para-hydroxy Atorvastatin	Ortho-hydroxy	Ortho-hydroxy	Para-hydroxy	Ortho-hydroxy	Para-hydroxy
Geo.Mean Comparison		Study No 10-VIN-095 (80mg)		Literature data (EU Innovator) [5] 80 mgFast	Literature Data (EU Innovatort 80 mg Fast		Literature[8] 80mgmean (%CV)	
Cmas (n mL.)	Test GeoMean ±SD	41.632 ±31.040	1.050 ±1.740	35.88 ± 17.50	22.28 ± 9.25	1.41± 0.97	32 (60)	2 (100)
	Reference GeoMean ±SD	38.887 ±19.694	0.707 ±0.785	37.75± 21.29	21.53 ± 8.95	1.24± 1.04		
AUCo.t (DK.hr/mL.)	Test GeoMean ±SD	207.961 ±96.994	15.894 ±12.262	235.56± 97.52	137.74± 49.47	20.09± 12.34	NA	NA
	Reference GeoMean ±SD	190.553 ±82.004	11.957 ±11.433	241.57± 103.89	122.41± 45.99	17.39± 11.04		
AUCo. Inf (ng hr/mL.)	Test GeoMean ±SD	213.646 ±97.532	21.731 ±13.723	241.86± 97.49	140.95± 49.79	27.16 ±13.10	211 (43)	29 (57)
	Reference GeoMean ±SD	196.763 ±82.479	22.055 ±46.710	248.26± 103.62	126.33 ±46.47	24.90± 13.54		

We would like to inform the agency that the following points were concluded based on the review performed for both the studies:

1) As mentioned from the above referenced tables, the mean pharmacokinetic parameters values for both the Cmax and AUC parameters for the study no 10-VIN-095 was comparable with the reported literature values.

2) The 90% Confidence intervals for both Cmax and AUC were within the regulatory acceptance limits and the test product met the bioequivalence requirements against the reference product.

3) The study was conducted as per the IRB approved protocol and the regulatory guidance, though the bioanalytical site was same the clinic sites are different for study no 10-VIN-095 (fasting) and study 09-VIN-105 (fed).

4) Dosing compliance met as per protocol requirements and the study was executed m accordance with the GCP and GLP requirements.

5) A bioanalytical method that was validated as per the principles of Bioanalytical method validation guidelines was applied in quantification of Atorvastatin, ortho hydroxy atorvastatin and parahydroxy atorvastatin in human plasma.

6) High intra-subject and inter-subject variability was observed for the pharmacokinetic parameters evaluated which are as per the published reported data.

Upon cross study comparison for the pharmacokinetic parameters evaluated in the BE studies conducted using different marketed reference products against Dr Reddy's test product along with the published literature data, the difference observed for the pharmacokinetic parameters can be related to the interindividual and inter ethnic variation in drug response that can be attributed to both genetic and environmental factors. Variations in genotype for drug metabolizing enzymes, drug transporters and drug receptors are associated with interindividual and interethnic variation in drug response.

Thus, we believe that the subset of the population involved in the biostudies conducted by the Dr Reddy's Laboratories limited, across different geographies and the published literature data has shown differences in the pharmacokinetic parameter values for Atorvastatin. Nevertheless the reasons we might believe for the differences observed in the pharmacokinetic parameter values of Atorvastatin Tablets 80mg studies conducted at different geographies, the test formulation of Atorvastatin 80mg tablets manufactured by Dr Reddy's laboratories limited, India is Bioequivalent to the Lipitor 80mg and 40mg tablets respectively under fasting and fed conditions.

Reference

1) FDA Draft Guidance on Atorvastatin Calcium
http://www.fda.gov/Drugs/GuidanceComplianceRegulatorylnformation/Guidances/ucm075214.htm

2) Clinical pharmacology and Biopharmaceutics review of Lipitor, NDA: 20-702, Pg 20

3) Effect of Cytochrome P450 3A5 Genotype on Atorvastatin Pharmacokinetics and Its Interaction with
Clarithromycin
http://pharmacotherapyjoumal.org/doilabs/10.1592/phco.31.10.942

4) UK- Denmark PAR –Scientific discussion (Atorin)
http://www.hma.eu/fileadmin/dateien/pipar/dk1216atorin/pannod5dkl216atorin.pdf

5) MHRA Public Assessment Report - UK
http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/conl40577.pdf
6) Bioequivalence Study Comparing a New 80 mg Atorvastatin Tablet to 80 mg Atorvastatin Commercial tablet. (Study No. NCT00917644)
http://clinicaltrials.gov/ct2/show/results/N"CT00917644?sect=XO125#all

7) MHRA UKPAR – Pfizer (Lipitor 5, 10, 20, 40 mg Chewable tablets)

http://www.mhra.gov.uklhome/
groups/par/documents/websiteresources/conl02999.pdf

8) A randomized, open label single dose crossover study to assess effects of atorvastatin
Or Valsartan co-administration on the pharmacokinetics ofNaltrexone HCl and Bupropion HCl Sustained release tablets in healthy adult subjects. Shwan F et al
http://cdn.celerion.com/uploads/2012/0 l/Celerion AAPS 2010-A Randomized Open-Label Single-
Dose Crossover Study to Assess the Effects of Atorvastatin or Valsartan.pdf

Reviewer's Comments for Deficiency Comment #2

Based on the information presented by the firm, the reviewer agrees with the firm that subject demographics may possibly play an important role in the atorvastatin pharmacokinetic profile differences that were observed.

It is important to note that the clinical sites where the fasting and fed studies for 80 mg strength were conducted are at different locations. The number of subjects dosed in study# **10-VIN-095** was 80 (77 subjects completed the study) that included **male and female subjects** belonging to ethnic race of **Caucasians**. The number of subjects dosed in study **09-VIN-105** was 80 (72 subjects completed the study) and included **only male volunteers** belonging to the ethnic race of **Asians**. Age, gender, food intake, and level of CYP3A4 expression and activity all influence the body's handling of Atorvastatin, an important characteristic of CYP3A4 is the large inter-individual variability in activity (about 5 fold), which reflects genetic polymorphism combined with modulation by environmental factors.

It is also important to note the following:

1) As mentioned above, the mean pharmacokinetic parameters values for both the Cmax and AUC parameters for the study no 10-VIN-095 was comparable with the reported literature values.

2) The 90% Confidence intervals for both Cmax and AUC were within the regulatory acceptance limits and the test product met the bioequivalence requirements against the reference product.

3) The study was conducted as per the IRB approved protocol and the regulatory guidance, though the bioanalytical site was same the clinic sites are different for study no 10-VIN-095 (fasting) and study 09-VIN-105 (fed).

4) Dosing compliance met as per protocol requirements and the study was executed m accordance with the GCP and GLP requirements.

5) A bioanalytical method that was validated as per the principles of Bioanalytical method validation guidelines was applied in quantification of Atorvastatin, ortho hydroxy atorvastatin and parahydroxy atorvastatin in human plasma.

6) High intra-subject and inter-subject variability was observed for the pharmacokinetic parameters evaluated which are as per the published reported data.

The reviewer agrees with the firm's response. The firm's response to this deficiency is **adequate**.

Deficiency Comment #3 (letter date: 15 June 2012): Following the inspection of the clinical site, Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany, from February 15, 2010 to February 19, 2010 by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the clinical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

a. Possibility of administration of wrong medication in study subjects as the treatment information on dosing container, as well as the source records concerning all drug product selection and repacking step were not provided.

Firm's Response to Deficiency Comment #3(a): (No New Data)

The investigational products used for the atorvastatin 80mg tablets study (Number: UA098) was administered directly from the original container, which was packed and labeled in compliance with national and EU GMP requirements and also released by QP (Qualified Person). As documented in the study file Annexure IV of Module 5.3.1.2, there was no transfer to a special application container.

b. Strict fasting conditions were not assured as all the subjects have free access to outdoor areas.

Firm's Response to Deficiency Comment #3 (b): (New Information)

Subjects were confined from the afternoon before dosing until the 24 hours post-dose samples were collected in each period. Before entering the Phase I area, staff members checked the contents of the study participant's bags. Only standardized meals and beverages were served during the in-house period, according to the study specific schedule based on the protocol requirements, therefore the fasting state of the subjects was assured. The outdoor area is visible, and controlled during the day and early evening and was locked after 10 p.m. The emergency exit is monitored by video. The compliance with the drinking restrictions

was documented in the CRF. As such strict fasting conditions were maintained for the conduct of this study.

c. Study data generated for certain periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.

Firm's Response to Deficiency Comment #3(c): (No New Information)

The study specific training and delegation of the operational staff was documented in the study file for UA098 and the same is provided in Annexure V of Module 5.3.1.2.

d. Blood sample collection time points were not assured.

Firm's Response to Deficiency Comment #3(d): (No New Information)

Blood sample collection time points were assured by documenting the actual time in the blood sample collection form ofthe CRF and signing with initials by the staff member who collected the sample. As an example, one CRF is attached as Annexure 1 in Module 5.3.1.2. A list of sampling deviations record is captured in the study report 'Appendix 16.2.2.1 Sampling deviations'. The same is provided as Annexure II in Module 5.3.1.2. Only actual times were used in the pharmacokinetic and statistical analysis to establish bioequivalence.

e. Fasting condition in subjects was not assured.

Firm's Response to Deficiency Comment #3(e): (No New Information)

Subjects were confined from at least 14 hours before dosing until the 24 hours post-dose samples were collected in each period. Before entering the Phase I area, staff members checked the contents of the study participant's bags. Only standardized meals and beverages were served during the in-house period, all subjects were maintained fasted condition (overnight) for at least 10 hours before dosing on Day 1. Subjects received a standard meal at about, -12 hours prior to dosing and at 4, 8 and 12 hours after dosing in each period and complied to protocol requirements. The compliance with the drinking restrictions was documented in the individual subject case report form. As an example, CRF is attached as Annexure III in Module 5.3.1.2. Thus, strict fasting conditions were maintained for the conduct of this study.

Reviewer's Comments for Deficiency Comment #3 (a to e):
The firm's response to this deficiency is **adequate**. For future submissions, the firm should accurately provide detailed information regarding its clinical study.

Deficiency Comment #4 (letter date: 15 June 2012): Similarly, following the inspection of the analytical site, (b) (4) to by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the

analytical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

f. Failure to select appropriate concentrations for evaluating dilution linearity during validation.

Firm's Response to Deficiency Comment #4(f): (new Data)

Fed Study

During the method validation, dilution integrity of the method was evaluated by diluting the stock solution of Drug, Metabolite-1 and Metabolite-2 prepared as spiked standards at concentrations 180ng/mL, 180ng/mL and 90.0ng/mL respectively in the screened plasma. Please refer Method Validation Report No. BRD-MV-210, Page no 65-70 in Module 5.3.1.4 of the original submission.

During study sample analysis of 09-VIN-105, total 21 samples were identified for repeat analysis under the category of "Above the upper limit of quantification" (AUL) (14 samples for drug and 7 samples for metabolite-1), from that maximum concentration was observed at 127ng/mL for Metabolite-1 while for drug it was observed at 116ng/mL. Repeat analysis was performed for Drug and Metabolite -1 by applying the dilution factor of two, the highest concentrations observed for both Drug and Metabolite 1 are well below the established dilution integrity concentration (i.e.180 ng/mL). Hence, the concentration selected for dilution integrity was appropriate and can be applied to 09-VIN-105 study sample analysis.

*While reviewing the data, we observed typographical errors in 'Table 09: Reanalysis of Study Samples (Fed Study)' of the Bioequivalence Summary Tables and also in 'Table 12b: Subject Samples Repeat Analysis for Metabolite-**I'** of the bioanalytical study report. The corrected copies are provided in Module 5.3.1.4 and Module 5.3.1.2 respectively.*

Fasting Study:

For study no.: lO-VIN-095, none of samples were identified as 'Above the upper limit of quantification (AUL)', hence there is no impact on the study.

g. Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.

Firm's Response to Deficiency Comment #4(g):

During study sample analysis of 09-VIN-105 and 10-VIN-095, none of the samples were identified as "Significant Response in pre-dose", hence there is no possibility for failure to follow SOPs concerning a subject sample with significant pre-dose concentration.

Firm's Response to Deficiency Comment #4: See above (New Data).

Reviewer's Comments for Deficiency Comment #4: The reviewer agrees with the firm's response to this deficiency. The corrected tables are provided below:

Bioequivalence Study No. 09-VIN-105 Atorvastatin Calcium 80 mg tablet (fed) for Drug (Atorvastatin)

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0.0	0.0	0.00	0.00	0.0	0.0	0.00	0.00
Poor Chromatography	0.0	1	0.00	0.03	0.0	1	0.00	0.03
Improper Sample Processing (ISP)	0.0	1	0.00	0.03	0.0	1	0.00	0.03
Value Above Upper Limit of CC (AUL)	6	8	0.15	0.21	6	8	0.15	0.21
Improper / Inconsistant Internal Standard (IIS) Area	0.0	2	0.00	0.05	0.0	2	0.00	0.05
Total	6	12	0.15	0.31	6	12	0.15	0.31

Bioequivalence Study No. 09-VIN-105 Atorvastatin Calcium 80 mg tablet (fed) for Metaboite-1 (Ortho –Hydroxy Atorvastatin)

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0.0	0.0	0.00	0.00	0.0	0.0	0.00	0.00
Analytical Batch Failure	54	54	1.34	1.34	54	54	1.34	1.34
Value Above Upper Limit of CC (AUL)	0	7	0.00	0.17	0	7	0.00	0.17
Improper Sample Processing (ISP)	0	1	0.00	0.02	0	1	0.00	0.02
Improper / Inconsistant Internal Standard (IIS) Area	2	1	0.05	0.02	2	1	0.05	0.02
Total	56	63	1.39	1.55	56	63	1.39	1.55

Bioequivalence Study No. 09-VIN-105 Atorvastatin Calcium 80 mg tablet (fed) for Metaboite-2 (Para –Hydroxy Atorvastatin)

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0.0	0.0	0.00	0.00	0.0	0.0	0.00	0.00
Improper Sample Processing (ISP)	0.0	1	0.00	0.03	0.0	1	0.00	0.03
Total	0.0	1	0.00	0.03	0.0	1	0.00	0.03

Total number of sample analyzed - 4015

Deficiency Comment #5 (letter date: 15 June 2012): The DBI has noticed that you were using a non-standard high-fat vegetarian breakfast in your fed study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBI does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.

Firm's Response to Deficiency Comment #5: (New Information)

We acknowledge the agency's comment and would like to inform the Agency that, the components and composition of the high-fat, high-calorie breakfast used for fed bioequivalence study is as per FDA's guidance 'Food-Effect Bioavailability and Bioequivalence Studies'.

Fed study menu (with Vegetarian high-fat, high-calorie breakfast) was planned according to USFDA guideline and menu fulfills all requirements pertaining to guideline. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately
800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

Soya bean contains 43% protein, which is higher than in other protein-rich foods, including meat and fish which contain about 20%. The proteins of soya bean yield all the essential amino acids in adequate amounts, except methionine and cystine. Texturized soya bean protein is being increasingly used as 'artificial meat' in ready-made foods.[1]

An animal protein is called "complete protein" as it contains all essential amino acids and plant (vegetable) protein is "incomplete protein". However, soya protein is an exception to plant protein [soya protein is deficient in methionine and cystine (essential amino acids)][1]*.*[2]*. There is no known effect of methionine on absorption of drug. Based on this, "meat protein" was replaced with "soya protein" with respect to protein source as a part of high-fat, high-calorie breakfast for fed BE study. Hence, "soya bean" was used instead of"meat" as a part ofHigh-fat, high-calorie breakfast in current study.*

REFERENCES:

1. Clinical Dietetics and Nutrition; fourth edition, by F.P. Antia & Philip Abraham, OXFORD University press.

2. Food Sources ofProtein: Animal and Vegetable Protein Sources and Content; adopted from source: http://www.dietaryfiberfood.com/protein/food-sources-of-protein.php

Reviewer's Comments for Deficiency Comment #5:

For future submissions, the firm should be informed of the following regarding the meal provided for non-fasting bioequivalence studies:

We recommend that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.4 The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference. In NDAs, it is recognized that a sponsor can choose to conduct food-effect BA studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal described above.

An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity[6].

Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBI does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.

[6] Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies; http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf. December 2002.

Deficiency Comments

None

3.9 Recommendations

1. The Division of Bioequivalence I (DBI) accepts the fasting BE study (study number 10-VIN-095) conducted by Dr. Reddy's Laboratories on its Atorvastatin Calcium Tablets, 50 mg (lot # EC9156) comparing it to Pfizer, Inc.'s Lipitor® (atorvastatin calcium) Tablets (lot # 04568V).

2. The Division of Bioequivalence I (DBI) accepts the fed BE study (study number 09-VIN-105) conducted by Dr. Reddy's Laboratories on its Atorvastatin Calcium Tablets, 50 mg (lot # EC9156) comparing it to Pfizer, Inc.'s Lipitor® (atorvastatin calcium) Tablets (lot # 04568V).

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8 at 37ºC + 0.5ºC using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specification(s):

NLT (b)(4)% (Q) of Atorvastatin dissolved in 30 minutes

3.10 Comments for Other OGD Disciplines

Discipline	Comment
N/A	None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202357

APPLICANT: Dr. Reddys Laboratories

DRUG PRODUCT: Atorvastatin Calcium Tablets, 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 according to the following FDA-recommended method and specification:

Medium	0.05 M Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Specifications	NLT (b)(4)% (Q) 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: 202357

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
17278	6/29/2012	Other (REGULAR)	Study Amendment	1	1
				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
07/05/2012

SHRINIWAS G NERURKAR
07/05/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/05/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202357	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength(s)	80 mg	
Applicant Name	Dr. Reddy's Laboratories Limited	
Applicant Address	Mailing Address: Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad - 500 072, India Factory Address: Bachepalli 502 325, India	
US Agent Name and the mailing address	Dr. Reddy's Laboratories, Inc. 200 Somerset Corporate Boulevard 7th Floor, Bridgewater, NJ 08807	
US agent's Telephone Number	Tel: 908-203-4937	
US Agent's Fax Number	Fax: 908-203-4980	
Original Submission Date(s)	27 September 2010	
Submission Date(s) of Amendment(s) Under Review	22 February 2011	
First Generic (Yes or No)	No	
Reviewer	Johnetta F. Walters, Ph.D.	
Study Number (s)	10-VIN-095	09-VIN-105
Study Type (s)	Fasting	Fed
Strength (s)	80 mg	80 mg
Clinical Site	**Veeda clinical research Pvt. Ltd.**	Nuvisan GmbH
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India.	Wegenerstraße 13 89231 Neu-Ulm Germany Tel: +49 731 – 9840 151 Fax: +49 731 – 9840 355
Analytical Site	(b) (4)	
Analytical Site Address		
OSI Status	**INADEQUATE**	
REVIEW RESULT	**INADEQUATE**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Fasting**	**80 mg**	**INADEQUATE**
1	**Fed**	**80mg**	**INADEQUATE**

1 EXECUTIVE SUMMARY

The firm had submitted an ANDA 091650 for Atorvastatin Calcium Tablets (10mg, 20mg and 40mg). The Division of Bioequivalence I (DBI) has already reviewed that submission and found it acceptable on basis of 2 acceptable BE studies on the 40mg Tablet [See DARRTS for ANDA 091650 at WALTERS, JOHNETTA F 07/20/2011 N/A 07/20/2011 REV-BIOEQ-01(General Review) Original-1 Archive]. **Instead of amending the ANDA 091650 for the 80mg Tablet, the firm opted to submit this stand alone ANDA 202357 for the 80 mg Tablet.** For the comparison of formulations (the 80 mg Tablet to vs. the 40 mg Tablet) see pages 67and 68.

Bioequivalence Studies:

This application contains the results of fasting (10-VIN-095) and fed (09-VIN-105) bioequivalence (BE) studies comparing the test product, Dr. Reddy's Atorvastatin Calcium Tablet, 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 subjects. **Both BE studies are incomplete because of 4 deficiencies.** Those are 1) pending OSI action, 2) low AUC values (T and R) in fasting BE study (see page 48) and 3) no potency (assay) data on the RLD and 4) a routine DBI advice on a non-standard high-fat vegetarian breakfast in your fed study. **The DBI however will communicate only 3 deficiencies to the firm (# 2 to 4).**

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 10-VIN-095, N=77 (Male=38, Female=39) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	120.89	109.02	1.11	104.56	117.61
AUC∞ (ng·hr/mL)	146.97	134.04	1.10	100.97	119.06
Cmax (ng/mL)	36.37	33.41	1.09	99.04	119.68

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. 09-VIN-105, N=72 (Male=72) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	260.85	294.38	0.89	85.35	91.99
AUC∞ (ng·hr/mL)	263.82	297.41	0.89	85.48	92.06
Cmax (ng/mL)	49.11	54.39	0.90	84.57	96.41

The firm has measured 2 metabolites viz. orthohydroxy atorvastatin (OA) and parahydroxy atorvastatin (PA) in both BE studies. As per our practice, the metabolite data are considered supportive when point estimates of 3 PK parameters (T/R of LSM of geometric means) are within 0.8 to 1.25. In the following table the point estimates for this

ANDA 202357 are compared with the point estimates from the firm's ANDA 091650. The non supportive data are high lighted in yellow.

	Current ANDA 202357 (Reddy) For the 80 mg Tablet		ANDA 091650 (Reddy) For the 40 mg Tablet	
PK parameter	Fasting BE study	Fed BE study	Fasting BE study	Fed BE study
OA AUCt	1.09	0.89	1.01	0.93
OA AUCi	1.12	0.89	1.01	0.94
OA Cmax	1.07	0.82	0.99	0.91
PA AUCt	1.33	0.93	1.06	0.98
PA AUCi	1.02	0.90	1.07	1.02
PA Cmax	1.49	0.84	1.11	0.95

This reviewer looked at the historical PA data from 8 ANDAs in our files and found the following items:

1. In the fasting BE study on the 80 mg Tablet in ANDAs 77575 (Sandoz) and 78773 (Teva), the Cmax for PA did not meet the point estimate limit of 1.25. But both fasting BE studies were accepted due to high variability of PA.

2. In all 8 ANDAs, the PA Cmax values (1 to 3 ng/mL) were low compared to Cmax values of Atorvastatin (120 ng/mL to 300 ng/mL) and OA (150 ng/mL to 250 ng/mL).

3. The PA variability is seen only in the fasting BE study and not in the fed BE study in all three ANDAs 77575, 78773 and the current ANDA.

On the basis of these observations, this reviewer, would accept the fasting BE study, but **will communicate 3 deficiencies to the firm.**

Dissolution Testing:

The firm has conducted acceptable comparative dissolution testing on the 80 mg strength using the FDA - recommended dissolution method, (DARRTS: ANDA 202357 ZHANG, HONGLING 03/02/2011 N/A 03/02/2011 REV-BIOEQ-02(Dissolution Review) Original-1 Archive]. On 18 March 2011, the firm has acknowledged the FDA – recommended dissolution method and specification. **The dissolution testing is acceptable**.

OSI Inspection:

The 2 BE studies were conducted at 2 different Clinical Sites and were analyzed at 1 Analytical Site.
A routine inspection was completed for the clinical site (Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany) on 02/15-19/2010 for NDA 022522. The outcome was Official Action Indicated (OAI). As per OSI, a possible regulatory letter and other

follow-up decisions are still in progress. As a result, this reviewer will forward these five (5) inspection findings to the firm for further justification.

A routine inspection was requested under NDA [redacted] for the analytical site [redacted] (also used for the fed study of the current ANDA) on [redacted]. The outcome was Voluntary Action Indicated (VAI). As a result, this reviewer will also forward these two (2) inspection findings to the firm for further justification.

A routine inspection was completed under [redacted] for the clinical site [redacted] (also used for the fed study of the current ANDA) on [redacted]. The outcome was No Action Indicated (NAI).

The DBI therefore will communicate these aforementioned findings to the firm.

REVIEWER'S NOTE ON SYSTEMIC OSI FINDINGS: There are 7 systemic issues that are applicable for all ANDAs Therefore, the DBE reviewer recommends all related ANDAs that conducted BE studies at this analytical site be reviewed.

Therefore, the application is incomplete due to findings extracted from the OSI inspection report. The firm should explain these findings.

Please see sections 3.10 and 3.11 for further details regarding the OSI inspections status of all sites.

The application, however, is **incomplete**.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Atorvastatin Calcium Tablets, EQ. 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	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**

[1] Electronic Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last accessed: 16 April 2010.

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

3.2 PK/PD Information[2]

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®

[2] Drugs at FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf. Last accessed: 15 March 2011.

	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[3]

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:	Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to the Individual Product Bioequivalence Recommendations Guidance on Progesterone Capsules

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base

[3] Draft Guidance on Atorvastatin Calcium: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082580.pdf. Recommended May 2008; Revised October 2010.

Subjects:	Normal healthy males and females, general population
Additional Comments:	Please see additional comments above
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:	Draft Guidance on Atorvastatin (Recommended May 2008; Revised Oct 2010)
Summary of OGD or DBE History (for details, see Appendix 4.4):	There is currently one approved generic drug product. ANDA 076477 (Ranbaxy Labs) The DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets[5]: ANDA 078773 (Teva) ANDA 077575 (Sandoz) ANDA 091226 (Matrix Labs) ANDA 090548 (Apotex) ANDA 091624 (Kudco) ANDA 091650 (Dr. Reddy's – 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	3
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

[4] The ortho- and parahydroxylated metabolites of atorvastatin are formed by ***presystemic metabolism*** and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

[5] DARRTS Search: Submission Search Results: http://darrts.fda.gov:7777/darrts/submissionSearch.do.

3.5 Pre-Study Bioanalytical Method Validation

3.5.1 Table 4A: Bioanalytical Method Validation of Atorvastatin (Fasting Study)

Information Requested	Data			
Bioanalytical method validation report location	Appendix 16.5			
	Section 17 D, E of Appendix 10-VIN-095 Bioanalytical Report			
Analyte	Atorvastatin			
Internal standard (IS)-1 (d5 Atorvastatin)	d5 Atorvastatin			
Method description	Liquid Liquid Extraction			
Anticoagulant	K_3 EDTA			
Limit of quantitation	0.200 ng/mL			
Average recovery of drug (Atorvastatin) (%)	79.6%			
Average recovery of Internal standard-1 (d5 Atorvastatin) (%)	80.65%			
Standard curve concentrations for Drug (Atorvastatin) (ng/mL)	STD10	STD9	STD8	STD7
	0.200 ng/mL	0.400 ng/mL	1.00 ng/mL	2.00 ng/mL
	STD6	STD5	STD4	STD3
	4.00 ng/mL	10.0 ng/mL	20.0 ng/mL	40.0 ng/mL
	STD2	STD1		
	100 ng/mL	200 ng/mL		
QC concentrations for Drug (Atorvastatin) (ng/mL)	**HQC**	**MQC**	**LQC**	**LLOQ QC**
	180 ng/mL	6.32 ng/mL	0.600 ng/mL	0.200 ng/mL
QC Intraday (Within) precision range for Drug (Atorvastatin) (%)	0.26 to 1.78	0.63 to 1.03	2.51 to 2.89	4.65 to 9.33
QC Intraday (Within) accuracy range for Drug (Atorvastatin) (%)	-7.78 to -2.78	-5.85 to -4.43	-11.50 to -5.00	-13.50 to 8.00
QC Interday (Between) precision range for Drug (Atorvastatin) (%)	2.42	1.02	4.14	12.51
QC Interday (Between) accuracy range for Drug (Atorvastatin) (%)	-5.00	-5.22	-7.33	-0.50
Bench-top stability (hrs)	06 Hours at ambient temperature			
Short Term Stock Solution Stability for Drug (Atorvastatin)	44 Hours at ambient temperature for 1000µg/mL concentration in Methanol.			
Short Term Spiking Solution Stability for Drug (Atorvastatin) (ULOQ Level)	43 Hours at ambient temperature for 10000ng/mL concentration in Methanol.			
Short Term Spiking Solution Stability for Drug (Atorvastatin) (LLOQ Level)	43 Hours at ambient temperature for 10.0ng/mL concentration in Methanol.			
Short Term Stock Solution Stability for ISTD-1 (d5 Atorvastatin)	45 Hours at ambient temperature for 1000µg/mL concentration in Methanol.			

Long Term Stock Solution Stability for Drug (Atorvastatin)	20 Days at 5±3°C for 1000µg/mL concentration in Methanol.
Long Term Spiking Solution Stability for Drug (Atorvastatin) (ULOQ Level)	20 Days at 5±3°C for 10000ng/mL concentration in Methanol.
Long Term Spiking Solution Stability for Drug (Atorvastatin) (LLOQ Level)	20 Days at 5±3°C for 10.0ng/mL concentration in Methanol.
Long Term Stock Solution Stability for ISTD-1 (d5 Atorvastatin)	20 Days at 5±3°C for 1000µg/mL concentration in Methanol.
Processed stability (Wet Extract)	43 Hours at 5±3°C in formic acid in water, 0.1%v/v: Acetonitrile (10:90v/v)
Processed stability (Dry Extract)	43 Hours at -20±5°C
Freeze-thaw stability (cycles)	V Cycles at -20±5°C and -78±8°C
Long-term storage stability (days)	49 Days at -20±5°C and -78±8°C
Dilution integrity	2 fold and 10 fold
Selectivity	No interfering peaks noted in blank plasma samples

3.5.2 Table 4B: Bioanalytical Method Validation of 2-Hydroxy Atorvastatin

Information Requested	Data			
Bioanalytical method validation report location	Appendix 16.5			
	Section 17 D, E of Appendix 10-VIN-095 Bioanalytical Report			
Metabolite-1 (2-Hydroxy Atorvastatin)	2-Hydroxy Atorvastatin			
Internal standard (IS)-2 d5 2-Hydroxy Atorvastatin	d5 2-Hydroxy Atorvastatin			
Method description	Liquid Liquid Extraction			
Anticoagulant	K_3 EDTA			
Limit of quantitation	0.200 ng/mL			
Average recovery of Metabolite-1 (2-Hydroxy Atorvastatin) (%)	86.41%			
Average recovery of Internal standard-2 (d5 2-Hydroxy Atorvastatin) (%)	79.73%			
Standard curve concentrations for Metabolite-1 (2-Hydroxy Atorvastatin) (ng/mL)	STD10	STD9	STD8	STD7
	0.200 ng/mL	0.400 ng/mL	1.00 ng/mL	2.00 ng/mL
	STD6	STD5	STD4	STD3
	4.00 ng/mL	10.0 ng/mL	20.0 ng/mL	40.0 ng/mL
	STD2	STD1		
	100 ng/mL	200 ng/mL		
QC concentrations for Metabolite-1 (2-Hydroxy Atorvastatin) (ng/mL)	**HQC**	**MQC**	**LQC**	**LLOQ QC**
	180 ng/mL	6.32 ng/mL	0.600 ng/mL	0.200 ng/mL
QC Intraday (Within) precision range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	0.85 to 1.76	0.65 to 2.12	2.30 to 3.62	6.44 to 15.37
QC Intraday (Within) accuracy range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	-6.11 to -1.11	- 6.01 to - 4.43	-10.00 to -3.67	-10.00 to 0.50
QC Interday (Between) precision range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	2.86	1.45	3.92	11.96
QC Interday (Between) accuracy range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	-4.44	-5.22	-6.50	-3.00
Bench-top stability (hrs)	06 Hours at ambient temperature for metabolite-1 (2-Hydroxy Atorvastatin)			
Short Term Stock Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin)	44 Hours at ambient temperature for 1000µg/mL concentration in Methanol.			
Short Term Spiking Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin) (ULOQ Level)	43 Hours at ambient temperature for 10000ng/mL concentration in Methanol.			
Short Term Spiking Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin) (LLOQ Level)	43 Hours at ambient temperature for 10.0ng/mL concentration in Methanol.			
Short Term Stock Solution Stability for ISTD-2 (d5 2-Hydroxy Atorvastatin)	44 Hours at ambient temperature for 1000µg/mL concentration in Methanol.			

Long Term Stock Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin)	20 Days at 5±3°C for 1000µg/mL concentration in Methanol.
Long Term Spiking Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin) (ULOQ Level)	20 Days at 5±3°C for 10000ng/mL concentration in Methanol.
Long Term Spiking Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin) (LLOQ Level)	20 Days at 5±3°C for 10.0ng/mL concentration in Methanol.
Long Term Stock Solution Stability for ISTD-2 (d5 2-Hydroxy Atorvastatin)	20 Days at 5±3°C for 1000µg/mL concentration in Methanol.
Processed stability (Wet Extract)	43 Hours at 5±3°C in formic acid in water, 0.1%v/v: Acetonitrile (10:90v/v) for metabolite-1 (2-Hydroxy Atorvastatin)
Processed stability (Dry Extract)	43 Hours at -20±5°C metabolite-1 (2-Hydroxy Atorvastatin)
Freeze-thaw stability (cycles)	V Cycles at -20±5°C and -78±8°C for metabolite-1 (2-Hydroxy Atorvastatin)
Long-term storage stability (days)	49 Days at -20±5°C and -78±8°C for metabolite-1 (2-Hydroxy Atorvastatin)
Dilution integrity	2 fold and 10 fold
Selectivity	No interfering peaks noted in blank plasma samples

3.5.3 Table 4C: Bioanalytical Method Validation of 4-Hydroxy Atorvastatin

Information Requested	Data			
Bioanalytical method validation report location	Appendix 16.5			
	Section 17 D, E of Appendix 10-VIN-095 Bioanalytical Report			
Metabolite-2 (4-Hydroxy Atorvastatin)	4-Hydroxy Atorvastatin			
Internal standard (IS)-3 d5 4-Hydroxy Atorvastatin	d5 4-Hydroxy Atorvastatin			
Method description	Liquid Liquid Extraction			
Anticoagulant	K_3 EDTA			
Limit of quantitation	0.100 ng/mL			
Average recovery of Metabolite-2 (4-Hydroxy Atorvastatin) (%)	78.76%			
Average recovery of Internal standard-3 (d5 4-Hydroxy Atorvastatin) (%)	80.08%			
Standard curve concentrations for Metabolite-2 (4-Hydroxy Atorvastatin) (ng/mL)	STD10	STD9	STD8	STD7
	0.100 ng/mL	0.200 g/mL	0.500 g/mL	1.00 ng/mL
	STD6	STD5	STD4	STD3
	2.00 ng/mL	5.00 ng/mL	10.0 ng/mL	20.0 ng/mL
	STD2	STD1		
	50.0 ng/mL	100 ng/mL		
QC concentrations for Metabolite-2 (4-Hydroxy Atorvastatin) (ng/mL)	**HQC**	**MQC**	**LQC**	**LLOQ QC**
	90.0 ng/mL	3.16 ng/mL	0.300 ng/mL	0.100 ng/mL
QC Intraday (Within) precision range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	0.72 to 1.51	0.83 to 2.31	2.10 to 3.88	7.55 to 11.91
QC Intraday (Within) accuracy range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	-6.56 to -1.44	-6.01 to -3.16	-7.33 to -2.33.	1.00 to 15.00
QC Interday (Between) precision range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	2.64	1.87	3.57	11.12
QC Interday (Between) accuracy range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	-4.56	-4.75	-4.67	7.00
Bench-top stability (hrs)	06 Hours at ambient temperature for Metabolite-2 (4-Hydroxy Atorvastatin)			
Short Term Stock Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin)	44 Hours at ambient temperature for 1000µg/mL concentration in Methanol.			
Short Term Spiking Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin) (ULOQ Level)	43 Hours at ambient temperature for 5000ng/mL concentration in Methanol.			
Short Term Spiking Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin) (LLOQ Level)	43 Hours at ambient temperature for 5.00ng/mL concentration in Methanol.			
Short Term Stock Solution Stability for ISTD-3 (d5 4-Hydroxy Atorvastatin)	44 Hours at ambient temperature for 1000µg/mL concentration in Methanol.			

Long Term Stock Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin)	20 Days at 5±3°C for 1000µg/mL concentration in Methanol.
Long Term Spiking Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin) (ULOQ Level)	20 Days at 5±3°C for 5000ng/mL concentration in Methanol.
Long Term Spiking Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin) (LLOQ Level)	20 Days at 5±3°C for 5.00ng/mL concentration in Methanol.
Long Term Stock Solution Stability for ISTD-3 (d5 4-Hydroxy Atorvastatin)	20 Days at 5±3°C for 1000µg/mL concentration in Methanol.
Processed stability (Wet Extract)	43 Hours at 5±3°C in formic acid in water, 0.1%v/v: Acetonitrile (10:90v/v) for Metabolite-2 (4-Hydroxy Atorvastatin)
Processed stability (Dry Extract)	43 Hours at -20±5°C for Metabolite-2 (4-Hydroxy Atorvastatin)
Freeze-thaw stability (cycles)	V Cycles at -20±5°C and -78±8°C for Metabolite-2 (4-Hydroxy Atorvastatin)
Long-term storage stability (days)	49 Days at -20±5°C and -78±8°C for Metabolite-2 (4-Hydroxy Atorvastatin)
Dilution integrity	2 fold and 10 fold
Selectivity	No interfering peaks noted in blank plasma samples

3.5.4 Table 04 (A) Bioanalytical Method Validation (Study No. 09-VIN-105) (Fed Study) - Atorvastatin

Information Requested	Data				
Bioanalytical method validation report location	Section 16.5				
	Section 17 C of Appendix 09-VIN-105 Bioanalytical Report				
Analyte	Atorvastatin				
Internal standard (IS)-1 (d5 Atorvastatin Calcium Salt)	d_5 Atorvastatin Calcium Salt				
Type of Method	Liquid-Liquid Extraction				
Limit of quantitation for Drug	0.100ng/mL				
Average recovery of Drug (%)	88.45%				
Average recovery of ISTD-1 (%)	89.42%				
Standard curve concentrations for Drug - Atorvastatin (ng/mL)	STD-10	STD-9	STD-8	STD-7	STD-6
	0.100 ng/mL	0.200 ng/mL	0.480 ng/mL	1.20 ng/mL	3.00 ng/mL
	STD-5	STD-4	STD-3	STD-2	STD-1
	6.00 ng/mL	12.0 ng/mL	25.0 ng/mL	50.0 ng/mL	100 ng/mL
QC concentrations for Drug (Atorvastatin) (ng/mL)	**HQC**	**MQC**	**LQC**	**LLOQ QC**	
	90.0ng/mL	3.60ng/mL	0.300ng/mL	0.100ng/mL	
QC Intraday (Within) precision range for Drug (Atorvastatin) (%)	2.48 to 3.68	1.79 to 2.15	3.12 to 9.98	4.12 to 7.32	
QC Intraday (Within) accuracy range for Drug (Atorvastatin) (%)	94.47 to 104.87	92.22 to 99.72	101.20 to 108.93	93.18 to 102.96	
QC Interday (Between) precision range for Drug (Atorvastatin) (%)	5.39	4.13	6.57	7.00	
QC Interday (Between) accuracy range for Drug (Atorvastatin) (%)	100.73	97.11	104.78	98.05	
Wet Extract Stability for Drug (Atorvastatin)	For 28 hours 43 minutes at 5°C $\pm$ 3°C.				
Dry Extract Stability for Drug (Atorvastatin)	For 28 hours 57 minutes at -20°C $\pm$ 5°C.				
Freeze Thaw Stability for Drug (Atorvastatin)	3 Cycles at -20°C $\pm$ 5°C and at -78°C $\pm$ 8°C.				
Bench Top Stability for Drug (Atorvastatin)	For 10 hours 07 minutes at ambient temperature.				
Autosampler Re-Injection Reproducibility for Drug (Atorvastatin)	For 37 hours 52 minutes at 5°C $\pm$ 3°C.				
Short Term Stock Solution Stability for Drug (Atorvastatin) and ISTD-1 (d5 Atorvastatin)	For Drug, 15 hours 32 minutes at ambient temperature; For ISTD-1, 15 hours 34 minutes at ambient temperature.				
Long Term Stock Solution Stability Drug (Atorvastatin) and ISTD-1 (d5 Atorvastatin)	For 33 days at 5°C $\pm$ 3°C				
Long Term Stability of Drug in Plasma For Drug (Atorvastatin)	For 75 days at -20°C $\pm$ 5°C and at -78°C $\pm$ 8°C.				
Dilution integrity	2 fold and 10 fold				
Selectivity	No interfering peaks noted in blank plasma samples				

3.5.5 Table 04 (B) Bioanalytical Method Validation (Study No. 09-VIN-105) (Fed Study) – 2 Hydroxy Atorvastatin

Information Requested	Data				
Bioanalytical method validation report location	Section 16.5				
	Section 17 C of Appendix 09-VIN-105 Bioanalytical Report				
Metabolite-1 (2-Hydroxy Atorvastatin)	2-Hydroxy Atorvastatin				
Internal standard-2 (d5 2-Hydroxy Atorvastatin, bis Sodium Salt)	d_5 2-Hydroxy Atorvastatin, bis Sodium Salt				
Type of Method	Liquid-Liquid Extraction				
Limit of quantitation for Metabolite-1 (2-Hydroxy Atorvastatin)	0.100ng/mL				
Average recovery of Metabolite-1 (2-Hydroxy Atorvastatin) (%)	82.57%				
Average recovery of ISTD-2 (d5 2-Hydroxy Atorvastatin) (%)	92.77%				
Standard curve concentrations for Metabolite-1 (2-Hydroxy Atorvastatin) (ng/mL)	STD-10	STD-9	STD-8	STD-7	STD-6
	0.100 ng/mL	0.200 ng/mL	0.480 ng/mL	1.20 ng/mL	3.00 ng/mL
	STD-5	STD-4	STD-3	STD-2	STD-1
	6.00 ng/mL	12.0 ng/mL	25.0 ng/mL	50.0 ng/mL	100 ng/mL
QC concentrations for Metabolite-1 (2-Hydroxy Atorvastatin) (ng/mL)	**HQC**	**MQC**	**LQC**	**LLOQ QC**	
	90.0ng/mL	3.60ng/mL	0.300ng/mL	0.100ng/mL	
QC Intraday (Within) precision range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	0.93 to 1.93	0.92 to 1.48	1.68 to 3.87	0.85 to 11.80	
QC Intraday (Within) accuracy range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	95.18 to 107.80	96.00 to 102.83	101.47 to 109.80	93.28 to 97.22	
QC Interday (Between) precision range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	5.67	3.20	4.22	9.62	
QC Interday (Between) accuracy range for Metabolite-1 (2-Hydroxy Atorvastatin) (%)	102.71	100.02	105.09	95.31	
Wet Extract Stability for Metabolite-1 (2-Hydroxy Atorvastatin)	For 28 hours 43 minutes at 5°C $\pm$ 3°C.				
Dry Extract Stability for Metabolite-1 (2-Hydroxy Atorvastatin)	For 28 hours 57 minutes at -20°C $\pm$ 5°C.				
Freeze Thaw Stability for Metabolite-1 (2-Hydroxy Atorvastatin)	3 Cycles at -20°C $\pm$ 5°C and at -78°C $\pm$ 8°C.				
Bench Top Stability for Metabolite-1 (2-Hydroxy Atorvastatin)	For 10 hours 07 minutes at ambient temperature.				
Autosampler Re-Injection Reproducibility for Metabolite-1 (2-Hydroxy Atorvastatin)	For 37 hours 52 minutes at 5°C $\pm$ 3°C.				
Short Term Stock Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin) and ISTD-2 (d5 2-Hydroxy Atorvastatin)	For Metabolite-1, 15 hours 32 minute at ambient temperature; For ISTD-2 15 hours 34 minutes at ambient temperature.				

Long Term Stock Solution Stability for Metabolite-1 (2-Hydroxy Atorvastatin) and ISTD-2 (d5 2-Hydroxy Atorvastatin)	For 33 days at 5°C ± 3°C
Long Term Stability of Drug in Plasma For Metabolite-1 (2-Hydroxy Atorvastatin)	For 75 days at -20°C ± 5°C and at -78°C ± 8°C.
Dilution integrity For Metabolite-1 (2-Hydroxy Atorvastatin)	2 fold and 10 fold
Selectivity For Metabolite-1 (2-Hydroxy Atorvastatin)	No interfering peaks noted in blank plasma samples

3.5.6 Table 04 (C) Bioanalytical Method Validation (Study No. 09-VIN-105) (Fed Study) – 4 Hydroxy Atorvastatin

Information Requested	**Data**				
Bioanalytical method validation report location	Section 16.5				
	Section 17 C of Appendix 09-VIN-105 Bioanalytical Report				
Metabolite-2 (4-Hydroxy Atorvastatin)	4-Hydroxy Atorvastatin				
Internal standard-3 (d5 4-Hydroxy Atorvastatin, bis Sodium Salt)	d_5 4-Hydroxy Atorvastatin, bis Sodium Salt				
Type of Method	Liquid-Liquid Extraction				
Limit of quantitation for Metabolite-2 (4-Hydroxy Atorvastatin)	0.0500ng/mL				
Average recovery of Metabolite-2 (4-Hydroxy Atorvastatin) (%)	66.82%				
Average recovery of ISTD-3 (d5 4-Hydroxy Atorvastatin) (%)	85.41%				
Standard curve concentrations for Metabolite-2 4-Hydroxy Atorvastatin (ng/mL)	STD-10	STD-9	STD-8	STD-7	STD-6
	0.0500 ng/mL	0.100 ng/mL	0.240 ng/mL	0.600 ng/mL	1.50 ng/mL
	STD-5	STD-4	STD-3	STD-2	STD-1
	3.00 ng/mL	6.00 ng/mL	12.5 ng/mL	25.0 ng/mL	50.0 ng/mL
QC concentrations for Metabolite-2 (4-Hydroxy Atorvastatin) (ng/mL)	**HQC**	**MQC**	**LQC**	**LLOQ QC**	
	45.0ng/mL	1.80ng/mL	0.150ng/mL	0.0500ng/mL	
QC Intraday (Within) precision range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	1.15 to 4.52	1.03 to 1.68	4.13 to 5.18	10.31 to 16.08	
QC Intraday (Within) accuracy range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	92.67 to 102.53	90.56 to 100.00	96.13 to 104.93	89.68 to 94.68	
QC Interday (Between) precision range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	5.46	4.41	6.06	11.82	
QC Interday (Between) accuracy range for Metabolite-2 (4-Hydroxy Atorvastatin) (%)	99.16	95.59	101.91	91.60	
Wet Extract Stability Metabolite-2 (4-Hydroxy Atorvastatin)	For 28 hours 43 minutes at 5°C $\pm$ 3°C.				
Dry Extract Stability Metabolite-2 (4-Hydroxy Atorvastatin)	For 28 hours 57 minutes at -20°C $\pm$ 5°C.				
Freeze Thaw Stability Metabolite-2 (4-Hydroxy Atorvastatin)	3 Cycles at -20°C $\pm$ 5°C and at -78°C $\pm$ 8°C.				
Bench Top Stability Metabolite-2 (4-Hydroxy Atorvastatin)	For 10 hours 07 minutes at ambient temperature.				
Autosampler Re-Injection Reproducibility Metabolite-2 (4-Hydroxy Atorvastatin)	For 37 hours 52 minutes at 5°C $\pm$ 3°C.				
Short Term Stock Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin) and ISTD-3 (3 (d5 4-Hydroxy Atorvastatin)	For Metabolite- 2, 15 hours 34 minutes at ambient temperature For ISTD-3 15 hours 35 minutes at ambient temperature.				

Long Term Stock Solution Stability for Metabolite-2 (4-Hydroxy Atorvastatin) and ISTD-3 (3 (d5 4-Hydroxy Atorvastatin	For 33 days at 5°C ± 3°C
Long Term Stability of Drug in Plasma Metabolite-2 (4-Hydroxy Atorvastatin)	For 75 days at -20°C ± 5°C and at -78°C ± 8°C.
Dilution integrity Metabolite-2 (4-Hydroxy Atorvastatin)	2 fold and 10 fold
Selectivity Metabolite-2 (4-Hydroxy Atorvastatin)	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Comments on the Pre-Study Method Validation:

For the fasting study, study number 10-VIN-095, the firm has submitted long term storage stability (LTSS) data for a total of 49 days. The fasting study exceeds this time period (51 days). For the fed study, study number 09-VIN-105 however, the firm has submitted LTSS data for a total of 75 days. Since the samples were analyzed at the same facility and employ the same method, standard operating procedures, etc, the reviewer accepts the extended data submitted in the fed bioequivalence study for both studies. The prestudy validation data of Atorvastatin, Orthohydroxy Atorvastatin and Parahydroxy Atorvastatin are adequate.

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)	Mean Parameters (+/-SD) (%CV)						Study Report Location
					T_{max} (h)*	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	AUC_{0-inf} (ng h/mL)	Kel (1/h)	$t_{½}$ (h)	
10-VIN-095	To assess the bioequivalence between Atorvastatin Calcium 80 mg Tablets of Dr. Reddy's Laboratories Limited, India and Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland Pharmaceutical, Dublin, Ireland., in healthy, adult, human subjects under fasting condition and to monitor adverse events and ensure the safety of subjects.	An open label, balanced, randomized, two-treatment, two-period, two-way crossover oral bioequivalence study in healthy, adult, human subjects under fasting condition.	**Test Product:** Atorvastatin Calcium 80 mg Tablets administered orally. [Batch No./Lot No: EC9156]	77completing (38Male and 39 Female) Healthy subjects mean age 37.73 years (Range: 19 to 54 years)	1.250 (0.33 – 3.00)	42.771 ± 26.2223 (61.31%)	134.571 ± 66.0272 (49.06%)	138.345 ± 67.0598 (48.47%)	0.1070 ± 0.05376 (50.25%)	8.215 ± 4.4938 (54.70%)	Module 5.3.1.2, Final Report
			Reference Product: Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets administered orally. [Batch No./Lot No.: 04568V]		0.500 (0.33 – 3.00)	36.631 ± 15.7228 (42.92%)	121.132 ± 58.3106 (48.14%)	125.014 ± 59.1525 (47.32%)	0.0958 ± 0.03738 (39.01%)	8.312 ± 3.4809 (41.88%)	

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
					T_{max} (h)*	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	Kel (1/h)	$t_{½}$ (h)	
09-VIN-105	To compare and evaluate the single-dose bioequivalence study between Atorvastatin Calcium **80** mg Tablets of Dr. Reddy's Laboratories Limited, India and Lipitor ® 80mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland Pharmaceutical, Dublin, Ireland., in healthy, adult, human subjects under fed condition. To monitor the adverse events and ensure the safety of subjects.	An open label, balanced, randomized, two-treatment, two-period, two-way crossover oral bioequivalence study in healthy, adult, human subjects under fed condition.	**Test Product:** Atorvastatin Calcium 80 mg Tablets administered orally. [Batch No./Lot No: EC9156]	72completing (72M) Healthy subjects mean age 29.32 years (Range: 18 to 43 years)	4.500 (1.00 – 6.00)	52.631 ± 20.7530 (39.43)	277.641 ± 106.8265 (38.48)	280.745 ± 107.2322 (38.20)	0.0797 ± 0.02071 (25.99)	9.331 ± 2.6395 (28.29)	Module 5.3.1.2, Final Report
			Reference Product: Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets administered orally. [Batch No./Lot No.: 04568V]		3.500 (1.00 – 8.00)	58.371 ± 22.6582 (38.82)	310.991 ± 109.3917 (35.18)	314.599 ± 109.6592 (34.86)	0.0790 ± 0.02457 (31.09)	9.859 ± 4.0570 (41.15)	

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. 10-VIN-095)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (units)	120.89	109.02	1.11	104.56	117.61
AUC∞ (units)	146.97	134.04	1.10	100.97	119.06
Cmax (units)	36.37	33.41	1.09	99.04	119.68

Drug Dose (# x mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. 09-VIN-105)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (units)	260.85	294.38	0.89	85.35	91.99
AUC∞ (units)	263.82	297.41	0.89	85.48	92.06
Cmax (units)	49.11	54.39	0.90	84.57	96.41

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE? Yes

Table 3. Reanalysis of Study Samples

Fasted Study, Study No. 10-VIN-095 - Atorvastatin **Additional information in Volume(s), Page(s)**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inconsistent Internal Standard (IIS) Area	0	1	0	0.02	0	1	0	0.02
Analytical Batch Failure	52	52	1.30	1.30	52	52	1.30	1.30
Total	52	53	1.30	1.32	52	53	1.30	1.32

Fasted Study, Study No. 10-VIN-095 – Orthohydroxy Atorvastatin **Additional information in Volume(s), Page(s)**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inconsistent Internal Standard (IIS) Area	1	2	0.02	0.05	1	2	0.02	0.05
Analytical Batch Failure	26	26	0.65	0.65	26	26	0.65	0.65
Total	27	28	0.67	0.70	27	28	0.67	0.70

Fasted Study, Study No. 10-VIN-095 Parahydroxy Atorvastatin **Additional information in Volume(s), Page(s)**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inconsistent Internal Standard (IIS) Area	0	1	0	0.02	0	1	0	0.02
Analytical Batch Failure	26	26	0.65	0.65	26	26	0.65	0.65
Total	26	27	0.65	0.67	26	27	0.65	0.67

Fed Study, Study No. 09-VIN-105 - Atorvastatin **Additional information in Volume(s), Page(s)**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Poor Chromatography	0	1	0.00	0.03	0	1	0.00	0.03
Improper Sample Processing (ISP)	0	1	0.00	0.03	0	1	0.00	0.03
Value Above Upper Limit of CC (AUL)	6	8	0.15	0.21	6	8	0.15	0.21
Improper / Inconsistent Internal Standard (IIS) Area	0	2	0.00	0.05	0	2	0.00	0.05
Total	6	12	0.15	0.31	6	12	0.15	0.31

Fed Study, Study No. 09-VIN-105 – Orthohydroxy Atorvastatin **Additional information in Volume(s), Page(s)**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Value Above Upper Limit of CC (AUL)	59	56	1.52	1.44	59	56	1.52	1.44
Improper Sample Processing (ISP)	0	1	0.00	0.03	0	1	0.00	0.03
Improper / Inconsistent Internal Standard (IIS) Area	0	3	0.00	0.08	0	3	0.00	0.08
Total	59	60	1.52	1.55	59	60	1.52	1.55

Fed Study, Study No. 09-VIN-105 - Atorvastatin **Additional information in Volume(s), Page(s)**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Improper Sample Processing (ISP)	0	1	0.00	0.03	0	1	0.00	0.03
Total	0	1	0.00	0.03	0	1	0.00	0.03

Please provide detailed explanation for all repeats not related to analytical reasons. N/A

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
VIN-BRD-016 (Ver.04)	03 Jun 2010	Repeat Analysis (Fasting Study)
VIN-BRD-016 (Ver.03)	25 Aug 2008	Repeat Analysis (Fed Study)

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria: **analytical and pharmacokinetic**	Yes; No pharmacokinetic repeats
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	N/A
Did reviewer reanalyze study results?	Yes
Was the study outcome changed based on reviewer reanalysis?	No
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DBE?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Comments from the Reviewer:

- The standard operating procedure (SOP) number VIN-BRD-016, Repeat Analysis, effective date: 25 April 2008 (for fed study no. 10-VIN-095), allows for the following bioanalytical repeats: *(1) Samples lost during processing, (2) Poor chromatography, (3) Significant response in the pre-dose subject sample, (4) Value above upper limit of calibration curve, (5) Improper sample processing, (6) Improper/inconsistent internal standard area, and (7) Analytical batch failure as per SOP VIN-BRD-013 (Analytical Batch Acceptance Criteria).*

- The standard operating procedure (SOP) number VIN-BRD-016, Repeat Analysis, effective date: 25 April 2008 (for fed study no. 09-VIN-105), allows for the following bioanalytical repeats: *(1) Samples lost during processing, (2) Poor chromatography, (3) Significant response in the pre-dose subject sample, (4) Value above upper limit of calibration curve, (5) Improper sample processing, (6) Improper/inconsistent internal standard area, and (7) Analytical batch failure as per SOP VIN-BRD-013 (Analytical Batch Acceptance Criteria).*

- For all analytical related repeats mentioned above, the SOP does mention these reasons for bioanalytical repeat analysis. Subsequently, the reviewer has evaluated the criteria and agrees that they are objective. The reviewer agrees that firm conducted its repeat analysis for the fasting study (10-VIN-095) and fed study (09-VIN-105) in accordance with its SOPs. The reviewer also agrees with the firm's reasons for reanalysis.

  The Analytical Batch Acceptance Criteria SOP, SOP No. VIN-BRD-013, has provided objective criteria for accepting and rejecting an analytical batch. For example, a batch for subject 54 failed due to QCs [two-thirds of all samples outside of the acceptance criteria (ISP)]. In this case, the SOP explicitly states the following:

  - Accept the QC samples of high (HQC), middle (MQC) and low (LQC) samples, if the calculated concentrations are within ±15.00% of nominal concentrations. The same criteria are applied for the additional quality control sample (AQC) if incorporated as per specific need.
  - Accept the analytical batch, when at least two third of all QC samples (for example, four out of six) are within the acceptance criteria.

  In the case of subject 54, the firm has rejected the batch as specified in its SOP. The firm has provided objective criteria for the failure of analytical batches.

As a result, the study repeat analysis is **adequate**.

3.7 Formulation

Location in appendix	Section 0
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

Location of DBE Dissolution Review	DARRTS: ANDA 202357. REV-BIOEQ-02(Dissolution Review). 03/02/2011.
Submitted Method (USP, FDA, or Firm)	FDA
Recommended Method (details below)	
Medium	0.05 M Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Specifications	NLT (b)(4)% (Q) in 30 minutes
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	S1
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 drug product
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.9 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable[6]	N/A
Waiver regulation cited?	N/A
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	N/A

[6] For Modified Release Dosage Forms, please note waiver is not applicable

3.10 Review of OSI Inspection Reports – Fasting Study (10-VIN-095)

3.10.1 Review of OSI Inspection Reports – Clinical Site for the Fasting Study

A routine inspection was completed for the clinical site (Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany) on 02/15-19/2010 for NDA 022522. The outcome was Official Action Indicated (OAI). As per OSI, a possible regulatory letter and other follow-up decisions are still in progress. Please see the email correspondence located in the Additional Attachments section of this review.

The OSI inspection report[7] identified the following findings:

1. *For each of the 4 dosing periods, the selection of the study drugs (test drug or reference material) for all 24 subjects, and the repackaging of the study drugs from 10-tablet blister packs into 24 plastic dosage-form containers, was not documented on a line-by-line basis for each study subject. Documentation includes only a one-line general statement indicating these steps were performed and checked. This same documentation procedure has been routinely utilized for other open-label studies conducted at this clinical site.*

2. *Although this was an open-label study, the clear plastic dosage-form containers in which the drugs were dispensed were labeled only with a subject number. The dispensing container labeling did not include the name of the medication (roflumilast 500) or any indication as to whether the tablet contained therein was the test drug (D-shaped yellow tablet, formula E) or the reference drug (round white tablet, formula B). The procedure of recording only the subject number on dosing containers has been routinely utilized for open-label studies conducted at this clinic.*

3. *While being housed at the clinic, study subjects were allowed unsupervised access to a large outdoor area behind the clinic and behind an adjoining building. Study subjects could access the outdoor area through a clinic entry/exit door that was kept unlocked at all times, including during the nigh time hours. The outdoor area is enclosed with an approximately 5-ft high chain link fence, but borders a parking lot on one side, and includes a large area behind an adjoining building that is not visible to clinic staff inside the facility.*

4. *For dosing period 2, study drugs were administered by a 'sub investigator' who did not attend the study initiation meeting at the clinical site, and who has no documented study-specific training.*

5. *Study records indicate that for dosing period 3, study drug selection (test or reference drug) for each of the 24 subjects, and dose preparation for each of*

[7] DARRTS, Search: NDA 022522. CONSULT REV-OSI-01(Bioequivalence Establishment Inspection Report Review). 04/23/2010.

the 24 subjects, was performed by a study nurse qualified by the Principle Investigator (Silvia Tschabbarow). However, study records indicate the accuracy of those procedures was checked prior to dosing only by another study nurse ([redacted] (b) (6)) for whom there is no documented study specific training.

6. *For all 24 subjects, study records fail to identify who performed blood sampling for the clinical laboratory samples obtained at screening and at the end of the study.*

7. *Study records do not indicate whether subjects fasted in accordance with the requirements of protocol section 9.4 prior to PK sampling at ambulatory visits (evening visit after initial release from clinic and for clinic visits on the five subsequent days).*

8. *Study records do not identify the medications were placed into controlled clinic and inventory records were not medication stored at the clinic. time or date study access storage at the maintained for study medication stored at the clinic.*

Following the OSI inspection, OSI recommended that both the clinical portions of the study NOT be acceptable for review due to the following (clinical) issues:

1. *Possibility of administration of wrong medication in study subjects as the treatment information on dosing container, as well as the source records were concerning all drug product selection and repacking step were not provided.*
2. *Strict fasting conditions were not assured as all the subjects have free access to outdoor areas. *
3. *Study data generated for certain Periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.*
4. *Blood sample collection time points are not assured.*
5. *Fasting condition in subjects was not assured.*

As per current DBI policy, the current reviewer will forward these OSI comments to the firm without prior assessment. The OSI inspection for this site is **incomplete**.

3.10.2 Review of OSI Inspection Reports – Analytical Site for the Fasting Study

A routine inspection for was requested for [redacted] (b) (4) for the analytical site [redacted] (b) (4) The outcome was Voluntary Action Indicated (VAI).

The OSI inspection report[8] identified the following findings:

1. *Failure to select appropriate concentration for evaluating dilution linearity during validation.*

2. *Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.*

As per current DBI policy, the current reviewer will also forward these OSI comments to the firm without prior assessment. The OSI inspection for this site is **incomplete**.

3.11 Review of OSI Inspection Reports – Fed Study (09-VIN-105)

3.11.1 Review of OSI Inspection Reports – Clinical Site

A routine inspection was completed for the clinical site (b) (4) (b) (4) on for (b) (4). The outcome was No Action Indicated (NAI).

3.11.2 Review of OSI Inspection Reports – Analytical Site

See section 3.10.2 above.

3.12 Deficiency Comments

1. The atorvastatin AUC values (T and R) in the firm's fed BE study 10-VIN-105 on the 80 mg Tablet appear to be as expected (almost double) when compared to those in the fed BE study on the 40mg Tablet from the previous ANDA (091650). While the atorvastatin AUC values (T and R) in the fasting BE study 10-VIN-095 on the 80 mg Tablet appear to be the same and not as expected when compared to those in the fasting BE study on the 40mg Tablet from your ANDA 091650. The firm should explain this discrepancy which reiterated in the table below.

		FASTING	FASTING	FED	FED
91650	**REDDY**	**T**	**R**	**T**	**R**
40mg	AUCT	125.94	130.62	107.03	113.44
Atorvastatin	AUCI	129.25	135.96	110.65	116.6
202357	**REDDY**	**T**	**R**	**T**	**R**
80mg	AUCT	120.89	109.02	260.85	294.38
Atorvastatin	AUCI	125.28	113.82	263.82	297.41

[8] DARRTS, Search: NDA (b) (4). CONSULT REV-OSI-01(Bioequivalence Establishment Inspection Report Review). 07/09/2010.

2. The firm should address the following as it relates to the OSI inspections of its clinical and analytical sites of the fasting and fed bioequivalence studies.

   a) Possibility of administration of wrong medication in study subjects as the treatment information on dosing container, as well as the source records were concerning all drug product selection and repacking step were not provided.
   *b) Strict fasting conditions were not assured as all the subjects have free access to outdoor areas. *
   c) Study data generated for certain Periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.
   d) Blood sample collection time points are not assured.
   e) *Fasting condition in subjects was not assured.*
   f) *Failure to select appropriate concentration for evaluating dilution linearity during validation.*
   g) *Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.*
   h) *Failure to select appropriate concentration for evaluating dilution linearity during validation.*
   i) *Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.*

3. The firm did not provide potency (assay) data on the RLD lot number 04568V. The DBI will request for the Certificate of Analysis (COA) of the RLD lot number 04568V.

4. The DB1 has noticed that the firm is using a non-standard high-fat vegetarian breakfast in the fed BE study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DB1 does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.

3.13 Recommendations

1. The Division of Bioequivalence I (DBI) finds the fasting BE study (study number 10-VIN-095) incomplete due to the 4 deficiencies mentioned above. Dr. Reddy's Laboratories Limited conducted the fasting BE study on its Atorvastatin Calcium Tablets, 50 mg (lot # EC9156) comparing it to Pfizer, Inc.'s Lipitor® (atorvastatin calcium) Tablets (lot # 04568V).

2. The Division of Bioequivalence I (DBI) finds the fed BE study (study number 09-VIN-105) incomplete due to the deficiencies 1 and 4. Dr. Reddy's Laboratories

Limited conducted the fasting BE study on its Atorvastatin Calcium Tablets, 50 mg (lot # EC9156) comparing it to Pfizer, Inc.'s Lipitor® (atorvastatin calcium) Tablets (lot # 04568V).

3. The DBI will request for the Certificate of Analysis (COA) of the RLD lot number 04568V.

4. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.05 M Phosphate Buffer, pH 6.8 at 37ºC + 0.5ºC using USP apparatus II (Paddle) at 75 rpm. The test product should meet the following specification(s):

   NLT (b)(4)% (Q) of Atorvastatin dissolved in 30 minutes

3.14 Comments for Other OGD Disciplines

Discipline	Comment
None	N/A

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	10-VIN-095
Study Title	An open label, balanced, randomized, two-treatment, two-period, two-way crossover oral bioequivalence study of Atorvastatin Calcium 80 mg Tablets of Dr. Reddy's Laboratories Limited, India and Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland Pharmaceutical, Dublin, Ireland., in healthy adult, human subjects under fasting conditions.
Clinical Site (Name & Address)	Nuvisan GmbH Wegenerstraße 13 89231 Neu-Ulm Germany Tel: +49 731 – 9840 151 Fax: +49 731 – 9840 355
Principal Investigator	Dr. med. Margarete Müller
Dosing Dates	Period 01-09 Jul 2010 and 13 Jul 2010 Period 02-23 Jul 2010 and 27 Jul 2010
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Subject sample analysis started on 09 Aug 2010 and Subject sample analysis completed on 28 Aug 2010
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)	51 days (First Sample Collection on 09 Jul 2010 to 28 Aug 2010 Analysis completed)

Table 6. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium 80 mg Tablets	Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets

Manufacturer	Dr. Reddy's Laboratories Limited, India.	Pfizer Ireland Pharmaceutical, Dublin, Ireland.
Batch/Lot No.	EC9156	04568V
Manufacture Date	Jul 2009	NA
Expiration Date	NA	Mar 2011
Strength	80mg	80mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)		Not Provided
Content Uniformity (expressed as mean, %CV or per USP)	Mean: 100.3 %, %CV: 1.0	N/A
Dose Administered	80mg	80mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	Yes
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	(b) (4)

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled: 80** **Dosed: 80** **Completed:** 77 **Samples Analyzed:** 77 **Data Analyzed:** 77
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme (Sequence of T and R)	AB: 01. 03. 05. 08. 09. 12. 14. 15. 17. 19. 21. 23. 25. 28. 29. 32. 33. 36. 38. 39. 42. 44. 46. 48. 50. 51. 53. 55. 57. 59. 62. 63. 65, 67,69, 72, 74, 76, 77, 80 BA: 02, 04, 06, 07, 10, 11, 13, 16, 18, 20, 22, 24, 26, 27, 30, 31, 34, 35, 37, 40, 41, 43, 45, 47, 49, 52, 54, 56, 58, 60, 61, 64, 66, 68, 70, 71, 73, 75, 78, 79

Blood Sampling Times	A total of 26 blood samples were collected during each period. Pre-dose blood sample of 6.0mL (0.00 hr) was collected within one hour prior to dosing. Post dose samples of 6.0 mL were drawn 0.167, 0.333, 0.50, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours following drug administration in each period.
Blood Volume Collected/Sample	6.0 mL
Anticoagulant Used	K3EDTA
Blood Sample Processing & Storage (include storage temperature)	All the blood samples were collected in ice bath before centrifugation. After collection of blood samples from all the subjects at each time point, study-personnel centrifuged the samples at 4000 rpm for 10 minutes at 4OC (short term excursion permitted up to S°C). Centrifuged plasma was transferred into two pre labeled (Project No., Subject No., Period, Sampling time point) RIA vials containing 0.05 ml of 1M sodium phosphate (NaH2P04) buffer in an ice water bath and transferred to deep freezer at -70°C until shipment of samples to analytical site. On receipt of the samples at analytical site (b) (4) samples were stored in deep freezer at -78k8OC until analysis. In first RIA vial, 1.0 mL of plasma was transferred and in second RIA vial, 1.0 mL of plasma (duplicate sample) was transferred, if the amount is less or more than 1.0 mL then buffer was adjusted accordingly.
IRB Approval	Yes; 16 June 2010
Informed Consent	Yes; 15 June 2010
Length of Fasting	Subjects were fasting overnight from at least 10 hours before dosing on Day 1.
Length of Confinement	Subjects were confined in the clinical facility of Nuvisan GmbH at least on -14 hours till 24 hours post-dose sample collection in each of the two periods.
Safety Monitoring	Blood pressure and pulse rate were measured during screening in supine position after **3** minutes of rest using an automated blood pressure monitor. Clinical examination was done at any time during the conduct of study, if the Clinical Research Physician feels it necessary. Subjects were questioned for well being on a regular base throughout the study. Safety laboratory assessment was done predose, after end of confinement in each period and during post study assessment. Pre dose safety laboratory assessment (CK, SGOT, SGPT) was done in each period. Hematology and Biochemical parameters CK, SGOT, SGPT, Amylase, Lipase, Bilirubin, Creatinine and Urea was done 24 h after each dose at the end of the confinement in each period. Poststudy safety assessment Hematology and Biochemical parameters were done at the end of study. Forty one (41) subjects reported adverse events during the study and the adverse events were neither life threatening nor serious.

Was the study design used for the fasting BE study acceptable?	No. See the comment below

Comments on Study Design:

The study design is **inadequate**. The firm did not provide potency (assay) data on the RLD lot number 04568V. The DBI will request for the Certificate of Analysis (COA) of the RLD lot number 04568V.

4.1.1.2 Clinical Results

Table 8A. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. 10-VIN-095			
		Treatment Groups	
		Test Product N = 77	**Reference Product N = 77**
Age (years)	**Mean ± SD**	37.73 ± 9.43	37.73 ± 9.43
	Range	19-54	19-54
Age Groups	**< 18**	0 (0%)	0 (0%)
	18 – 40	44(57.14%)	44(57.14%)
	41 – 64	33(42.86%)	33(42.86%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	**Male**	38(49.35%)	38(49.35%)
	Female	39 (50.65%)	39 (50.65%)
Race	**Asian**	0(0%)	0(0%)
	Black	0 (0%)	0 (0%)
	Caucasian	77 (100%)	77 (100%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	**Mean + SD**	24.02 ± 2.40	24.02 ± 2.40
	Range	18.79 to 29.89	18.79 to 29.89
Other Factors			

Table 9. Dropout Information, Fasting Bioequivalence Study

Subject No.	**Reason**	**Period**	**Replaced?**
14	Subject was drop-out due to adverse event (Epididymitis) after treatment A (Test) administration in period 01.	01	No
27	Subject was drop-out due to adverse event (Scarlet fever) after treatment B (reference) administration in period 01.	01	No
28	Subject was drop-out due to adverse event (laboratory parameters exceed values -Increase of lipase) after treatment A (test) administration in period 01.	01	No

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. 10-VIN-095	
	Test	Reference
General		
Myalgia	1(1.26%)	-
Cold	1(1.26%)	-
Cough	1(1.26%)	-
Tiredness	2(2.53%)	2(2.56%)
Scarlet fever	-	1(1.28%)
Calf pain both sides	1(1.26%)	-
Pain at puncture site	1(1.26%)	-
Orthostasis	1(1.26%)	-
Toothache	1(1.26%)	-
Formication left forearm	-	1(1.28%)
Formication both forearms	-	1(1.28%)
Nervous System		
Headache*	13(16.45%)	06(7.69%)
Dizziness	1(1.26%)	3(3.85%)
Digestive System		
Flatulence	2(2.53%)	-
Heartburn	1(1.26%)	-
Abdominal pain	3(3.80%)	-
Nausea	1(1.26%)	-
Vomiting	2(2.53%)	-
Pasty stool	1(1.26%)	-
Queasiness	1(1.26%)	-
Watery stool	1(1.26%)	-
Urogenital System		
Epididymitis	1(1.26%)	-
Other		
Increase of creatinephosphokinase	1(1.26%)	2(2.56%)
Increase of lipase	1(1.26%)	-
Total	38 (48.10%)	16 (20.51%)

Subjects Experiencing Emesis

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
21	Test	I	19:40	12
21	Test	I	20:00	12.667

Do any of the adverse events require statistical analysis consideration (e.g. emesis)? Yes

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*? Yes
The 2 subjects therefore were not dropped from the statistical analysis.

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

The number of total adverse events with the test drug product was double that of the reference drug product. **However, those were due to commonly seen events such as headache, and GI disturbance and mild in nature. Each adverse event was resolved.** The clinician did not drop those subjects from the study. The reviewer does not expect this to alter the outcome of the study. No serious adverse events were reported.

Are there any other safety concerns based on the adverse event profile? No

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Sampling deviations*	013, 019, 026, 037, 039, 041, 043, 045, 046, 075, 077	006, 017, 018, 024, 039, 044, 056, 064, 065, 079, 080

Did dropouts/adverse events/protocol deviations affect the study outcome? No

Comments on Dropouts/Adverse Events/Protocol Deviations:

- 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.

- The dropouts and data presented above were generated in accordance with standard operating procedures (SOPs).

4.1.1.3 Bioanalytical Results

Table 12. Assay Validation – Within the Fasting Bioequivalence Study

Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.200	0.400	1.00	2.00	4.00	10.0	20.0	40.0	2 100	1 200
Inter day Precision (%CV)	3.42	3.07	2.25	2.45	2.67	2.35	2.21	2.19	2.24	2.90
Inter day Accuracy (%Actual)	-1.50	1.75	2.00	1.50	1.25	1.00	-0.50	-0.75	-2.20	-2.50
Linearity	0.200 to 200									
Linearity Range (ng/mL)	0.200									
Sensitivity/LOQ (ng/mL)	0.9926 to 0.9996									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	LQC 0.600	MQC 6.32	AQC 36.0	HQC 180
Inter day Precision (%CV)	3.53	2.19	2.37	2.58
Inter day Accuracy (%Actual)	-1.33	-0.47	-0.28	-1.11

Orthohydroxy Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.200	0.400	1.00	2.00	4.00	10.0	20.0	40.0	100	200
Inter day Precision (%CV)	3.50	3.46	1.94	1.90	2.31	1.42	1.40	1.43	1.57	1.63
Inter day Accuracy (%Actual)	-1.50	1.75	2.00	1.50	1.25	1.00	-0.50	-1.00	-2.10	-1.50
Linearity	0.200 to 200									
Linearity Range (ng /mL)	0.200									
Sensitivity/LOQ (ng /mL)	0.9967 to 0.9997									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	LQC 0.600	MQC 6.32	AQC 36.0	HQC 180
Inter day Precision (%CV)	3.94	1.79	2.01	1.87
Inter day Accuracy (%Actual)	-1.33	-1.11	-0.83	-0.56

Parahydroxy Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	0.500	1.00	2.00	5.00	10.0	20.0	50.0	1 100
Inter day Precision (%CV)	4.32	3.33	2.37	2.13	2.35	1.91	1.36	1.56	1.79	1.67
Inter day Accuracy (%Actual)	-1.10	1.50	1.20	1.00	1.00	0.40	-0.50	-1.00	-1.80	-1.10
Linearity	0.100 to 100									

Linearity Range (ng /mL)	0.100
Sensitivity/LOQ (ng /mL)	0.9952 to 0.9998

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	LQC 0.300	MQC 3.16	AQC 18.0	HQC 90.0
Inter day Precision (%CV)	3.72	1.91	1.97	1.94
Inter day Accuracy (%Actual)	-1.33	-1.27	-0.56	-0.22

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes; Subjects 59 – 74
Were chromatograms serially or randomly selected?	Serially
Were the chromatograms submitted by the firm acceptable?	Yes

Was the Study Assay Validation acceptable? Yes

Summary/Conclusions, Study Assays:

The study assay is adequate.

4.1.1.4 Pharmacokinetic Results

Table 13. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 17 and Figure 1

Fasting Bioequivalence Study, Study No. 10-VIN-095									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	134.569	49.07	48.69	401.84	121.135	48.14	32.58	298.76	1.11
AUC∞ (hr *ng/ml)	168.654	39.95	72.42	416.57	145.627	41.44	52.60	301.71	1.16
Cmax (ng/ml)	42.761	61.22	10.10	124.00	36.632	42.92	12.30	87.50	1.17
Tmax* (hr)	1.250	.	0.33	3.00	0.500	.	0.33	3.00	2.50
Kel (hr^{-1})	0.031	88.03	0.00	0.09	0.037	76.79	0.00	0.09	0.85
T1/2 (hr)	27.538	137.82	7.76	233.19	25.858	121.80	7.66	208.96	1.06

Tmax values are presented as median, range

Reviewer's Note: The Tmax range as indicated by the RLD labeling is 1-2 hours. The mean Tmax of the test drug product is 1.25, which falls within the expected range. Additionally, since this product is given on a chronic basis, the observed difference in Tmax is not considered to be of great concern with respect to safety or efficacy.

Table 14. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study, Study No. 10-VIN-095						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	121.240	77	109.102	77	111.13%	105.58% - 116.96%
AUC∞ (hr *ng/ml)	125.074	77	113.024	77	110.66%	105.26% - 116.34%
Cmax (ng/ml)	36.549	77	33.490	77	109.14%	99.85% - 119.28%

Table 15. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10-VIN-095							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	120.89	77	109.02	77	1.11	104.56	117.61
AUC∞ (hr *ng/ml)	125.28	77	113.82	77	1.10	103.87	116.62
Cmax (ng/ml)	36.37	77	33.41	77	1.09	99.04	119.68

Orthohydroxy Atorvastatin 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10-VIN-095							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	208.20	77	190.57	77	1.09	103.37	115.46
AUC∞ (hr *ng/ml)	288.29	77	258.04	77	1.12	.	.
Cmax (ng/ml)	41.71	77	38.88	77	1.07	97.30	118.26

Parahydroxy Atorvastatin 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10-VIN-095							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	15.91	77	11.95	77	1.33	117.64	150.60
AUC∞ (hr *ng/ml)	30.57	77	29.88	77	1.02	84.41	124.01
Cmax (ng/ml)	1.05	77	0.71	77	1.49	131.34	168.87

Table 16. Additional Study Information, Fasting Study No. 10-VIN-095

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	Below	
Root mean square error, AUC0-t	0.2192	
Root mean square error, AUC∞	0.2295	
Root mean square error, Cmax	0.3527	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	77	77
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and	Agree	Agree

AUC∞		
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	77	0.97	0.72*	0.99
Reference	77	0.96	0.68**	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	*There is one subject (subject 35, period II, test treatment) that has a lower ratio of AUCt/AUCi; the AUCt/AUC1 ratio of all other subjects range from 0.89-0.99. ** There is one subject (subject 41, period I, reference treatment) that has a lower ratio of AUCt/AUCi; the AUCt/AUC1 ratio of all other subjects range from 0.90-0.99.			

Was the fasting bioequivalence study acceptable? No, there are 4 deficiencies.

The atorvastatin AUC values (T and R) for the 80 mg Tablet appeared to be low. Those are high lighted in yellow. This reviewer therefore compared PK data from this fasting BE study with other studies from ANDA 091650 (40mg Tablet from Reddy) and ANDA 76477 (80mg Tablet from Ranbaxy). DBI will request firm to explain this phenomenon.

		FASTING	FASTING	FED	FED
91650	**REDDY**	**T**	**R**	**T**	**R**
40mg	AUCT	125.94	130.62	107.03	113.44
Atorvastatin	AUCI	129.25	135.96	110.65	116.6
	CMAX	28.71	30.24	13.89	15.17
	TMAX	0.83	0.67	4.5	4.5
	THALF	5.45	7.52	9.99	9.69
OA	AUCT	232.95	231.54	103.13	110.96
	AUCI	240.2	238.78	107.48	114.81
	CMAX	23.48	23.78	7.68	8.48
PA	AUCT	33.75	31.92	20.02	20.4
	AUCI	48.44	45.24	31.18	30.44
	CMAX	1.6	1.44	0.7	0.73
Analytical site					(b) (4)

202357	REDDY	T	R	T	R
80mg	AUCT	120.89	109.02	260.85	294.38
Atorvastatin	AUCI	125.28	113.82	263.82	297.41
	CMAX	36.37	33.41	49.11	54.39
	TMAX	1.25	0.5	4.5	3.835
	THALF	27.538	25.858	8.519	8.332
OA	AUCT	208.2	190.57	322.77	362.88
	AUCI	288.29	258.04	327.15	367.7
	CMAX	41.71	38.88	36.39	44.25
PA	AUCT	15.91	11.95	52.47	56.65
	AUCI	30.57	29.88	58.72	65.1
	CMAX	1.05	0.71	2.75	3.3
Analytical site		(b) (4)			

76477	RANBAXY	T	R	T	R
80mg	AUCT	202.06	191.17	197.12	203.01
	AUCI	210.42	196.88	204.84	206.46
	CMAX	53.2	51.71	34.75	40.14
	TMAX	1.5	1.3	3.35	3.08
	THALF	6.42	6.98	7.22	8.25
OA	AUCT	156.25	147.84	134.48	137.41
	AUCI	162	154.78	143.1	141.57
	CMAX	25.47	24.12	15.38	17.1
PA	AUCT	21.4	19.67	23.12	23.67
	AUCI	37.79	37.25	42.02	42.64
	CMAX	1.639	1.44	1.52	1.63
Analytical site		(b) (4)			

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

The pharmacokinetic and statistical analyses are adequate. The reviewer used the SAS code, CALCKE, for statistical analysis and verification of the data. This particular SAS code allows the reviewer to select the values which are used as the time points to calculate the elimination rate constant, K_{EL} (Note: AUCI and THALF are dependent variables), along with other PK parameters. The following time points were selected to calculate the K_{EL}:

Ke first: T19 (8 hours)

Ke last: T22 (16 hours)

The firm has also analyzed the data of seventy-seven subjects. The reviewer agrees with the firm's assessment.

The firm has measured 2 metabolites viz. orthohydroxy atorvastatin (OA) and parahydroxy atorvastatin (PA) in both BE studies. As per the DBI practice, the metabolite data are considered supportive when point estimates of 3 PK parameters (T/R of LSM of geometric means) are within 0.8 to 1.25. In the following table the point estimates for this ANDA 202357 are compared with the point estimates from the firm's ANDA 091650. The non supportive data are high lighted in yellow.

	Current ANDA 202357 (Reddy) For the 80 mg Tablet		ANDA 091650 (Reddy) For the 40 mg Tablet	
PK parameter	Fasting BE study	Fed BE study	Fasting BE study	Fed BE study
OA AUCt	1.09	0.89	1.01	0.93
OA AUCi	1.12	0.89	1.01	0.94
OA Cmax	1.07	0.82	0.99	0.91
PA AUCt	1.33	0.93	1.06	0.98
PA AUCi	1.02	0.90	1.07	1.02
PA Cmax	1.49	0.84	1.11	0.95

This reviewer looked at the historical PA data from 8 ANDAs in our files and found the following items:

1. In the fasting BE study on the 80 mg Tablet in ANDAs 77575 (Sandoz) and 78773 (Teva), the Cmax for PA did not meet the point estimate limit of 1.25. But both fasting BE studies were accepted due to high variability of PA.

2. In all 8 ANDAs, the PA Cmax values (1 to 3 ng/mL) were low compared to Cmax values of Atorvastatin (120 ng/mL to 300 ng/mL) and OA (150 ng/mL to 250 ng/mL).

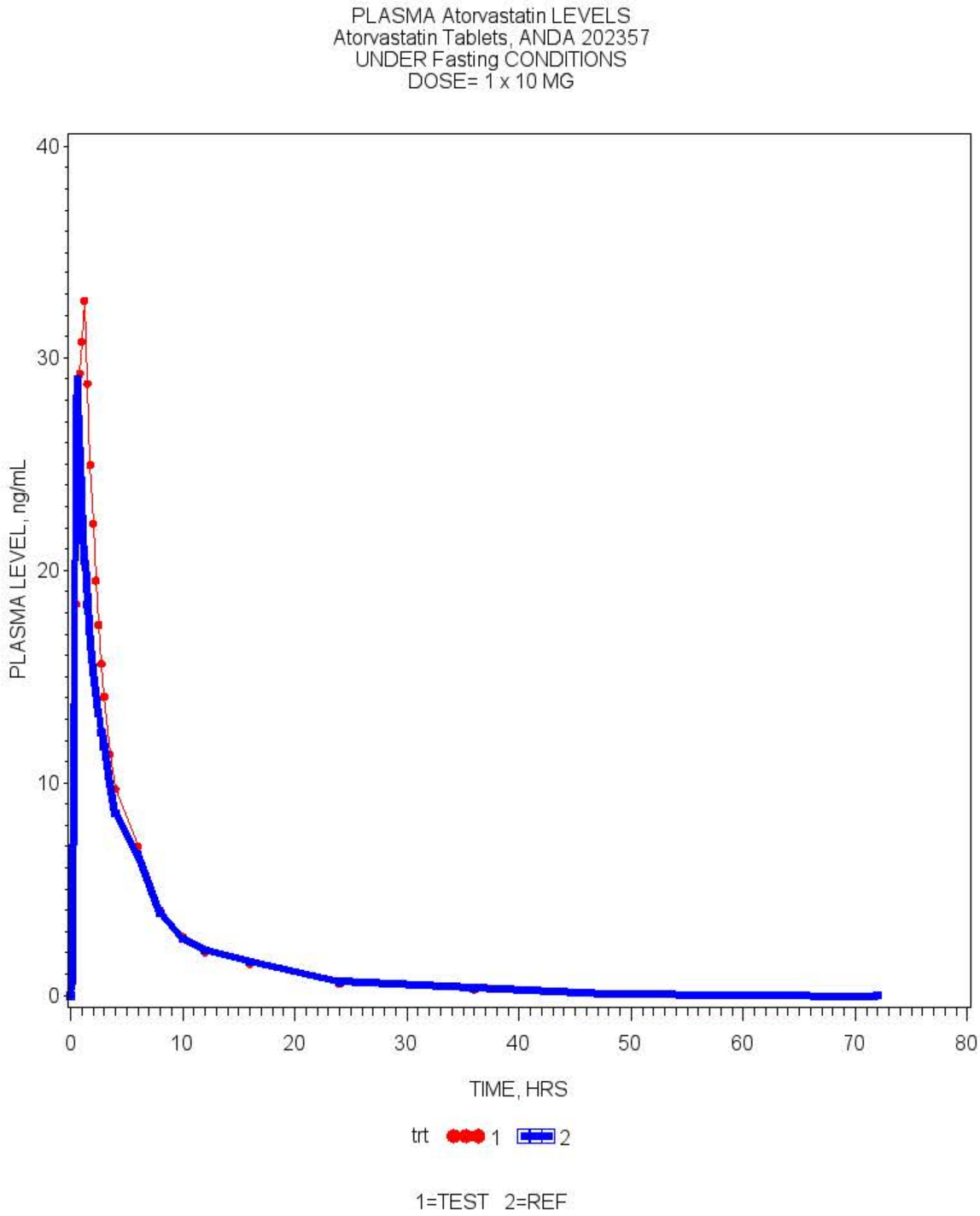
3. The PA variability is seen only in the fasting BE study and not in the fed BE study in all three ANDAs 77575, 78773 and the current ANDA.

On the basis of these observations, this reviewer, accepts the fasting BE study,

Table 17. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n= 77)		Reference (n= 77)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.64	140.18	0.73	193.47	0.88
0.33	8.97	104.87	13.55	88.00	0.66
0.50	18.42	75.01	27.42	58.67	0.67
0.67	24.36	75.97	28.99	52.62	0.84
0.83	29.27	77.80	25.60	53.21	1.14
1.00	30.75	72.93	23.31	55.62	1.32
1.25	32.69	72.28	20.45	58.79	1.60
1.50	28.78	63.89	18.40	58.59	1.56
1.75	24.96	59.71	16.47	57.83	1.52
2.00	22.20	55.55	15.28	60.68	1.45
2.25	19.52	54.14	14.31	67.69	1.36
2.50	17.44	52.94	13.29	71.72	1.31
2.75	15.61	53.26	12.37	69.86	1.26
3.00	14.06	50.20	11.72	79.95	1.20
3.50	11.35	48.42	9.97	78.17	1.14
4.00	9.71	46.69	8.57	80.84	1.13
6.00	7.00	47.55	6.64	50.91	1.05
8.00	4.00	54.31	3.87	52.61	1.03
10.00	2.76	61.78	2.67	56.92	1.04
12.00	2.05	65.51	2.13	69.17	0.96
16.00	1.51	71.26	1.59	64.90	0.95
24.00	0.56	96.63	0.65	77.93	0.87
36.00	0.28	122.01	0.35	89.80	0.80
48.00	0.08	247.60	0.09	200.13	0.82
72.00	0.01	555.57	0.01	650.60	1.50

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 18. Study Information

Study Number	09-VIN-105
Study Title	An open label, balanced, randomized, two-treatment, two-period, two-way crossover oral bioequivalence study of Atorvastatin Calcium 80 mg Tablets of Dr. Reddy's Laboratories Limited, India and Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland Pharmaceutical, Dublin, Ireland., in healthy adult, human subjects under fed conditions
Clinical Site (Name & Address)	**Veeda clinical research Pvt. Ltd.** Shivalik Plaza – A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India. Phone: +91-79-3001 3000
Principal Investigator	Dr. Dharmesh Domadia
Dosing Dates	12 Aug 2009 and 26 Aug 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	03 Sep 2009 to 16 Sep 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)	36 days (First Sample Collection on 12 Aug 2009 to 16 Sep 2009 Analysis completed on)

Table 19. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Atorvastatin Calcium 80 mg Tablets	Lipitor® 80 mg (Containing Atorvastatin Calcium) Tablets
Manufacturer	Dr. Reddy's Laboratories Limited, India.	Pfizer Ireland Pharmaceutical, Dublin, Ireland.
Batch/Lot No.	EC9156	04568V
Manufacture Date	Jul 2009	NA
Expiration Date	NA	Mar 2011

Strength	80mg	80mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)		Not Provided
Content Uniformity (expressed as mean, %CV or per USP)	Mean: 100.3 %, %CV: 1.0	N/A
Dose Administered	80mg	80mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling?	Yes
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	(b) (4)

Table 20. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	**Enrolled: 80** **Dosed: 80** **Completed:72** **Samples Analyzed: 72** **Data Analyzed: 72**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme (Sequence of T and R)	AB; 02, 04, 06, 08, 09, 11, 14, 16, 18, 19, 21, 22, 25, 28, 29, 31, 34, 36, 37, 39, 41, 42, 46, 48, 49, 52, 55, 56, 57, 59, 61, 63, 65, 68, 71, 72, 74, 75, 77, 78 BA: 01, 03, 05, 07, 10, 12, 13, 15, 17, 20, 23, 24, 26, 27, 30, 32, 33, 35, 38, 40, 43, 44, 45, 47, 50, 51, 53, 54, 58, 60, 62, 64, 66, 67, 69, 70, 73, 76, 79, 80
Blood Sampling Times	Pre-dose blood sample of 5.0mL (0.00 hr) was collected within one hour prior to dosing. Post dose samples of 5.0mL were drawn 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours following drug administration in each period.
Blood Volume Collected/Sample	5.0 mL
Anticoagulant Used	K_3EDTA

Blood Sample Processing & Storage (include storage temperature)	All the blood samples were collected in ice bath. After collection of blood samples from all the subjects at each time point, one study-personnel centrifuged the samples at 4000 rpm for 10 minutes at 4'C (short term excursion permitted up to 8'~). Transfer centrifuged plasma into two pre labeled (Project No., Subject No., Period, Sampling time point and Sample code) cry0 vials containing 0.05 ml of 1M sodium phosphate (NaH2P04) buffer in an ice water bath and transferred to deep freezer at -70'~ until analysis. In first cry0 vial, approximately 1 mL of plasma was transferred and in second cryo vial, 1.0 mL of plasma (duplicate sample) was transferred, if the amount was less or more than one mL then buffer were adjusted accordingly(Refer to section 10.2.3 for protocol deviation).
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Subjects were fasting overnight from at least 10 hours before scheduled time for start of high-fat high-calorie breakfast on Day 0.
Length of Confinement	Upon entering into the study, the subjects were housed in the clinical facility of Veeda clinical research Pvt. Ltd. on Day -3 till 24 hours post-dose sample collection in each of the two periods.
Safety Monitoring	Blood pressure and pulse rate were measured during screening in supine position after **3** minutes of rest using an automated blood pressure monitor. Clinical examination was done at any time during the conduct of study, if the Clinical Research Physician feels it necessary. Subjects were questioned for well being on a regular base throughout the study. Safety laboratory assessment was done predose, after end of confinement in each period and during post study assessment. Pre dose safety laboratory assessment (CK, SGOT, SGPT) was done in each period. Hematology and Biochemical parameters CK, SGOT, SGPT, Amylase, Lipase, Bilirubin, Creatinine and Urea was done 24 h after each dose at the end of the confinement in each period. Poststudy safety assessment Hematology and Biochemical parameters were done at the end of study. Six (6) subjects reported adverse events during the study and the adverse events were neither life threatening nor serious.

Standard FDA Meal Used?	No	
If No, then meal components and composition is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	55.94	518.3
Carbohydrate	27.5	254.8
Protein	16.56	153.4
Total		926.5

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study	
Component	**Calories**
Buttered bread with cheese	245.2
Whole Milk	257.8
Soya Cutlet	423.5
Total	926.5

Was the study design used for the fed BE study acceptable?	No. The see comment below

Comments on Study Design:

Was the study design used for the fed BE study acceptable?	No; 1) The firm has used a non-standard high-fat vegetarian breakfast in its fed study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBE does not encourage the use of vegetarian breakfasts for fed bioequivalence studies and 2) The firm did not provide potency (assay) data on the RLD lot number 04568V. The DBI will request for the Certificate of Analysis (COA) of the RLD lot number 04568V.

4.1.2.2 Clinical Results

Table 21A. Demographics Profile of Subjects Completing the Bioequivalence Study

		Fed Bioequivalence Study No. 09-VIN-105	
		Treatment Groups	
		Test Product N = 72	Reference Product N = 72
Age (years)	Mean ± SD	29.32 ± 6.26	29.32 ± 6.26
	Range	18-43	18-43
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	70(97.22%)	70(97.22%)
	41 – 64	2(2.78%)	2(2.78%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	72(100%)	72(100%)
	Female	0 (0%)	0 (0%)
Race	Asian	72(100%)	72(100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean + SD	21.50 ± 1.92	21.50 ± 1.92
	Range	19.02 to 24.80	19.02 to 24.80
Other Factors			

Table 22. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
15	Self Withdrawn-before dosing in period 01 He was withdrawn at 10:41 hours without any treatment.	01	No
14	Withdrawn - adverse event He was withdrawn at 09:30 hours for treatment A (Test).	01	No
25	Withdrawn - adverse event He was withdrawn at 09:24 hours for treatment A (Test).	01	No

55	Withdrawn - adverse event He was withdrawn at 09:51 hours for treatment A (Test).	01	No
73	Withdrawn - adverse event He was withdrawn at 09:30 hours for treatment B (reference).	01	No
60	Drop out-did not reported to the facility for period 02 admission He was withdrawn at 19:01 hours for treatment B (reference).	02	No
71	Withdrawn - found positive in urine screen for drugs of abuse He was withdrawn at 19:01 hours for treatment A (Test).	02	No
47	Withdrawn - adverse event He was withdrawn at 22:04 hours for treatment B (reference).	02	No

Table 23. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups Study No. 09-VIN-105	
	Test	Reference
Gastrointestinal		
Emesis*	3(3.95%)	1 (1.33%)
Abdominal Pain	1 (1.36%)	-
Etc.	--	--
Other organ sys.		
P.Vivax Malaria	-	1 (1.33%)
TOTAL	4(5.31%)	2 (2.66%)

Subjects Experiencing Emesis

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
25	A	I	9:24	0.4
73	B	I	9:30	0.3
14	A	I	9:30	0.5
55	A	I	9:51	0.75

Do any of the adverse events require statistical analysis consideration (e.g. vomiting)? Yes

If yes, does the time exceed the Tmax limit according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*? No. The subjects were subsequently excluded from statistical analysis.

Was the adverse event profile observed during the fed bioequivalence study the same for the test and reference product? Yes

Table 24. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Sampling deviations*	18, 65, 68, 71, 72	05, 19, 60, 67, 70, 72, 77
Other Deviation	^	^

Did dropouts/adverse events/protocol deviations affect the study outcome?
No

Comments on Dropouts/Adverse Events/Protocol Deviations:

- Subjects 14, 25, 55, an 73 were dropped from the study during period I after experiencing emesis within two times the median Tmax following administration of the test (14, 25, and 55) and reference (73) drug products.

- 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 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.

- The dropouts and data presented above were generated in accordance with standard operating procedures (SOPs).

4.1.2.3 Bioanalytical Results

Table 225. Assay Validation – Within the Fed Bioequivalence Study

Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	0.480	1.20	3.00	6.00	12.0	25.0	50.0	100
Inter day Precision (%CV)	4.07	3.33	2.68	2.36	2 34	2.62	2 33	2.6	2.74	2.62
Inter day Accuracy (%Actual)	98.90	100.5	102.7	104.2	101.7	101.2	99.2	100.0	95.60	96.20
Linearity	0.100 to 100									
Linearity Range (ng/mL)	0.100									
Sensitivity/LOQ (ng/mL)	0.9951 to 0.9994									

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	LQC 0.300	MQC 3.60	AMQC 10.0	DIL HQC 90.0	HQC 90.0
Inter day Precision (%CV)	3.72	2.73	3.02	0.51	2.71
Inter day Accuracy (%Actual)	91.33	94.44	92.50	92.11	91.89

Orthohydroxy Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.10	0.20	0.48	1.20	3.00	6.00	12.0	25.0	50.0	100
Inter day Precision (%CV)	4.38	4.25	2.89	2.02	1.89	1.79	1.37	1.54	1.54	1.68
Inter day Accuracy (%Actual)	98.90	100.50	102.92	103.33	101.33	100.50	99.17	100.00	95.80	97.30
Linearity	0.100 to 100									
Linearity Range (ng/mL)	0.100									
Sensitivity/LOQ (ng/mL)	0.9964 to 0.9993									

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	LQC 0.300	MQC 3.60	AMQC 10.0	DIL HQC 90.0	HQC 90.0
Inter day Precision (%CV)	3.34	2.13	1.89	0.84	1.74
Inter day Accuracy (%Actual)	101.67	104.44	105.00	103.44	102.78

Parahydroxy Atorvastatin										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.05	0.10	0.24	0.60	1.50	3.00	6.00	12.5	25.0	50.0
Inter day Precision (%CV)	4.69	4.05	2.78	2.27	1.88	1.85	1.48	1.56	1.49	1.65
Inter day Accuracy (%Actual)	96.40	106.00	102.50	103.00	101.33	101.00	99.67	98.40	95.60	96.40

Linearity	0.0500 to 50.0
Linearity Range (ng/mL)	0.0500
Sensitivity/LOQ (ng/mL)	0.9954 to 0.9991

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	LQC 0.150	AMQC 0.500	MQC 1.80	DIL HQC 45.0	HQC 45.0
Inter day Precision (%CV)	4.28	2.51	2.19	0.67	1.70
Inter day Accuracy (%Actual)	92.00	96.40	95.00	93.78	93.78

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially; Subjects 53-74
Were the chromatograms submitted by the firm acceptable?	Yes

Was the Study Assay Validation acceptable? Yes

Summary/Conclusions, Study Assays:

The chromatograms are adequate.

Table 236. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	**Effective Date of SOP**	**SOP Title**
VIN-BRD-016 (Ver.03)	25 Aug 2008	Repeat Analysis

Table 247. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

The study assay is adequate.

4.1.2.4 Pharmacokinetic Results

Table 28. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 2 and Figure 3

Fed Bioequivalence Study, Study No. 09-VIN-105									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	277.641	38.48	145.50	764.85	310.991	35.18	137.74	725.60	0.89
AUC∞ (hr *ng/ml)	280.534	38.19	146.81	769.18	313.912	34.89	140.05	730.32	0.89
Cmax (ng/ml)	52.631	39.43	26.70	119.00	58.371	38.82	22.10	115.00	0.90
Tmax* (hr)	4.500	.	1.00	6.00	3.835	.	1.00	8.00	1.17
Kel (hr^{-1})	0.087	21.94	0.03	0.12	0.086	17.65	0.04	0.12	1.01
T1/2 (hr)	8.519	30.91	5.60	20.70	8.332	21.38	5.58	15.95	1.02

* Tmax values are presented as median, range

Table 29. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study, Study No. 09-VIN-105						
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	260.848	72	294.379	72	88.61%	85.35% - 91.99%
AUC∞ (hr *ng/ml)	263 997	72	298.056	72	88.57%	85.33% - 91.93%
Cmax (ng/ml)	49.111	72	54.387	72	90.30%	84.57% - 96.41%

Table 250. 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. 09-VIN-105						
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	260.85	72	294.38	72	0.89	85.35 - 91.99
AUC∞ (hr *ng/ml)	263.82	72	297.41	72	0.89	85.48 - 92.06
Cmax (ng/ml)	49.11	72	54.39	72	0.90	84.57 - 96.41

Orthohydroxy Atorvastatin 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 09-VIN-105							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	322.77	72	362.88	72	0.89	86.52	91.44
AUC∞ (hr *ng/ml)	327.15	72	367.70	72	0.89	86.55	91.46
Cmax (ng/ml)	36.39	72	44.25	72	0.82	78.03	86.66

Parahydroxy Atorvastatin 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 09-VIN-105							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	52.47	72	56.65	72	0.93	88.67	96.75
AUC∞ (hr *ng/ml)	58.72	72	65.10	72	0.90	84.88	95.84
Cmax (ng/ml)	2.75	72	3.30	72	0.84	78.82	88.66

Table 31. Additional Study Information, Fed Study No. 09-VIN-105

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	See below	
Root mean square error, AUC0-t	0.1349	
Root mean square error, AUC∞	0.1334	
Root mean square error, Cmax	0.2358	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	72	72
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	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
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	72	0.99	0.96	1.00
Reference	72	0.99	0.97	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Was the fed bioequivalence study acceptable? Yes

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

The pharmacokinetic and statistical analyses are adequate. The reviewer used the SAS code, CALCKE, for statistical analysis and verification of the data. This particular SAS code allows the reviewer to select the values which are used as the time points to calculate the elimination rate constant, K_{EL} (Note: AUCI and THALF are dependent variables), along with other PK parameters. The following time points were selected to calculate the K_{EL}:

Ke first: T22 (12 hours)

Ke last: T25 (36 hours)

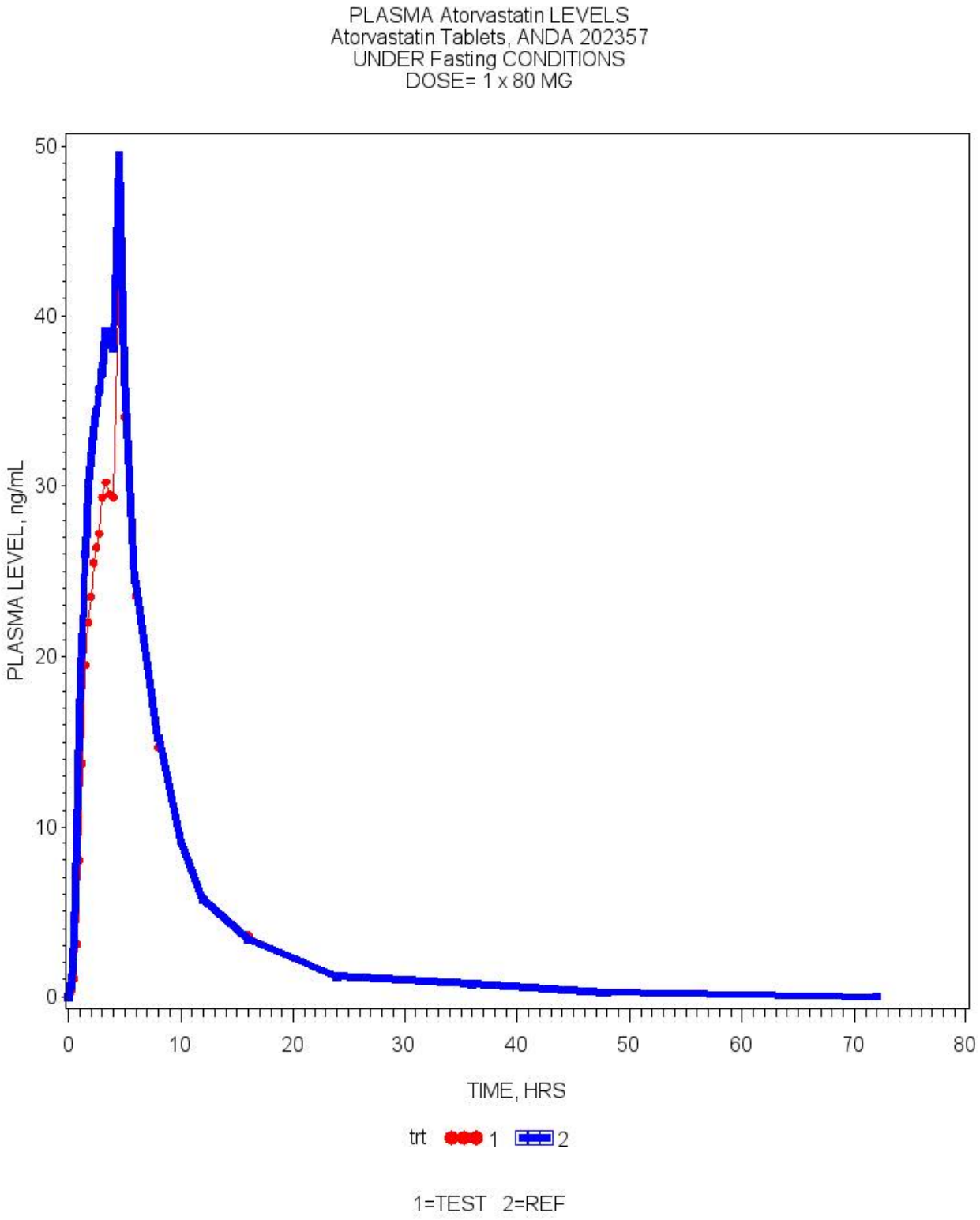
The firm has also analyzed the data of seventy-two subjects. The reviewer agrees with the firm's assessment.

The 90% confidence intervals for LCmax of the active metabolites, orthohydroxy atorvastatin (OA) and parahydroxy atorvastatin (PA) , were not within the suggested BE limits of 80.00% - 125.00% but the point estimates for the LCamx of OA and PA were within the limits of 0.8 to 1.25 and thus may be considered supportive.

Table 32. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n= 72)		Reference (n= 72)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	0.35	109.68	0.61	253.37	0.58
0.50	1.09	182.49	3.61	167.94	0.30
0.75	3.10	232.14	9.32	148.25	0.33
1.00	8.02	203.50	16.36	115.33	0.49
1.25	13.75	150.80	21.17	98.03	0.65
1.50	19.54	101.53	26.01	82.41	0.75
1.75	22.03	86.71	29.99	74.47	0.73
2.00	23.51	81.25	31.55	68.01	0.75
2.25	25.52	72.43	33.24	62.96	0.77
2.50	26.42	62.85	34.38	59.63	0.77
2.75	27.24	55.52	35.68	54.95	0.76
3.00	29.35	50.92	36.67	49.66	0.80
3.33	30.26	48.46	39.13	49.37	0.77
3.67	29.54	49.96	38.29	47.84	0.77
4.00	29.37	45.38	38.04	51.44	0.77
4.50	43.49	43.62	49.53	44.09	0.88
5.00	34.05	48.88	36.60	46.86	0.93
6.00	23.58	59.30	24.30	42.81	0.97
8.00	14.70	57.82	15.22	57.30	0.97
10.00	9.13	52.38	9.13	49.79	1.00
12.00	5.80	58.49	5.68	52.35	1.02
16.00	3.62	64.50	3.34	44.40	1.08
24.00	1.22	58.49	1.20	52.87	1.02
36.00	0.80	80.43	0.75	63.13	1.07
48.00	0.28	65.85	0.27	67.52	1.04
72.00	0.03	237.16	0.03	267.69	1.02

Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation

Test Formulation Data for the 80 mg Tablet:

S. No.	Component	Quantity per Unit (mg)	% (w/w)	Pharmaceutical Function
				(b) (4)
1.	Atorvastatin calcium (b) (4)			(b) (4)
2.	Basic butylated methacrylate copolymer (b) (4)			
3.	Lactose monohydrate (b) (4)			
4.	Microcrystalline cellulose (b) (4)			
5.	Methanol (b) (4)			
				(b) (4)
6.	Atorvastatin calcium (b) (4)			(b) (4)
7.	Lactose monohydrate (b) (4)			
8	Crospovidone (b) (4)			
9.	Sodium bicarbonate (b) (4)			
10.	Sodium lauryl sulphate (b) (4)			
11.	(b) (4)			
				(b) (4)
12.	Crospovidone (b) (4)			(b) (4)
13.	Hydroxy propyl cellulose (b) (4)			
14.	Magnesium Stearate (b) (4)			
				(b) (4)
				(b) (4)
15.	(b) (4)			(b) (4)
16.	Talc (b) (4)			
17				(b) (4)
18				
19.				
				(b) (4)
				(b) (4)

Excipients				
Strengths		**Excipient**	**Amount/unit**	**Maximum Potency from IIG (mg)**
80 mg		Basic butylated methacrylate copolymer (b) (4)	(b) (4)	
		Lactose monohydrate (b) (4)		
		Microcrystalline cellulose (b) (4)		
		Methanol (b) (4)		
		Lactose monohydrate (b) (4)		
		Sodium bicarbonate (b) (4)		
		Sodium lauryl sulphate (b) (4)		
		(b) (4)		
		Crospovidone (b) (4)		
		Hydroxy propyl cellulose (b) (4)		
		Magnesium Stearate (b) (4)		
		(b) (4)		
		Talc (b) (4)		
		(b) (4)		

(b) (4)

		[redacted]		
MDD used for calculation[11]	80 mg of Atorvastatin/ day			

Strengths/ [redacted]	Components within [redacted]	Amount/tablet (mg)	Amount/day	Maximum Potency from IIG (mg)
80 mg/White	Polyvinyl alcohol - [redacted]	[redacted]		
	Titanium Dioxide, [redacted]			
	Talc, [redacted]			
	Lecithin [redacted]			
	Xanthan gum, [redacted]			
MDD used for calculation[12]	80 mg of Atorvastatin/ day			

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	YES
If no, are they all above/within IIG (per day) limits?	N/A
If no, are additional data or Pharm/Tox consult necessary?	z
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	YES
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	N/A
Are all strengths of the RLD product dose-proportional?	N/A
Are all strengths of the test formulation acceptable	YES
Additional Attachment for Formulation Calculations	N/A

[11] The MDD of this drug product is 80 mg/day. Clinical Pharmacology: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=672&sec=monindi. Last accessed: 26 April 2011.
[12] The MDD of this drug product is 80 mg/day. Clinical Pharmacology: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=672&sec=monindi. Last accessed: 26 April 2011.

4.2.1 Polymorphic Consideration for Atorvastatin Calcium Tablet Drug Products

Due to the OGD's recent concern of the effect of polymorphism on in vitro and in vivo performance of a drug product, polymorphic identification of an API compound with multiple polymorphs such as atorvastatin would contribute toward the process of determining an appropriate and discriminatory dissolution method for use in the quality program of the drug product. Polymorphism has been linked to a product's stability, impurity profile, and solubility of the active ingredient. Following is a list of ANDAs of atorvastatin calcium tablet products which have been reviewed by the DBE and the polymorph(s) identified by the respective DBE reviewer for each product. The evaluation of the polymorphic form and/or composition of the API is primarily carried out the OGD Division of Chemistry. The polymorphic identification list below is for the information purpose of the DBE reviewers only.

Application Number	Submitter	Reviewer	Polymorph (s)
ANDA-091650	DR REDDYS LABORATORIES LTD	Johnetta Walters	(b) (4)
ANDA-202357	DR REDDYS LABORATORIES LTD	Johnetta Walters	
			(b) (4)
			(b) (4
			(b) (4)
ANDA-091226	MATRIX LABORATORIES LTD	Hongling Zhang	
ANDA-078773	TEVA PHARMACEUTICALS USA	Suman Dandamudi	
ANDA-077575	SANDOZ INC	Li Gong	
ANDA-091624	KUDCO IRELAND LTD	Johnetta Walters	(b) (4) (b) (4)
ANDA-090548	APOTEX INC	Li Gong	(b) (4)
ANDA-076477	RANBAXY LABORATORIES LIMITED	Surendra Shrivastava	(b) (4) (b) (4) (b) (4) (b) (4)
NDA 020702 (Lipitor)	Pfizer		(b) (4) (b) (4) (b) (4)

4.3 Dissolution Data

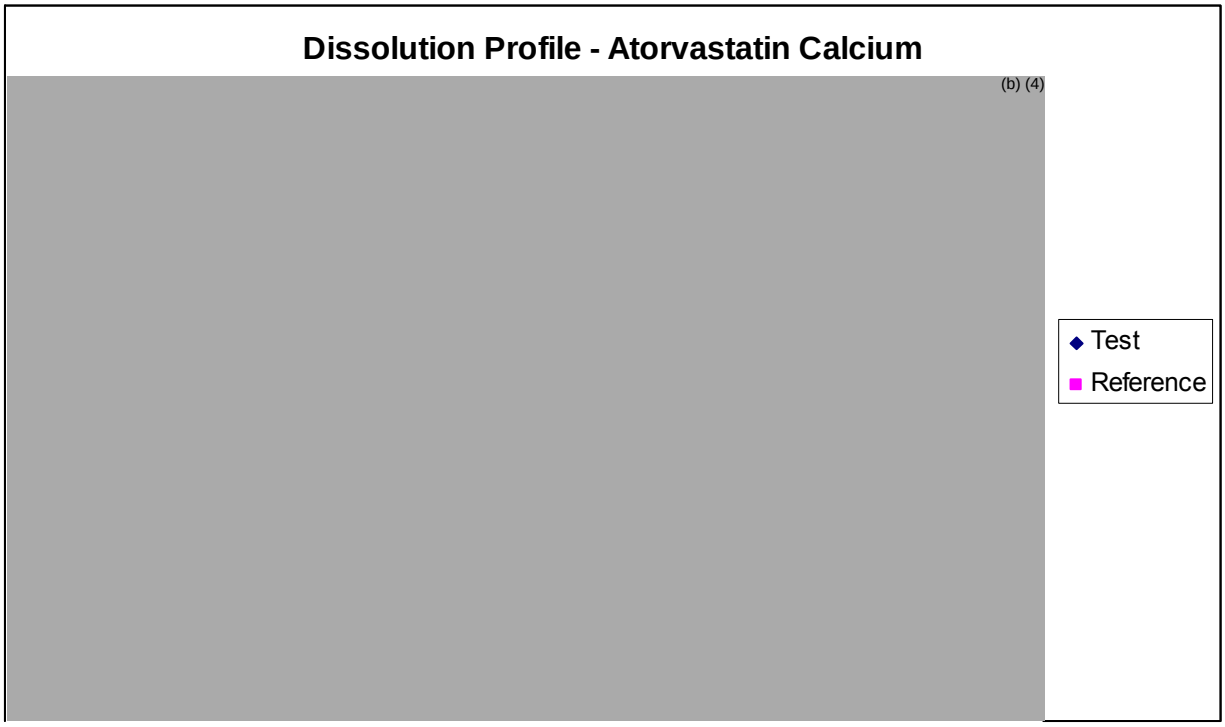
Dissolution Review Path	DARRTS: ANDA 202357; REV-BIOEQ-02(Dissolution Review). 03/02/2011.

Table 33. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	Dissolution media (Phosphate buffer pH 6.8) (b) (4)
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Dr. Reddy's Laboratories Limited (Generics), Located at Bachepalli – 502 325, INDIA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						5 min	**10 min**	**15 min**	**30 min**	**45min**	
BO01585	09/08/09	Atorvastatin calcium Tablets 80 mg, Batch No.: EC9156 Mfg. date: 07/2009	80 mg Tablets	12	Mean	24	55	82	98	99	Module 5.3.1.2
					Range	(b) (4)					
					%CV	23.6	17.1	13.3	1.9	1.7	
BO01258	25/07/09	Lipitor® 80mg Batch No.: 04568V Exp .date :03/2011	80 mg Tablets	12	Mean	98	102	103	103	104	
					Range	(b) (4)					
					%CV	1.8	1.2	0.9	1.2	1.2	

Figure 5. Dissolution Profiles



4.4 Detailed Regulatory History (If Applicable)

Contains Nonbinding Recommendations

Draft Guidance on Atorvastatin Calcium

This draft guidance, once finalized, will represent 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: EQ 80 mg Base
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). For general information on this approach, please refer to the Individual Product Bioequivalence Recommendations Guidance on Progesterone Capsules.

---

2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: EQ 80 mg Base
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see additional comments above.

Analytes to measure (in appropriate biological fluid): Atorvastatin and its active metabolites, ortho and para- hydroxylated atorvastatin in plasma

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, 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: EQ 10 mg, 20 mg and 40 mg Base based on (i) acceptable bioequivalence studies on the EQ 80 mg Base strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across 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.accessdata.fda.gov/scripts/cder/dissolution/. 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.

Recommended May 2008; Revised Oct 2010

4.5 Consult Reviews

N/A

4.6 SAS Output

4.6.1 Fasting Study Data

Fasting CONCENTRATION DATASET

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18
1	(b) (4)																						
2																							
3																							
4																							
5																							
6																							
7																							
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23																							
24																							

4.7 Additional Attachments

From: CDER OSI BEQ
Sent: Monday, April 09, 2012 3:38 PM
To: Chun, Nam; Walters, Johnetta F.; CDER OSI BEQ
Subject: RE: Please provide OSI inspection history for below sites. Thanks!

Yes; also formerly L.A.B.

From: Chun, Nam
Sent: Monday, April 09, 2012 3:33 PM
To: Walters, Johnetta F.; CDER OSI BEQ
Subject: RE: Please provide OSI inspection history for below sites. Thanks!

Hi,

Can you please confirm that AAI Pharma Deutschland GmbH & Co. is indeed Nuvisan?

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: Monday, April 09, 2012 3:25 PM
To: Chun, Nam
Subject: FW: Please provide OSI inspection history for below sites. Thanks!

Hi Esther,

When I search the reports for NDA 022522 (listed as Nuvisan in my information table and the information obtained from CDER OSI BEQ below), the report lists the following:

Inspection of the clinical portion was conducted at AAI Pharma
Deutschland GmbH & Co. KG, Wegener-str. 13, 89231 Neu-Ulm,
Germany. Inspection of the analytical portion was conducted at
(b) (4)

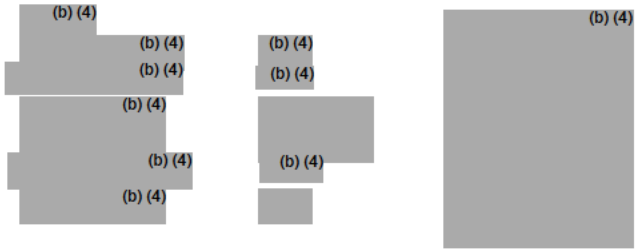
Is there a way to confirm that AAI Pharma Deutschland GmbH & Co. is indeed Nuvisan prior to my conducting a review of this OSI inspection report?

Thanks,

Johnetta

Johnetta F. Walters, Ph.D.
Review Pharmacologist
USFDA/CDER/OPS/OGD/DBI
MPN1, Room 1358, HFD-650
Telephone: (240) 276 - 8802
Facsimile: (240) 276 - 8766

From: CDER OSI BEQ
Sent: Thursday, April 05, 2012 5:03 PM
To: Chun, Nam; CDER OSI BEQ
Cc: Walters, Johnetta F.
Subject: RE: Please provide OSI inspection history for below sites. Thanks!



Nuvisan
ANDA 40-557 Clin 4/19/04 VAI
NDA 22-522 Clin 2/15/10 OAI [A possible regulatory letter and other follow-up decisions are still in progress.]

From: Chun, Nam
Sent: Thursday, April 05, 2012 11:22 AM
To: CDER OSI BEQ
Cc: Walters, Johnetta F.
Subject: Please provide OSI inspection history for below sites. 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, April 05, 2012 10:24 AM

To: Chun, Nam
Subject: OSI Inspection Status Request

Hi Esther,

Could you please check the OSI status of the following clinical and analytical sites?

ANDA No.	202357		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	80 mg		
Applicant Name	Dr. Reddy's Laboratories Limited		
Applicant Address	Mailing Address: Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad - 500 072, India Factory Address: Bachepalli 502 325, India		
US Agent Name and the mailing address	Dr. Reddy's Laboratories, Inc. 200 Somerset Corporate Boulevard 7th Floor, Bridgewater, NJ 08807		
US agent's Telephone Number	Tel: 908-203-4937		
US Agent's Fax Number	Fax: 908-203-4980		
Original Submission Date(s)	27 September 2010		
Submission Date(s) of Amendment(s) Under Review	N/A		
First Generic (Yes or No)	No		
Reviewer	Johnetta F. Walters, Ph.D.		
Study Number (s)	10-VIN-095	09-VIN-105	
Study Type (s)	Fasting	Fed	
Strength (s)	80 mg	80 mg	
Clinical Site	**Veeda clinical research Pvt. Ltd.**	Nuvisan GmbH	
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India.	Wegenerstraße 13 89231 Neu-Ulm Germany Tel: +49 731 – 9840 151 Fax: +49 731 – 9840 355	
Analytical Site	(b) (4)		
Analytical Site Address			
OSI Status			
REVIEW RESULT			
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**

Thanks,

Johnetta

Johnetta F. Walters, Ph.D.

Review Pharmacologist
USFDA/CDER/OPS/OGD/DBI
MPN1, Room 1358, HFD-650
Telephone: (240) 276 - 8802
Facsimile: (240) 276 - 8766

BIOEQUIVALENCE DEFICIENCIES

ANDA: 202357

APPLICANT: Dr. Reddys Laboratories

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

1. You have not provided the potency (assay) data of the reference listed drug (RLD) lot 04568V (80 mg). Please provide the Certificate of Analysis (COA) of the RLD lot number 04568V.

2. As shown in the table below, the atorvastatin CMAX and AUC values for both test and reference treatments in your current fed bioequivalence (BE) study No. 10-VIN-105 on the 80 mg tablet strength, using the dosage of 1x80 mg, were approximately two times (or greater) those determined for the fed BE study on the 40 mg strength (ANDA 091650) of both test and reference treatments (using the dosage of 1x40 mg), as expected. However, the atorvastatin CMAX and AUC values for both test and reference treatments in your current fasting BE study No. 10-VIN-095 on the 80 mg tablet strength, using the dosage of 1x80 mg, were comparable with those determined for the fasting BE study on the 40mg strength (ANDA 091650) (using the dosage of only 1x40 mg). Please explain this observed inconsistency in the pharmacokinetic (PK) results for these BE studies.

		FASTING (D=1x40 mg)	FASTING (D=1x40 mg)	FED (D=1x40 mg)	FED (D=1x40 mg)
91650	**REDDY**	**T**	**R**	**T**	**R**
40mg Atorvastatin	AUCT (hr.ng/mL)	125.94	130.62	107.03	113.44
	AUCI (hr.ng/mL)	129.25	135.96	110.65	116.6
	CMAX (ng/mL)	28.71	30.24	13.89	15.17
		FASTING (D=1x80 mg)	**FASTING (D=1x80 mg)**	**FED (D=1x80 mg)**	**FED (D=1x80 mg)**
202357	**REDDY**	**T**	**R**	**T**	**R**
80mg Atorvastatin	AUCT (hr.ng/mL)	120.89	109.02	260.85	294.38
	AUCI (hr.ng/mL)	125.28	113.82	263.82	297.41
	CMAX (ng/mL)	36.37	33.41	49.11	54.39

D: Dose

Following the inspection of the clinical site, Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany, from February 15, 2010 to February 19, 2010 by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the clinical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

a. *Possibility of administration of wrong medication in study subjects as the treatment information on dosing container, as well as the source records concerning all drug product selection and repacking step were not provided.*
b. *Strict fasting conditions were not assured as all the subjects have free access to outdoor areas.*
c. *Study data generated for certain periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.*
d. *Blood sample collection time points were not assured.*

e. Fasting condition in subjects was not assured.

Similarly, following the inspection of the analytical site, [redacted] on [redacted] to by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

f. Failure to select appropriate concentrations for evaluating dilution linearity during validation.
g. Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.

3. The DBI has noticed that you were using a non-standard high-fat vegetarian breakfast in your fed study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBI does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.

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: 202357

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
16616	9/27/2010	Bioequivalence Study	Fasting Study	1	1
16616	9/27/2010	Bioequivalence Study	Fed Study	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
06/04/2012

SHRINIWAS G NERURKAR
06/04/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/07/2012

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202357	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength (s)	80 mg	
Applicant Name	Dr.Reddy's Laboratories Limited	
Address	Dr.Reddy's Laboratories Limited, Integrated Product Development, Bachupally, Quthubullapur Mandal, Survey No: 42, 45 and 46, R R Dist- 500 072, AP., India	
Applicant's Point of Contact	Dr.V. Venkateswarlu	
Contact's Phone Number	91-40-44346272	
Contact's Fax Number	91-40-44346253	
Submission Date(s)	9/27/2010	
First Generic	No	
Reviewer	Hongling Zhang, Ph.D.	
Study Number (s)	10-VIN-095	09-VIN-105
Study Type (s)	Fasting	Fed
Strength(s)	1 x 80 mg	1 x 80 mg
Clinical Site	**Veeda clinical research Pvt. Ltd.**	
Clinical Site Address	Shivalik Plaza – A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India	
Analytical Site	(b) (4)	
Analytical Address		

OUTCOME DECISION	**INADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
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. The firm's dissolution testing using the FDA-recommended method is acceptable. However, the firm's proposed specification of "NLT (b) (4) **%** (Q) in **30** minutes" is not acceptable. Based on the firm's dissolution data, the DBE recommends the following specification for the firm's test product: NLT (b) (4) **%** (Q) in **30** minutes. The firm should acknowledge the acceptance of this specification.

The in vitro dissolution testing is **inadequate**.

NON DISSOLUTION TESTING ITEMS:

The long-term storage stability data that the firm provided is sufficient to cover the maximum storage period of the study samples for the submitted bioequivalence studies.

The firm provided the SAS files in the electronic format for fasting and fed BE studies.

The DBE will review the fast and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
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.					

Dissolution Method listed in the Internal Dissolution Database (NOT TO BE RELEASED UNDER FOI):

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	Dissolution media (Phosphate buffer pH 6.8) ((b) (4))[1]
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount of Atorvastatin is dissolved in 30 minutes	
Dissolution Testing Site (Name, Address)	Dr. Reddy's Laboratories Limited (Generics), Located at Bachepalli – 502 325, INDIA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						5 min	**10 min**	**15 min**	**30 min**	**45min**	
BO01585	09/08/09	Atorvastatin calcium Tablets 80 mg, Batch No.: EC9156 Mfg. date: 07/2009	80 mg Tablets	12	Mean	24	55	82	98	99	Module 5.3.1.2
					Range	(b) (4)					
					%CV	23.6	17.1	13.3	1.9	1.7	
BO01258	25/07/09	Lipitor® 80 mg Batch No.: 04568V Exp .date :03/2011	80 mg Tablets	12	Mean	98	102	103	103	104	
					Range	(b) (4)					
					%CV	1.8	1.2	0.9	1.2	1.2	

[1] According to the firm's 'analytical procedure' submitted in module 3.2.P.5.2, the concentration of the phosphate used in the dissolution medium is 0.05 M.

II. COMMENT:

1. There is no USP method for Atorvastatin Calcium Tablets, but there is an FDA-recommended dissolution method which is available in the public dissolution database on the Office of Generic Drugs (OGD) website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.

2. The dissolution data showed that the variability (%CV) for the test products was high (13.3% - 23.6%) at the first three sampling time points (5, 10 and 15 minutes). Since these sampling time points are considered as the early time points, and the variability was low (less than 2%) for the later sampling times, in addition, over (b) (4)% drug released in 30 minutes, the reviewer considers the dissolution testing that the firm conducted using the FDA-recommended method is acceptable. However, the firm's proposed specification of "NLT (b) (4)% (Q) in 30 minutes" is not acceptable. Based on the firm's dissolution data, the DBE recommends the following specification for the firm's test product: NLT (b) (4)% (Q) in 30 minutes. The firm's dissolution data for the test product met this specification at S1 level.

III. DEFICIENCY COMMENTS:

The firm's proposed specification of "NLT (b) (4)% (Q) in 30 minutes" is not acceptable. The firm should acknowledge the acceptance of the DBE recommended specification of "NLT (b) (4)% (Q) in 30 minutes" for its test product, Atovastatin Calcium Tablets, 80 mg.

IV. RECOMMENDATION:

The *in vitro* dissolution testing conducted by Dr. Reddy's Laboratories Limited, on its Atorvastatin Calcium Tablets, 80 mg (lot # EC9156) along with the reference product, Lipitar® (atorvastatin) Tablets, 80 mg (lot # 04568V) by Pfizer, using the FDA-recommended dissolution method is **incomplete** due to above mentioned deficiency.

The firm should be informed of the above deficiency comment and recommendation.

BIOEQUIVALENCE DEFICIENCY

ANDA: 202357

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable. However, your proposed specification of "NLT (b)(4)% (Q) in 30 minutes" is not acceptable. Based on the dissolution data, the DBE recommends a more appropriate specification for your Atorvastatin Calcium Tablets, 80 mg. Please acknowledge your acceptance of the following FDA recommended dissolution method and specification:

The dissolution should be conducted in 900 ml 0.05 M Phosphate Buffer pH 6.8, using USP apparatus II (paddle) at 75 rpm at 37 ± 5° C.

The product should meet the following specification:

NLT (b)(4)% (Q) of labeled amount of atorvastatin in the dosage form should be dissolved in **30 minutes**.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

ANDA: 202357

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13301	9/27/2010	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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

/s/

HONGLING ZHANG
02/28/2011

BING V LI
03/01/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/02/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202357

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 #:202357
Firm Name:Dr Reddy's Laboratories Limited
ANDA Name:Atorvastatin Calcium Tablets, 80 mg (base)
RLD Name:Lipitor by Pfizer

Electronic AP Routing Summary Located:
Z:\Chemistry Division III\Team 34\Electronic AP Summary\202357.ap.doc

AP/TA Letter Located:
Z:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\202357.apltr.DOC

Project Manager Evaluation: **Date: 7/12/12 Initials:** RG

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 9/27/10	Date of Application 9/27/10	Date Acceptable for Filing 11/9/10
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#:** 21125 (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) 6/29/12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 7/5/12 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 5/18/12 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:
☒ Labeling Endorsement, Date emailed: 7/12/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 7/12/12

☒ 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: 7/12/2012**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =_____ NDA#_____
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day	Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP
☐ OTHER:

Comments:ANDA submitted on 9/27/2010, BOS=Lipitor NDA 20702, PIII certs to '893, '995 and 'RE667, PIV to '104, '156 and '971. ANDA ack for filing with a PIV certification on 9/27/2010(LO dated 11/9/2010). Patent Amendment rec'd on 4/27/2012-RR from Pfizer in NY, NY signed and dated 11/30/2010, RR from Warner Lambert in Morris Plains NJ signed but not dated-track and confirm shows delivery on 11/30/2010, CA 10 CV 1135 filed in the D of DE on 12/27/2010 for infringement of the '156 patent, on 8/29/2011 CA 10 CV 1135 was dismissed without prejudice. Therefore, the '156 patent is no longer a barrier to the approval of this ANDA, furthermore since Dr. Reddy's was not sued on the '104 and '971 patents these patents are not a barrier to the approval either.
Ranbaxy, the sponsor of ANDA 76477 was awarded 180 day exclusivity for this product. Ranbaxy's 180 day exclusivity expired on 5/28/2012.
There are no patent, exclusivity or other legal barriers to the approval of this ANDA. Application is eligible for immediate Full Approval.

2. ***Labeling Endorsement***

Reviewer, BT:
Date7/12/12
InitialsBT/RG for

Labeling Team Leader, RW:
Date7/12/12
InitialsRW/RG for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, July 12, 2012 11:04 AM
To: Turner, Betty; Gaines, Robert
Subject: RE: ANDA 202357

I concur

From: Turner, Betty
Sent: Thursday, July 12, 2012 11:03 AM
To: Gaines, Robert; Wu, Ruby (Chi-Ann)
Subject: RE: ANDA 202357

Good morning Bob,

I have checked USP, Medwatch, DARRTS, OB, REMS and Drugs@FDA and there are no changes to report since last labeling review was completed.

Thanks,

Betty

From: Gaines, Robert
Sent: Thursday, July 12, 2012 9:15 AM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 202357

Good morning Betty and Ruby.

The subject Atorvastatin ANDA by DRL is ready for approval. Please provide labeling endorsement.

Thanks

Bob

<< File: 202357 label rev.pdf >> << File: 202357.ltr.DOC >>

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date _____**
OGD Regulatory Counsel **Initials_____**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 7/12/12**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date_____**
Assoc. Dir. For Chemistry **Initials_____**
Comments: (First generic drug review)

OGD Office Management Evaluation

6. Peter Rickman **Date 7/17/2012**
Director, DLPS **Initials wpr**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes ☐ No ☒
Petition: Yes☐ No☒
Comments: BOS=Lipitor NDA 20702, Applicant initially provided PIII certs to '893, '995 and 'RE667 patents which have since expired. the applicant also provided PIV certs to '104, '156 and '971 patents. Applicant met all notification requirements and was sued for infringement of the '156 patent only. On 8/29/2011 this CA was dismissed without prejudice. Ranbaxy, (ANDA 76477) was awarded 180 day exclusivity for this product. Ranbaxy's 180 day exclusivity expired on 5/28/2012. Chemistry acceptable 6/29/2012 and 7/13/2012. Bio acceptable 7/5/2012 (fasting and fed studies 80 mg). Labeling acceptable 5/18/2012 per AP Summary, TL sign-off 7/12/2012. EER acceptable 4/25/2012. Application is eligible for immediate Full Approval.

AND/OR

7. Robert L. West
Deputy Director, OGD
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes☐ No☐
Petition: Yes☐ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Date _____
Initials _____

Comments:

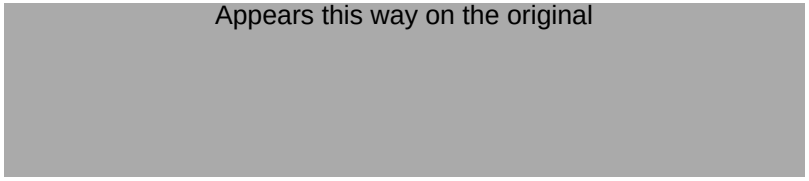
8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments:
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

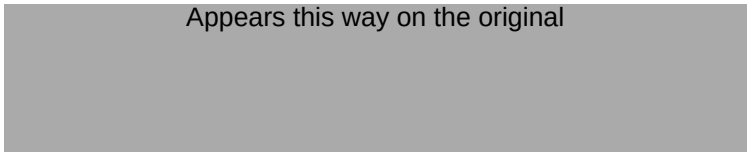
9. Project Manager
Date 7/17/12
Initials RG

Check Communication and Routing Summary into DARRTS

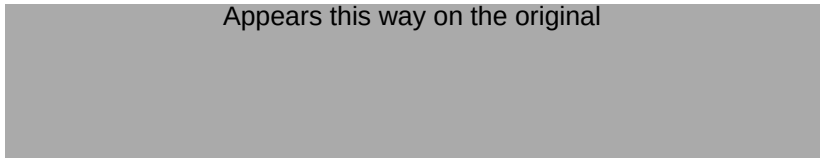
EER DATA:



DARRTS Application History:



Orange Book Report:



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

/s/

ROBERT T GAINES
07/17/2012

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

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Fax: (908) 203-4980

www.drreddys.com

June 29, 2012

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855-2810

Reference: ANDA # 202357, eCTD Seq 0016
Atorvastatin Calcium Tablets, 80 mg
Bioequivalence Response to Information Request
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Bioequivalence Amendment. This is in response to the deficiency letter dated June 18, 2012 which has been provided along with this cover letter for reviewer's convenience.

FDA COMMENT:

1. *You have not provided the potency (assay) data of the reference listed drug (RLD) lot 04568V (80 mg). Please provide the Certificate of Analysis (COA) of the RLD lot number 04568V.*

RESPONSE:

We would like to inform the Agency that, the Certificate of Analysis (COA) for the RLD lot number 04568V was already provided in the original ANDA submission in Section 16.1.6, page 271 of fed study report and in Section 16.1.6, page 274 of fasting study report. However, a copy of the same is provided in ***Module 5.3.1.2*** for quick reference.

FDA COMMENT:

2. *As shown in the table below, the atorvastatin C_{max} and AUC values for both test and reference treatments in your current fed bioequivalence (BE) study No. 10-VIN-105 on the 80 mg tablet strength, using the dosage of 1x80 mg, were approximately two times (or greater) those determined for the fed BE study on the 40 mg strength (ANDA 091650) of both test and reference treatments (using the dosage of 1x40 mg), as expected. However, the atorvastatin C_{max} and AUC values for both test and reference treatments in your current fasting BE study No. 10-VIN-095 on the 80 mg tablet strength, using the dosage of 1x80 mg, were comparable with those determined for the fasting BE study on the 40 mg strength (ANDA091650) (using the dosage of only 1x40 mg). Please explain this observed inconsistency in the pharmacokinetic (PK) results for these BE studies.*

		FASTING (D=1x40 mg)	*FASTING (D=1x40 mg)*	*FED (D=1x40 mg)*	*FED (D=1x40 mg)*
91650	*REDDY*	*T*	*R*	*T*	*R*
40 mg	*AUCT (hr.ng/mL)*	*125.94*	*130.62*	*107.03*	*113.44*
Atorvastatin	*AUCI (hr.ng/mL)* *C_{MAX} (ng.mL)*	*129.25* *28.71*	*135.96* *30.24*	*110.65* *13.89*	*116.6* *15.17*
		FASTING (D=1x80 mg)	*FASTING (D=1x80 mg)*	*FED (D=1x80 mg)*	*FED (D=1x80 mg)*
202357	*REDDY*	*T*	*R*	*T*	*R*
80 mg	*AUCT (hr.ng/mL)*	*120.89*	*109.02*	*260.85*	*294.38*
Atorvastatin	*AUCI (hr.ng/mL)* *C_{MAX} (ng.mL)*	*125.28* *36.37*	*113.82* *33.41*	*263.82* *49.11*	*297.41* *54.39*

D: Dose

RESPONSE:

We acknowledge the agency's concern on the differences observed in the pharmacokinetic results in the Bioequivalence studies conducted by DRL.

As per US-FDA draft guidance[1] on the bioequivalence studies for atorvastatin to support ANDA for generic products stipulates the requirement to assess bioequivalence of atorvastatin under fasting and fed conditions and to provide supportive PK analysis of ortho and para hydroxy atorvastatin in general population. Dr Reddy's Laboratories Ltd. has conducted both the studies as per the IRB approved study protocol and in accordance with the applicable GCP and GLP principles.

The 90% confidence intervals for pharmacokinetic parameters i.e. C_{max}, AUC_{0-t} and AUC_{0-inf} were evaluated for plasma Atorvastatin and are within the regulatory acceptance interval of 80.00-125.00% and the test product is bioequivalent to the reference product, the complete details of the studies are provided in ***Table-I.***

As per the information available in summary basis of approval (SBOA) for the innovator product "Lipitor", the administration of Atorvastatin is associated with large variability as evidenced by percent relative standard deviation (%RSD) values for pharmacokinetic parameters ranging from 30-50%. In a study conducted to assess intra-subject and inter-subject variability, intra-subject variability accounted for 66.1% of the variability in Cmax[2].

The high inter-subject variability in pharmacokinetic parameters for atorvastatin has also been observed in subjects without renal disease. Age, gender, food intake, and level of CYP3A4 expression and activity all influence the body's handling of Atorvastatin, an important characteristic of CYP3A4 is the large inter-individual variability in activity (about 5fold), which reflects genetic polymorphism combined with modulation by environmental factors. CYP3A5 genotype has minimal effects on the pharmacokinetic parameters of atorvastatin[3]. Food decreases C_{max} and AUC by 25% and 9% respectively.

The pharmacokinetic parameter values for Atorvastatin are evaluated and the details (Study no Fast # **10-VIN-095, Fed # 09-VIN-105)** are presented below ***Table-I.***

Table-I

Study type	**Fasting**		**Fed**	
Study No.	**10-VIN-095**		**09-VIN-105**	
	Clinical	Bioanalytical	(b) (4)	Bioanalytical
Study Sites	Nuvisan GmbH, Germany	(b) (4)	(b) (4)	
No. of Subjects	80 (77 subjects completed the study)		80 (72 subjects completed the study)	
Race	Caucasian: 77		Asian: 72	
Pharmacokinetic Parameters of Test Vs Reference				
		Test	**Reference**	**Test**	**Reference**
C_{max} (ng/mL)	Geo.mean	36.646	33.417	49.111	54.387
	Min-Max	10.06-124.37	12.32-87.49	26.70-119.00	22.10-115.0
	CV%	61.31	42.92	39.43	38.82
AUC_{0-t} (ng.hr/mL)	Geo.mean	120.887	109.008	260.848	294.379
	Min-Max	48.71-401.83	32.57-298.80	145.50-764.85	137.74-725.60
	CV%	49.06	48.14	38.48	35.18
AUC_{0-inf} (ng.hr/mL)	Geo.mean	124.713	112.920	263.997	298.056
	Min-Max	51.79-416.56	34.55-301.90	146.72-768.96	140.05-731.84
	CV%	48.47	47.32	38.20	34.86
Ratio (90% Confidence Interval)					
C_{max}	109.14% (99.85 - 119.28) %		90.30% (84.57 - 96.41)%		
AUC_{0-t}	111.13% (105.58 - 116.96)%		88.61% (85.35-- 91.99) %		
AUC_{0-inf}	110.66% (105.26 - 116.34)%		88.57% (85.33% - 91.93)%		

The test and reference lots used in the BE studies were of same lot numbers and the % difference in the potency of the test and reference lots was found to be (b) (4)% and (b) (4) % respectively, which is less than (b)% of regulatory acceptance limit. The lot numbers of test and reference products used is tabulated below as **Table-II.**

Table-II : Atorvastatin Calcium Tablets, 80mg studies

Study No	**Fast: 10-VIN-095 Fed: 09-VIN-105**	
Product	Test (Atorvastatin)	Reference (Lipitor)
Batch/Lot No	EC9156	04568V
Potency %	(b) (4)	

The clinic sites where the fasting and fed studies for 80 mg strength were conducted are at different locations. The number of subjects dosed in study# **10-VIN-095** was 80 (77 subjects completed the study) that included male and female subjects belonging to ethnic race of Caucasians. The number of subjects dosed in study **09-VIN-105** was 80 (72 subjects completed the study) and included only male volunteers belonging to the ethnic race of Asians. The demographics of the subjects from all the studies are provided in **Table –III.**

Table-III : Demographic Table for Atorvastatin 80mg Tablets

Strength	**80 mg**			
	Fasting		**Fed**	
Study No	**10-VIN-095**		**09-VIN-105**	
Study Sites	Clinic	Bioanalytical	(b) (4)	Bioanalytical
	Nuvisan GmbH		(b) (4)	
Number of Subjects	80 (77 subjects completed the study)		80 (72 subjects completed the study)	
Race	Caucasian: 77		Asian: 72	
Demographics	Age: Mean (Range)	37.73 (19-54)	Age: Mean (Range)	29.32 (18-43)
	Weight: Mean (Range)	70.97 (52.50-93.90)	Weight: Mean (Range)	59.76 (50.40- 79.10)
	BMI: Mean (Range)	24.02 (18.79 to 29.89)	BMI: Mean (Range)	21.50 (19.02 to 24.80)
	Sex	Male:38	Sex	Male: 72
		Female: 39		Female: 0

- Dosing compliance was checked by the trained personnel as per the approved study protocol. There are no significant protocol deviations observed during the conduct of the study which would have an impact on the overall outcome of the study.

- The plasma samples were analyzed using validated bioanalytical methods for quantifying plasma Atorvastatin, ortho-hydroxy atorvastatin and para-hydroxy atorvastatin.

- The intersubject and intra subject variability was observed very high in both the studies, approximately greater than 30%.

- We would like to bring to agency note that Dr Reddy's laboratories Limited had also conducted few other, two-way crossover bioequivalence studies under fasting state only at (b) (4) (Clinical Site- Clinical Hospital of the Ministry of Health, Moldavia) for Atorvastatin 80mg tablets respectively against Canadian and European Union reference products. These studies were conducted as per GCP and GLP requirements and met the bioequivalence requirements as per the applicable regulatory guidelines, the pharmacokinetic data was evaluated is presented below for your reference as **Table-IV**.

Table –IV

Study type	**80 mg Fasting**		**80 mg Fasting**	
Market	**Canada**		**Europe**	
Study No.	**ATV-BESD-15-RDL/11**		**ATV-BESD-10-RDL/09**	
	Clinical	Bioanalytical	Clinical	Bioanalytical
Study Sites	Clinical Hospital of the Ministry of Health, Moldavia	(b) (4)	Clinical Hospital of the Ministry of Health, Moldavia	(b) (4)
Number of Subjects	80 (80 subjects completed the study)		80 (79 subjects completed the study)	
Race	Caucasian: 80		Caucasian: 80	
Pharmacokinetic Parameters of Test Vs Reference				
	Test	**Reference**	**Test**	**Reference**
C_{max} (ng/mL) Geo.mean	59.520	55.587	49.157	49.277
C_{max} (ng/mL) Min-Max	14.132 - 302.160	11.124 - 374.652	16.28 - 596.776	19.739 - 244.832
C_{max} (ng/mL) CV%	73.048	87.778	116.374	64.372
AUC_{0-t} (ng.hr/mL) Geo.mean	238.377	229.984	188.315	183.990
AUC_{0-t} (ng.hr/mL) Min-Max	77.462 - 808.621	66.250 - 1098.729	77.92 -1592.449	51.681 -665.620
AUC_{0-t} (ng.hr/mL) CV%	52.787	74.424	85.179	58.499
AUC_{0-inf} (ng.hr/mL) Geo.mean	244.762	236.882	195.270	191.528
AUC_{0-inf} (ng.hr/mL) Min-Max	80.989 - 814.589	71.925 - 1102.821	83.57 - 1597.926	56.776 -674.067
AUC_{0-inf} (ng.hr/mL) CV%	51.781	72.896	82.958	56.822
Ratio (90% Confidence Interval)				
C_{max}	107.07 % (94.41 - 121.44)%		99.84 % (89.91 – 110.86)	
AUC_{0-t}	103.65 % (95.96 – 111.96)%		102.30 % (96.27 – 108.72)	
AUC_{0-inf}	103.33% (95.84 – 111.40)%		101.91 % (96.00 – 108.18)	

- A cross study comparison of the pharmacokinetic parameters evaluated from the studies conducted by Dr Reddy's laboratories Ltd against marketed reference products in US (study No. **10-VIN-095) Europe (study no ATV-BESD-10-RDL/09) and Canada (Study no ATV-BESD-15-RDL/11)** were provided along with the available published literature information for the PK parameters of Atorvastatin in the below mentioned table as **Table-V**.

It was observed the geometric means for atorvastatin when reference product was administered in study no 10-VIN-095, are comparable with the reported literature data.

Table-V

Geo. Mean Comparison		Studies Conducted by Dr Reddy's Laboratories limited			Published literature data			
		Study No. ATV-BESD-15-RDL/11 (80 mg) Canada	**Study No 10-VIN-095 (80mg) US**	**Study No ATV-BESD-10-RDL/09 (80mg) Europe**	**Literature Data (EU Innovator)[4] 80 mg Fast**	**Literature data (EU Innovator)[5] 80 mg Fast**	**Literature data (Clinicaltrials.gov)[6] BE Study 80 mg Fast Pfizer US**	**Literature data (EU Innovator)[7] 80 mg Fast T-2x40 mg R -80 mg Geo. Mean**
C_{max} (ng/mL)	Test Geo Mean ±SD	59.520 ±54.230	36.346 ±26.222	49.157 ±75.544	55.55 ±22.06	40.70 ±19.36	43.17 ±31.70	29.24
	Ref Geo Mean ±SD	55.587 ±62.339	33.417± 15.722	49.277 ±36.149	60.52 ±22.19	39.69 ±18.06	43.05 ±36.47	28.85
AUC_{0-t} (ng.hr/mL)	Test Geo Mean ±SD	238.377 ±142.708	120.887 ±66.027	188.315 ±188.787	194.82 ±67.37	161.08 ±70.25	162.50 ±100.56	127.49
	Ref Geo Mean ±SD	229.984 ±208.695	109.008 ±58.310	183.990 ±122.483	173.44 ±59.34	155.0 ±70.53	170.47 ±119.70	120.79
$AUC_{0-\infty}$ (ng.hr/mL)	Test Geo Mean ±SD	244.762 ±142.999	124.713 ±67.059	195.270 ±189.239	198.12 ±67.43	166.47 ±70.37	168.13 ±100.77	131.13
	Ref Geo Mean ±SD	236.882 ±208.740	112.920 ±59.152	191.528 ±122.944	177.23 ±59.48	162.85 ±68.88	176.17 ±120.18	124.03

- The metabolite data (Ortho and Para hydroxy atorvastatin) measured in the BE study of 10-VIN-095 were also compared with the literature data which is comparable, please refer to the below mentioned table (Table VI) for reference

Table-VI : Ortho Hydroxy and Para Hydroxy Atorvastatin Pharmacokinetic data

		Studies Conducted by Dr Reddy's Laboratories limited		Literature Data				
		Ortho-hydroxy Atorvastatin	Para-hydroxy Atorvastatin	Ortho-hydroxy	Ortho-hydroxy	Para-hydroxy	Ortho-hydroxy	Para-hydroxy
Geo. Mean Comparison		Study No 10-VIN-095 (80mg)		Literature data (EU Innovator) [5] 80 mg Fast	Literature Data (EU Innovator)[4] 80 mg Fast		Literature[8] 80 mg mean (%CV)	
C_{max} (ng/mL)	Test Geo Mean ±SD	41.632 ±31.040	1.050 ±1.740	35.88 ± 17.50	22.28 ± 9.25	1.41± 0.97	32 (60)	2 (100)
	Reference Geo Mean ±SD	38.887 ±19.694	0.707 ±0.785	37.75± 21.29	21.53 ± 8.95	1.24± 1.04		
AUC_{0-t} (ng.hr/mL)	Test Geo Mean ±SD	207.961 ±96.994	15.894 ±12.262	235.56± 97.52	137.74± 49.47	20.09± 12.34	NA	NA
	Reference Geo Mean ±SD	190.553 ±82.004	11.957 ±11.433	241.57± 103.89	122.41± 45.99	17.39± 11.04		
AUC_{0-inf} (ng.hr/mL)	Test Geo Mean ±SD	213.646 ±97.532	21.731 ±13.723	241.86± 97.49	140.95± 49.79	27.16 ±13.10	211 (43)	29 (57)
	Reference Geo Mean ±SD	196.763 ±82.479	22.055 ±46.710	248.26± 103.62	126.33 ±46.47	24.90± 13.54		

We would like to inform the agency that the following points were concluded based on the review performed for both the studies:

1) As mentioned from the above referenced tables, the mean pharmacokinetic parameters values for both the C_{max} and AUC parameters for the study no **10-VIN-095** was comparable with the reported literature values.

2) The 90% Confidence intervals for both C_{max} and AUC were within the regulatory acceptance limits and the test product met the bioequivalence requirements against the reference product.

3) The study was conducted as per the IRB approved protocol and the regulatory guidance, though the bioanalytical site was same the clinic sites are different for study no 10-VIN-095 (fasting) and study 09-VIN-105 (fed).

4) Dosing compliance met as per protocol requirements and the study was executed in accordance with the GCP and GLP requirements.

5) A bioanalytical method that was validated as per the principles of Bioanalytical method validation guidelines was applied in quantification of Atorvastatin, ortho hydroxy atorvastatin and parahydroxy atorvastatin in human plasma.

6) High intra-subject and inter-subject variability was observed for the pharmacokinetic parameters evaluated which are as per the published reported data.

Upon cross study comparison for the pharmacokinetic parameters evaluated in the BE studies conducted using different marketed reference products against Dr Reddy's test product along with the published literature data, the difference observed for the pharmacokinetic parameters can be related to the interindividual and inter ethnic variation in drug response that can be attributed to both genetic and environmental factors. Variations in genotype for drug metabolizing enzymes, drug transporters and drug receptors are associated with interindividual and interethnic variation in drug response.

Thus, we believe that the subset of the population involved in the biostudies conducted by the Dr Reddy's Laboratories limited, across different geographies and the published literature data has shown differences in the pharmacokinetic parameter values for Atorvastatin. Nevertheless the reasons we might believe for the differences observed in the pharmacokinetic parameter values of Atorvastatin Tablets 80mg studies conducted at different geographies, the test formulation of Atorvastatin 80mg tablets manufactured by Dr Reddy's laboratories limited, India is Bioequivalent to the Lipitor 80mg and 40mg tablets respectively under fasting and fed conditions.

References:

1) FDA Draft Guidance on Atorvastatin Calcium
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075214.htm

2) Clinical pharmacology and Biopharmaceutics review of Lipitor, NDA: 20-702, Pg 20

3) Effect of Cytochrome P450 3A5 Genotype on Atorvastatin Pharmacokinetics and Its Interaction with Clarithromycin http://pharmacotherapyjournal.org/doi/abs/10.1592/phco.31.10.942

4) UK - Denmark PAR –Scientific discussion (Atorin)
http://www.hma.eu/fileadmin/dateien/pipar/dk1216atorin/parmod5_dk1216atorin.pdf

5) MHRA Public Assessment Report - UK
http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con140577.pdf
6) Bioequivalence Study Comparing a New 80 mg Atorvastatin Tablet to 80 mg Atorvastatin Commercial tablet. (Study No. NCT00917644)
http://clinicaltrials.gov/ct2/show/results/NCT00917644?sect=X0125#all

7) MHRA UKPAR – Pfizer (Lipitor 5, 10, 20, 40 mg Chewable tablets)
http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con102999.pdf

8) A randomized, open label single dose crossover study to assess effects of atorvastatin Or Valsartan co-administration on the pharmacokinetics of Naltrexone HCl and Bupropion HCl Sustained release tablets in healthy adult subjects. Shwan F et al
http://cdn.celerion.com/uploads/2012/01/Celerion_AAPS_2010-A_Randomized_Open-Label_Single-Dose_Crossover_Study_to_Assess_the_Effects_of_Atorvastatin_or_Valsartan.pdf

FDA COMMENT:

3. *Following the inspection of the clinical site, Nuvisan GmbH, Wegenerstrase 13, 89231 Neu-Ulm, Germany, from February 15, 2010 to February 19, 2010 by the office of Scientific Investigation (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the clinical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:*

a. *Possibility of administration of wrong medication in study subjects as the treatment information on dosing container as well as the source records concerning all drug product selection and repacking step were not provided.*

RESPONSE:

The investigational products used for the atorvastatin 80mg tablets study (Number : UA098) was administered directly from the original container, which was packed and labeled in compliance with national and EU GMP requirements and also released by QP (Qualified Person). As documented in the study file ***Annexure IV*** of ***Module 5.3.1.2***, there was no transfer to a special application container.

b. *Strict fasting conditions were not assured as all the subjects have free access to outdoor areas.*

RESPONSE:

Subjects were confined from the afternoon before dosing until the 24 hours post-dose samples were collected in each period. Before entering the Phase I area, staff members checked the contents of the study participant's bags. Only standardized meals and beverages were served during the in-house period, according to the study specific schedule based on the protocol requirements, therefore the fasting state of the subjects was assured. The outdoor area is visible, and controlled during the day and early evening and was locked after 10 p.m. The emergency exit is monitored by video. The compliance with the drinking restrictions was documented in the CRF. As such strict fasting conditions were maintained for the conduct of this study.

c. *Study data generated for certain periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.*

RESPONSE:

The study specific training and delegation of the operational staff was documented in the study file for UA098 and the same is provided in ***Annexure V*** of ***Module 5.3.1.2.***

d. Blood sample collection time points were not assured.

RESPONSE:

Blood sample collection time points were assured by documenting the actual time in the blood sample collection form of the CRF and signing with initials by the staff member who collected the sample. As an example, one CRF is attached as ***Annexure 1*** in ***Module 5.3.1.2.*** A list of sampling deviations record is captured in the study report 'Appendix 16.2.2.1 Sampling deviations'. The same is provided as ***Annexure II*** in ***Module 5.3.1.2***. Only actual times were used in the pharmacokinetic and statistical analysis to establish bioequivalence.

e. Fasting condition in subjects was not assured.

RESPONSE:

Subjects were confined from at least 14 hours before dosing until the 24 hours post-dose samples were collected in each period. Before entering the Phase I area, staff members checked the contents of the study participant's bags. Only standardized meals and beverages were served during the in-house period, all subjects were maintained fasted condition (overnight) for at least 10 hours before dosing on Day 1. Subjects received a standard meal at about, -12 hours prior to dosing and at 4, 8 and 12 hours after dosing in each period and complied to protocol requirements. The compliance with the drinking restrictions was documented in the individual subject case report form. As an example, CRF is attached as ***Annexure III*** in ***Module 5.3.1.2.*** Thus, strict fasting conditions were maintained for the conduct of this study.

FDA COMMENT:

4. Similarly, following the inspection of the analytical site, (b) (4) , on (b) (4) to by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

a. Failure to select appropriate concentrations for evaluating dilution linearity during validation.
b. Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.

RESPONSE:

We acknowledge the agency's comment. We have revisited our study reports, to verify the above listed specific objectionable findings from FDA for another application.

a. Failure to select appropriate concentrations for evaluating dilution linearity during validation.

Fed Study:

During the method validation, dilution integrity of the method was evaluated by diluting the stock solution of Drug, Metabolite-1 and Metabolite-2 prepared as spiked standards at concentrations 180ng/mL, 180ng/mL and 90.0ng/mL respectively in the screened plasma. Please refer Method Validation Report No. BRD-MV-210, Page no 65-70 in Module 5.3.1.4 of the original submission.

During study sample analysis of 09-VIN-105, total 21 samples were identified for repeat analysis under the category of "Above the upper limit of quantification" (AUL) (14 samples for drug and 7 samples for metabolite-1), from that maximum concentration was observed at 127ng/mL for Metabolite-1 while for drug it was observed at 116ng/mL. Repeat analysis was performed for Drug and Metabolite -1 by applying the dilution factor of two, the highest concentrations observed for both Drug and Metabolite 1 are well below the established dilution integrity concentration (i.e.180 ng/mL). Hence, the concentration selected for dilution integrity was appropriate and can be applied to 09-VIN-105 study sample analysis.

While reviewing the data, we observed typographical errors in 'Table 09: Reanalysis of Study Samples (Fed Study)' of the Bioequivalence Summary Tables and also in 'Table 12b: Subject Samples Repeat Analysis for Metabolite-1' of the bioanalytical study report. The corrected copies are provided in ***Module 5.3.1.4*** and ***Module 5.3.1.2*** respectively.

Fasting Study:

For study no.:10-VIN-095, none of samples were identified as 'Above the upper limit of quantification (AUL)', hence there is no impact on the study.

b. Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.

During study sample analysis of 09-VIN-105 and 10-VIN-095, none of the samples were identified as "Significant Response in pre-dose", hence there is no possibility for failure to follow SOPs concerning a subject sample with significant pre-dose concentration.

FDA COMMENT:

5. *The DBI has noticed that you were using a non-standard high-fat vegetarian breakfast in your fed study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBI does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.*

RESPONSE:

We acknowledge the agency's comment and would like to inform the Agency that, the components and composition of the high-fat, high-calorie breakfast used for fed bioequivalence study is as per FDA's guidance '*Food-Effect Bioavailability and Bioequivalence Studies'*.

Fed study menu (with Vegetarian high-fat, high-calorie breakfast) was planned according to USFDA guideline and menu fulfills all requirements pertaining to guideline. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

Soya bean contains 43% protein, which is higher than in other protein-rich foods, including meat and fish which contain about 20%. The proteins of soya bean yield all the essential amino acids in adequate amounts, except methionine and cystine. Texturized soya bean protein is being increasingly used as 'artificial meat' in ready-made foods.[1]

An animal protein is called "complete protein" as it contains all essential amino acids and plant (vegetable) protein is "incomplete protein". However, soya protein is an exception to plant protein [soya protein is deficient in methionine and cystine (essential amino acids)][1, 2]. There is no known effect of methionine on absorption of drug. Based on this, "meat protein" was replaced with "soya protein" with respect to protein source as a part of high-fat, high-calorie breakfast for fed BE study. Hence, "soya bean" was used instead of "meat" as a part of High-fat, high-calorie breakfast in current study.

REFERENCES:

1. Clinical Dietetics and Nutrition; fourth edition, by F.P. Antia & Philip Abraham, OXFORD University press.

2. Food Sources of Protein: Animal and Vegetable Protein Sources and Content; adopted from source: http://www.dietaryfiberfood.com/protein/food-sources-of-protein.php

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of June 29, 2012.

Please contact the undersigned at 908-203-4977 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,
DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi.

Jaya Ayyagari,
Senior Manager – Regulatory Affairs as Designee for
Kimberly Ernst,
Director – Regulatory Affairs

BIOEQUIVALENCE AMENDMENT

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Dr. Reddy's Laboratories Limited — TEL: 908-203-7022

ATTN: Kimberly Ernst — FAX: 908-203-4980

FROM: Nam J. Chun — FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on September 27, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

Reference is also made to your amendment dated February 21, 2011 and March 18, 2011.

The Division of Bioequivalence I has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** 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 I, 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: 202357

APPLICANT: Dr. Reddys Laboratories

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

1. You have not provided the potency (assay) data of the reference listed drug (RLD) lot 04568V (80 mg). Please provide the Certificate of Analysis (COA) of the RLD lot number 04568V.

2. As shown in the table below, the atorvastatin C_{MAX} and AUC values for both test and reference treatments in your current fed bioequivalence (BE) study No. 10-VIN-105 on the 80 mg tablet strength, using the dosage of 1x80 mg, were approximately two times (or greater) those determined for the fed BE study on the 40 mg strength (ANDA 091650) of both test and reference treatments (using the dosage of 1x40 mg), as expected. However, the atorvastatin C_{MAX} and AUC values for both test and reference treatments in your current fasting BE study No. 10-VIN-095 on the 80 mg tablet strength, using the dosage of 1x80 mg, were comparable with those determined for the fasting BE study on the 40mg strength (ANDA 091650) (using the dosage of only 1x40 mg). Please explain this observed inconsistency in the pharmacokinetic (PK) results for these BE studies.

		FASTING (D=1x40 mg)	FASTING (D=1x40 mg)	FED (D=1x40 mg)	FED (D=1x40 mg)
91650	REDDY	T	R	T	R
40mg Atorvastatin	AUCT (hr.ng/mL)	125.94	130.62	107.03	113.44
	AUCI (hr.ng/mL)	129.25	135.96	110.65	116.6
	CMAX (ng/mL)	28.71	30.24	13.89	15.17
		FASTING (D=1x80 mg)	FASTING (D=1x80 mg)	FED (D=1x80 mg)	FED (D=1x80 mg)
202357	REDDY	T	R	T	R
80mg Atorvastatin	AUCT (hr.ng/mL)	120.89	109.02	260.85	294.38
	AUCI (hr.ng/mL)	125.28	113.82	263.82	297.41
	CMAX (ng/mL)	36.37	33.41	49.11	54.39

D: Dose

3. Following the inspection of the clinical site, Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany, from February 15, 2010 to February 19, 2010 by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the clinical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

   a. *Possibility of administration of wrong medication in study subjects as the treatment information on dosing container, as well as the source records concerning all drug product selection and repacking step were not provided.*
   b. *Strict fasting conditions were not assured as all the subjects have free access to outdoor areas.*
   c. *Study data generated for certain periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.*
   d. *Blood sample collection time points were not assured.*
   e. *Fasting condition in subjects was not assured.*

4. Similarly, following the inspection of the analytical site, (b) (4) (b) (4) on (b) (4) (b) (4) to by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

   a. *Failure to select appropriate concentrations for evaluating dilution linearity during validation.*
   b. *Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.*

5. The DBI has noticed that you were using a non-standard high-fat vegetarian breakfast in your fed study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBI does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.

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
06/15/2012

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

June 27, 2012

Office of Generic Drugs,
Food and Drug Administration,
Center for Drug Evaluation and Research,
Document Control Room,
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773 (240-276-9327)

Reference: ANDA # 202357, eCTD Seq.0015
Atorvastatin Calcium Tablets, 80mg
Telephone Amendment
Submitted via Electronic Submission Gateway

Dear Sir/Madam,

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a 'Telephone Amendment' in response to deficiency letter dated June 26, 2012. A copy of the ***deficiency letter*** is provided along with this cover letter for quick reference.

FDA comment:

(b) (4)

RESPONSE:

(b) (4)

The revised drug product release specification is provided in ***Module 3.2.P.5.1*** and an updated certificate of analysis for the exhibit batch is provided in ***Module 3.2.P.5.4*** of this submission.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also verify that all the files in the submission were checked and verified to be free of viruses using McAfee® VirusScan® Enterprise, Program Version 8.7i and scan engine 5400 with a virus definition dated June 27, 2012.

Please contact the undersigned at 908-203-4977 by phone or by fax at 908-203-4980 or by email at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A-Jayalakshmi

Jaya Ayyagari
Senior Manger - Regulatory Affairs as Designee for
Kimberly Ernst
Director - Regulatory Affairs

TELEPHONE AMENDMENT FAX

ANDA: 91650

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: Dr. Reddy's Laboratories Inc.
ATTN: Jaya Ayyagari

TEL: 908-203-4977
FAX: 908-203-4980

FROM: Matthew Vera

FDA CONTACT PHONE: 240-276-8493

Dear Sir / 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, and 40 mg.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to this deficiency with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of the Chemist at 240-276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

CHEMISTRY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 91650 APPLICANT: Dr. Reddy's Laboratories Inc.

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

The deficiency presented below represents a telephone deficiency.

Please note: The following deficiency also applies to ANDA 202357 for atorvastatin calcium tablets, 80 mg:

(b) (4)

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

June 25, 2012

Office of Generic Drugs,
Food and Drug Administration,
Center for Drug Evaluation and Research,
Document Control Room,
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773 (240-276-9327)

Reference: ANDA # 202357, eCTD Seq.0014
Atorvastatin Calcium Tablets, 80mg
Telephone Amendment –Chemistry
Submitted via Electronic Submission Gateway

Dear Sir/Madam,

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a 'Telephone Amendment' in response to deficiency letter dated June 21, 2012. A copy of the ***deficiency letter*** is provided along with this cover letter for quick reference.

FDA comment:

(b) (4)

RESPONSE:

As recommended by the agency, the specification and test procedure for Crospovidone NF is revised to make in-line with the current NF monograph and the revised Specification and Certificate of Analysis are provided in ***Module 3.2.P.4.1*** and Test Procedure is provided in ***Module 3.2.P.4.2*** of this submission.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also verify that all the files in the submission were checked and verified to be free of viruses using McAfee® VirusScan® Enterprise, Program Version 8.7i and scan engine 5400 with a virus definition dated June 25, 2012.

DR. REDDY'S

Please contact the undersigned at 908-203-4977 by phone or by fax at 908-203-4980 or by email at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A Jayalakshmi

Jaya Ayyagari
Senior Manger - Regulatory Affairs as Designee for
Kimberly Ernst
Director - Regulatory Affairs

TELEPHONE AMENDMENT FAX

ANDA: 202357

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: Dr. Reddy's Laboratories Inc. TEL: 908-203-4977
ATTN: Jaya Ayyagari FAX: 908-203-4980

FROM: Matthew Vera FDA CONTACT PHONE: 240-276-8493

Dear Sir / Madam:

This facsimile is in reference to your abbreviated new drug application dated Sept 27, 2010 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to this deficiency with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of the Chemist at 240-276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

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CHEMISTRY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 202357 APPLICANT: Dr. Reddy's Laboratories Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The deficiency presented below represents a telephone deficiency.

(b) (4)

[redacted]

* * * COMMUNICATION RESULT REPORT (JUN. 21. 2012 10:41AM) * * *

FAX HEADER 1: OFF OF GENERIC DRUGS
FAX HEADER 2:

TRANSMITTED/STORED : JUN. 21. 2012 10:40AM FILE MODE OPTION	ADDRESS	RESULT	PAGE
1484 MEMORY TX	19084501476	OK	2/2

REASON FOR ERROR
E-1) HANG UP OR LINE FAIL
E-2) BUSY
E-3) NO ANSWER
E-4) NO FACSIMILE CONNECTION

TELEPHONE AMENDMENT FAX

ANDA: 202357

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: Dr. Reddy's Laboratories Inc.
ATTN: Jaya Ayyagari

TEL: 908-203-4977
FAX: 908-203-4980

FROM: Matthew Vera

FDA CONTACT PHONE: 240-276-8493

Dear Sir / Madam:

This facsimile is in reference to your abbreviated new drug application dated Sept 27, 2010 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

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TELEPHONE AMENDMENT FAX

ANDA: 202357

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: Dr. Reddy's Laboratories Inc.
ATTN: Jaya Ayyagari

TEL: 908-203-4977
FAX: 908-203-4980

FROM: Matthew Vera

FDA CONTACT PHONE: 240-276-8493

Dear Sir / Madam:

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CHEMISTRY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 202357 APPLICANT: Dr. Reddy's Laboratories Inc.

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The deficiency presented below represents a telephone deficiency.

(b) (4)

[redacted]

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

/s/

MATTHEW D VERA
06/21/2012

LAXMA R NAGAVELLI
06/21/2012

BIOEQUIVALENCE AMENDMENT

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Dr. Reddy's Laboratories Limited TEL: 908-203-7022

ATTN: Kimberly Ernst FAX: 908-203-4980

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on September 27, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

Reference is also made to your amendment dated February 21, 2011 and March 18, 2011.

The Division of Bioequivalence I has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** 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 I, 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: 202357

APPLICANT: Dr. Reddys Laboratories

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

1. You have not provided the potency (assay) data of the reference listed drug (RLD) lot 04568V (80 mg). Please provide the Certificate of Analysis (COA) of the RLD lot number 04568V.

2. As shown in the table below, the atorvastatin C_{MAX} and AUC values for both test and reference treatments in your current fed bioequivalence (BE) study No. 10-VIN-105 on the 80 mg tablet strength, using the dosage of 1x80 mg, were approximately two times (or greater) those determined for the fed BE study on the 40 mg strength (ANDA 091650) of both test and reference treatments (using the dosage of 1x40 mg), as expected. However, the atorvastatin C_{MAX} and AUC values for both test and reference treatments in your current fasting BE study No. 10-VIN-095 on the 80 mg tablet strength, using the dosage of 1x80 mg, were comparable with those determined for the fasting BE study on the 40mg strength (ANDA 091650) (using the dosage of only 1x40 mg). Please explain this observed inconsistency in the pharmacokinetic (PK) results for these BE studies.

		FASTING (D=1x40 mg)	FASTING (D=1x40 mg)	FED (D=1x40 mg)	FED (D=1x40 mg)
91650	REDDY	T	R	T	R
40mg Atorvastatin	AUCT (hr.ng/mL)	125.94	130.62	107.03	113.44
	AUCI (hr.ng/mL)	129.25	135.96	110.65	116.6
	CMAX (ng/mL)	28.71	30.24	13.89	15.17
		FASTING (D=1x80 mg)	FASTING (D=1x80 mg)	FED (D=1x80 mg)	FED (D=1x80 mg)
202357	REDDY	T	R	T	R
80mg Atorvastatin	AUCT (hr.ng/mL)	120.89	109.02	260.85	294.38
	AUCI (hr.ng/mL)	125.28	113.82	263.82	297.41
	CMAX (ng/mL)	36.37	33.41	49.11	54.39

D: Dose

3. Following the inspection of the clinical site, Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-Ulm, Germany, from February 15, 2010 to February 19, 2010 by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the clinical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

   a. *Possibility of administration of wrong medication in study subjects as the treatment information on dosing container, as well as the source records concerning all drug product selection and repacking step were not provided.*
   b. *Strict fasting conditions were not assured as all the subjects have free access to outdoor areas.*
   c. *Study data generated for certain periods were not assured as documentation during inspection in support of study-specific training of staff could not be provided.*
   d. *Blood sample collection time points were not assured.*
   e. *Fasting condition in subjects was not assured.*

4. Similarly, following the inspection of the analytical site, (b) (4) , on (b) (4) (b) (4) to by the Office of Scientific Investigations (OSI), for another application, Form FDA-483 was issued for the site. Subsequently, the analytical site provided its response to Form 483 and this response was included in the final evaluation by the OSI. For considering the impact of similar study conduct and site practices by the same analytical facility on the bioequivalence (BE) studies of the current ANDA, the DBI reviewed the aforementioned OSI inspection report and found that the following specific objectionable findings could potentially compromise the results of your bioequivalence studies:

   a. *Failure to select appropriate concentrations for evaluating dilution linearity during validation.*
   b. *Failure to follow SOPs concerning a subject sample with significant pre-dose concentration.*

5. The DBI has noticed that you were using a non-standard high-fat vegetarian breakfast in your fed study (Study No. 09-VIN-105). Currently, there are no adequate data from which to conclude that a high-fat vegetarian breakfast served prior to dosing in bioequivalence fed studies will have the same effect on drug absorption as the standard FDA high-fat breakfast using meat as the main protein source. Therefore, the DBI does not encourage the use of vegetarian breakfasts for any future fed bioequivalence studies.

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
06/15/2012

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

June 14 2012

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855

Reference : ANDA # 202357 , eCTD Seq 0013
Atorvastatin Calcium Tablets, 80 mg
Gratuitous (Chemistry) Amendment
Submitted via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a gratuitous Chemistry Amendment. This submission addresses the request received through teleconference from CMC review team (OGD and DMEP) on May 29, 2012 and the subsequent telephonic deficiency dated June 01 and June 04, 2012 for ANDA 091650 for Atorvastatin Tablets 10 mg, 20 mg and 40 mg .

As indicated in the Telephone chemistry amendment dated June 14, 2012 for ANDA 091650, the

(b) (4)

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® VirusScan® Enterprise, Program Version 8.7i and scan engine 5400 with a virus definition dated June 14,2012 .

DR. REDDY'S

Please contact the undersigned at 908-203-4977 by phone or by fax at 908-203-4980 or by e-mail at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi

Jaya Ayyagari
Senior Manger – Regulatory Affairs as Designee for
Kimberly Ernst
Director – Regulatory Affairs

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

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May 23, 2012

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855

Reference : ANDA # 202357 , eCTD Seq 0012
Atorvastatin Calcium Tablets, 80 mg
Gratuitous (Chemistry) Amendment
Submitted via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a gratuitous Chemistry Amendment. This submission addresses the comments received for ANDA 091650 via telephonic deficiency letter dated May 18, 2012.Referrence is made to the telephonic chemistry amendment dated May 21, 2012 and May 22, 2012 submitted for ANDA 091650 .

As indicated in the response # 1 for ANDA 091650 (May 21,2012 amendment) we would like to confirm that (b) (4)

(b) (4)

As indicated under response # 2 for ANDA 091650 (May 21,2012 amendment) , the certificate of analysis of the material used in the Ames test (Batch number ABAA0840) showing the levels of each degradant present in the sample is provided in ***Module 3.2.P.5.6.***

Please note that the level of (b) (4) in the material used in above Ames test is (b) (4) % (at RRT: (b) (4)).

DR. REDDY'S

We would also like to propose the following specification limits for (b) (4) and (b) (4)

Impurity	Release	Stability
(b) (4)	NMT (b) (4) %	NMT (b) (4) %
	NMT %	NMT %

The revised drug product release and stability specifications are provided in **Module 3.2.P.5.1**.

Reference is made to the telephonic amendments dated May 21, 2012 and May 22, 2012 for ANDA 091650 for a detailed justification for (b) (4) limits.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® VirusScan® Enterprise, Program Version 8.7i and scan engine 5400 with a virus definition dated May 22, 2012.

Please contact the undersigned at 908-203-4977 by phone or by fax at 908-203-4980 or by e-mail at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi.

Jaya Ayyagari
Senior Manger – Regulatory Affairs as Designee for
Kimberly Ernst
Director – Regulatory Affairs

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
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Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

May 17, 2012

Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855

Ref : ANDA # 091650, eCTD Seq 0013
Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg
&
ANDA # 202357, eCTD Seq 0011
Atorvastatin Calcium Tablets, 80 mg.
Labeling Amendment
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 091650 for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg and ANDA # 202357, Atorvastatin Calcium Tablets, 80 mg.Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a labeling amendment in response to the labeling deficiency letter dated May 16, 2012. A copy of the letter is provided along with the cover letter for quick reference.

FDA Comment:

1. ***CONTAINER:***

   *Revise the "*Each tablet contains ... ' statement to read "'Each film-coated tablet contains Atorvastatin calcium equivalent to_X_ mg atorvastatin".*

RESPONSE

We acknowledge the agency's comment .We commit to revise the container labels as recommended by the agency and submit the revised labels as a post approval change.

FDA Comment:

(b) (4)

RESPONSE

We acknowledge the agency's comment .We would like to clarify that we have withdrawn the (b) (4) (b) (4) via Gratuitous CMC amendment dated February , 2012. The change was also reflected in the revised PI submitted to agency on March 05, 2012.

FDA Comment:

3. ***INSERT:***

FULL PRESCRIBING INFORMATION: CONTENTS•

i. *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).

ii. *Revise subheading "6.2 Postintroduction Reports" to read "6.2 Postmarketing Experience".*

iii. *Revise subheadings 14.2 and 14.3 to read as follows;*

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

14.3 Hypertriglyceridemia (Fredrickson Type IV)

iv. *Revise the subheading 7.1 to read "7.1 Strong Inhibitors of CYP 3A4".*

v. *Delete the following subtitles locate under subheading 7.1.*
Clarithromycin
Combination of Protease Inhibitors
Itraconazole

Revise your labeling as instructed above, and submit final printed labeling electronically.

RESPONSE

We acknowledge the agency's comment .We commit to revise the container labels as recommended by the agency and submit the revised labels as a post approval change.

ANDA # 091650, eCTD Seq 0013
Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg
&
ANDA # 202357, eCTD Seq 0011
Atorvastatin Calcium Tablets, 80 mg.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of May 17, 2012.

Please contact the undersigned at 908-203-4977 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi.

Jaya Ayyagari,
Senior Manager – Regulatory Affairs as Designee for
Kimberly Ernst
Director, Regulatory Affairs

Please send an email to the labeling reviewer (betty.turner@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8728)

TO: Dr. Reddy's Laboratories Limited

TEL: (908) 203-7022

ATTN: Kimberly Ernst

FAX: (908) 203-4980

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, 80 mg.

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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

ANDA Number: 202357 Date of Submission: March 5, 2012

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

LABELING DEFICIENCIES:

1. **CONTAINER:**

   Revise the "*Each tablet contains..." statement to read "*Each film-coated tablet contains Atorvastatin calcium equivalent to __X__ mg atorvastatin".

2. (b) (4)

3. **INSERT:**

   FULL PRESCRIBING INFORMATION: CONTENTS*

   i. 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)

   ii. Revise subheading "6.2 Postintorduction Reports" to read "6.2 Postmarketing Experience".

   iii. 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)

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

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

Revise your labeling as instructed above, and submit final printed 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/

BETTY B TURNER
05/15/2012
For Wm Peter Rickman

Please send an email to the labeling reviewer (betty.turner@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8728)

TO: Dr. Reddy's Laboratories Limited

TEL: (908) 203-7022

ATTN: Kimberly Ernst

FAX: (908) 203-4980

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, 80 mg.

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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

ANDA Number: 202357 Date of Submission: March 5, 2012

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

LABELING DEFICIENCIES:

1. **CONTAINER:**

   Revise the "*Each tablet contains…" statement to read "*Each film-coated tablet contains Atorvastatin calcium equivalent to __X__ mg atorvastatin".

2. (b) (4)

3. **INSERT:**

   FULL PRESCRIBING INFORMATION: CONTENTS*

   i. 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)

   ii. Revise subheading "6.2 Postintorduction Reports" to read "6.2 Postmarketing Experience".

   iii. 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)

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

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

Revise your labeling as instructed above, and submit final printed 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/

BETTY B TURNER
05/15/2012
For Wm Peter Rickman

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

April 27, 2012

Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855

Ref : ANDA # 202357, eCTD Seq 0010
Atorvastatin Calcium Tablets, 80 mg.
Patent Amendment: Update on Paragraph IV certification and request for approval
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets 80 mg, Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a patent amendment.

The original ANDA submission for Atorvastatin Calcium Tablets, 80 mg dated September 27,2010 included a paragraph IV certification for Patents 5,686,104 ; 5,969,156 and 6,126,971 . A copy of the return receipt acknowledging the receipt of Paragraph IV notification by the Patent /NDA holder is provided as **Exhibit # 1** to the cover letter.

We would like to confirm that patent infringement actions were brought against Dr. Reddy's Laboratories (Case no 10-01135-LPS) for Patent 5,969,156 within the stipulated time. The case has been dismissed with Dr. Reddy's maintaining all of its paragraph IV certifications and having the right to launch prior to expiration of these patents. A copy of the stipulation of dismissal is attached as **Exhibit # 2.**

Dr Reddy's was not sued for the patents 5,686,104 and 6,126,971.

Based on the above information, Dr Reddy's Laboratories request the approval of the application upon the expiry of the 180 day exclusivity associated with the first generic applicant.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of April 26, 2012,

Please contact the undersigned at 908-203-4977 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A Jayalakshmi

Jaya Ayyagari,
Senior Manager – Regulatory Affairs as Designee for
Kimberly Ernst
Director, Regulatory Affairs

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4900
Fax: (908) 203-4970

www.drreddys.com

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

TO: **Jeffrey B. Kindler**
CEO & Chairman of the Board
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

President
Warner-Lambert Company
201 Tabor Road
Morris Plains, NJ 07950

FROM: **Dr. Reddy's Laboratories, Ltd.**
Dr. Reddy's Laboratories, Inc.

DATED: **November 29, 2010**

RE: **NOTICE OF PARAGRAPH IV CERTIFICATION RE: DR. REDDY'S LABORATORIES, LTD.'S AND DR. REDDY'S LABORATORIES, INC.'S ATORVASTATIN CALCIUM TABLETS, EQ. 80 MG BASE; US PATENT NOS. 5,686,104, 5,969,156 AND 6,126,971**

Dear Sirs:

Pursuant to § 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act ("the Act") and § 314.95 of Title 21 of the Code of Federal Regulations ("CFR"), please be advised that Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively, "DRL") have filed a patent certification pursuant to § 505(j)(2)(A)(vii)(IV) of the Act and § 314.94(a)(12)(i)(A)(4) of Title 21 of the CFR in support of their Abbreviated New Drug Application ("ANDA") with respect to Atorvastatin Calcium tablets, eq. 80 mg base ("DRL's Atorvastatin Calcium 80 mg Tablets"). We understand that US Patent Nos. 5,686,104 ("the '104 patent"), 5,969,156 ("the '156 patent") and 6,126,971 ("the '971 patent") are assigned to Warner-Lambert Company, now Pfizer, Inc. ("Pfizer"). We also understand that Pfizer is the holder of the application under § 505(b) of the Act (New Drug Application or "NDA") in connection with Atorvastatin Calcium Tablets, eq. 80 mg base.

DRL provides the following information:

(1) The U.S. Food and Drug Administration ("FDA") has received an ANDA submitted by DRL containing the required bioavailability or bioequivalence data or information with respect to Atorvastatin Calcium Tablets, eq. 80 mg base;

(2) The ANDA number is 202357;

(3) The established name of the proposed drug product, as defined in § 502(e)(3) of the Act, is atorvastatin calcium;

(4) The active ingredient of the proposed drug products is atorvastatin calcium, the strength is eq. 80 mg base and the dosage form is oral tablets;

(5) The U.S. patent numbers and expiration dates, as known to DRL, of the patents alleged to be invalid, unenforceable or not infringed in this certification are:

a) U.S. Patent No. 5,686,104 ("the '104 patent"), which is listed in the Electronic "Approved Drug Product with Therapeutic Equivalents" ("Orange Book") as expiring on November 11, 2014, with pediatric exclusivity expiring on May 11, 2015;

b) U.S. Patent No. 5,969,156 ("the '156 patent"), which is listed in the Electronic "Approved Drug Product with Therapeutic Equivalents" ("Orange Book") as expiring on July 8, 2016, with pediatric exclusivity expiring on January 8, 2017; and

c) U.S. Patent No. 6,126,971 ("the 971 patent"), which is listed in the Electronic "Approved Drug Product with Therapeutic Equivalents" ("Orange Book") as expiring on July 19, 2013, with pediatric exclusivity expiring on July 19, 2013.

(6) The information detailed in this letter and the attached memo is supplied for the sole purpose of complying with the above-referenced statutes and regulations, and neither DRL nor its attorneys waive any attorney-client privilege or attorney work product immunity concerning the subject matter of this communication; and

(7) DRL reserves its right to supplement this letter and the attached memorandum detailing the factual and legal bases for DRL's assertion of invalidity, unenforceability and/or non-infringement of the '104, '156 and

'971 patents should subsequent investigations reveal additional grounds for asserting invalidity, unenforceability and/or non-infringement.

DRL is seeking approval from the FDA to market and sell DRL's Atorvastatin Calcium Tablets, eq. 80 mg base. DRL certified with the FDA pursuant to § 505(j)(2)(A)(vii)(IV) of the Act and 21 C.F.R. § 314.94(a)(12)(i)(A)(4) ("Paragraph IV Certification") that the '104, '156 and '971 patents are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer to sell or importation into the U.S. of the DRL's Atorvastatin Calcium 80 mg Tablets for which DRL has submitted its application.

Offer of Confidential Access: In addition to and not in lieu of the limitations contained in 21 U.S.C. § 355(j)(5)(C)(i)(III) (as amended December 8, 2003) DRL hereby offers conditional access to only those portions of DRL's ANDA that, in DRL's judgment, are needed by Pfizer to determine whether an action under Section 355 should be filed. Access to the information is and shall be limited to only those attorneys acting as outside counsel for Pfizer that are needed to evaluate the information and such persons who are to have access shall be identified to DRL's counsel, Bruce D. Radin, Esq., at Budd Larner, P.C., before access is granted. Such persons so identified shall agree in writing that the information can only be used for the stated purpose. Any tangible form of information derived from a review of the material shall be destroyed, with notice to DRL, within 45 days of inspection or upon the filing of an action against DRL, whichever is earlier. Access may only be had at the office of Budd Larner, P.C. at a time and date convenient to the parties.

Pursuant to 21 C.F.R. § 314.95(c)(7), DRL authorizes the following agent to accept service of process:

Bruce D. Radin, Esq.
Budd Larner, P.C.
150 John F. Kennedy Parkway
Short Hills, New Jersey 07078

Attached hereto is a memorandum setting forth DRL's detailed factual and legal bases supporting this Paragraph IV Certification.

Dr. Reddy's Laboratories, Ltd.
Dr. Reddy's Laboratories, Inc.

By: _____
Lee Banks, Esq.,
Vice President Legal Department
Dr. Reddy's Laboratories, Inc.

UNITED STATES POSTAL SERVICE

First-Class Mail
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USPS
Permit No. G-10

• Sender: Please print your name, address, and ZIP+4 in this box •

(b) (6)

Dr. Reddy's Laboratories, Inc.
200 Somerset Corp. Blvd.
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Search Results

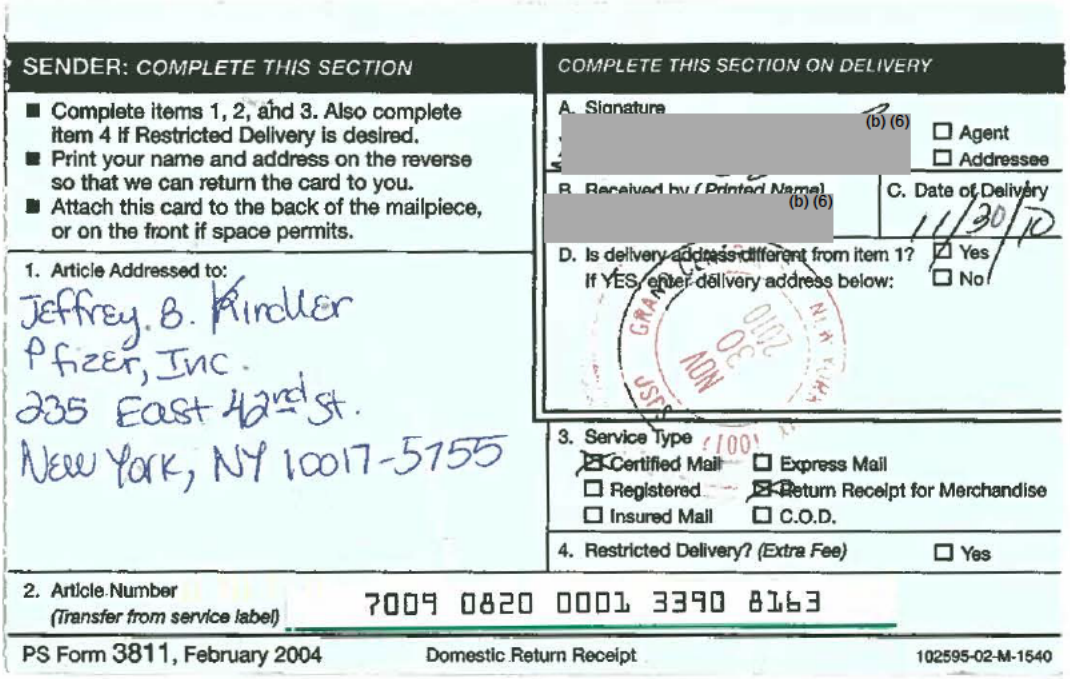
Label/Receipt Number: **7009 0820 0001 3390 8163**
Expected Delivery Date: **December 1, 2010**
Class: **Priority Mail®**
Service(s): **Certified Mail™**
Return Receipt
Status: **Delivered**

Track & Confirm
Enter Label/Receipt Number.
700
Go >

Your item was delivered at 12:32 pm on November 30, 2010 in NEW YORK, NY 10017.

Detailed Results:

- **Delivered, November 30, 2010, 12:32 pm, NEW YORK, NY 10017**
- **Arrival at Unit, November 30, 2010, 8:26 am, NEW YORK, NY 10017**
- **Acceptance, November 29, 2010, 4:30 pm, BRIDGEWATER, NJ 08807**



SENDER: *COMPLETE THIS SECTION*

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:
Jeffrey. B. Kindler
Pfizer, Inc.
235 East 42nd St.
New York, NY 10017-5755

COMPLETE THIS SECTION ON DELIVERY

A. Signature (b) (6) ☐ Agent ☐ Addressee

B. Received by (Printed Name) (b) (6) C. Date of Delivery 11/30/10

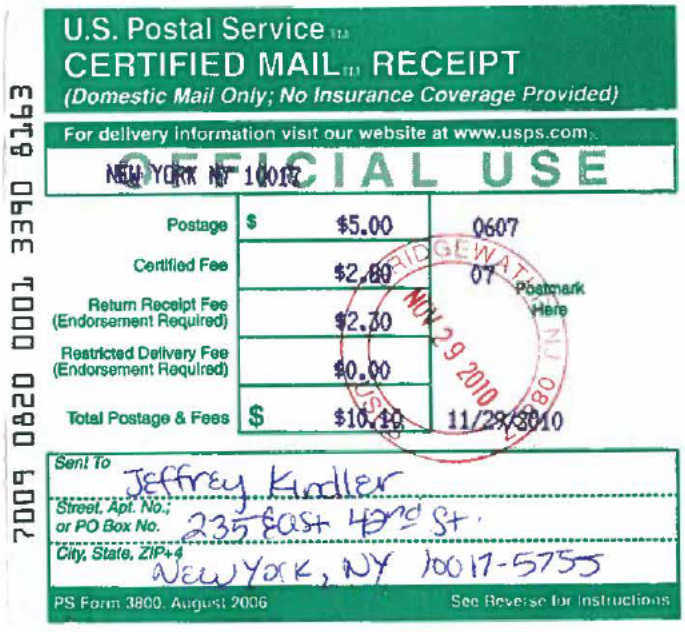
D. Is delivery address different from item 1? ☑ Yes
If YES, enter delivery address below: ☐ No

3. Service Type
☑ Certified Mail ☐ Express Mail
☐ Registered ☑ Return Receipt for Merchandise
☐ Insured Mail ☐ C.O.D.

4. Restricted Delivery? *(Extra Fee)* ☐ Yes

2. Article Number *(Transfer from service label)* 7009 0820 0001 3390 8163

PS Form 3811, February 2004 Domestic Return Receipt 102595-02-M-1540



U.S. Postal Service™
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For delivery information visit our website at www.usps.com®
NEW YORK NY 10017
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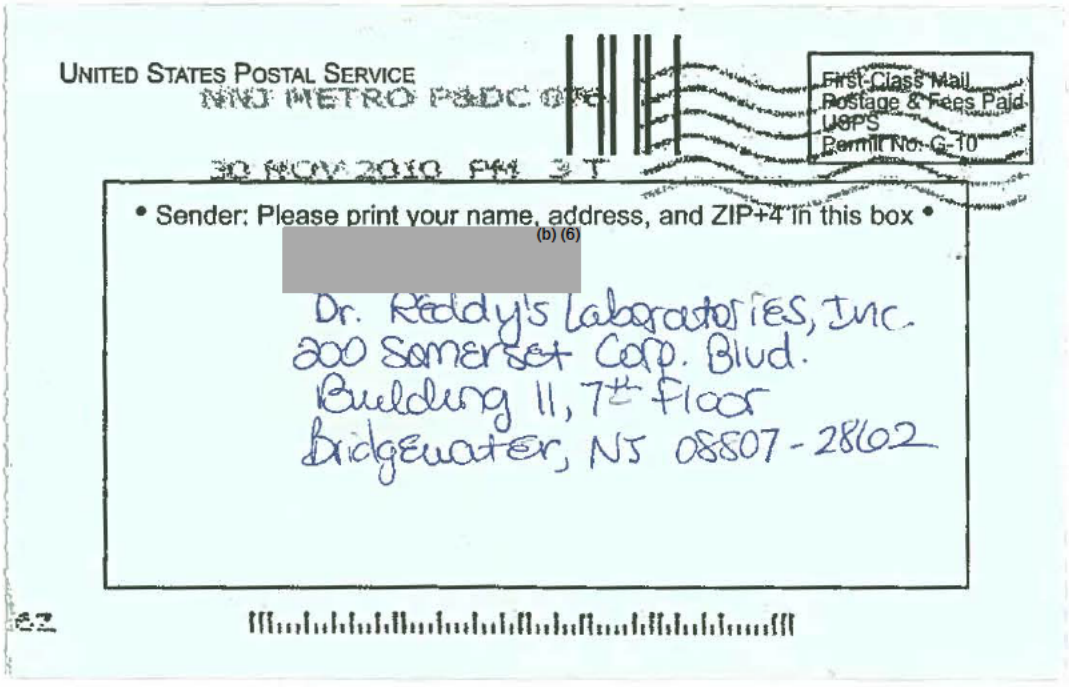
Postage	$ $5.00	0607
Certified Fee	$2.80	07 Postmark Here
Return Receipt Fee (Endorsement Required)	$2.30	
Restricted Delivery Fee (Endorsement Required)	$0.00	
Total Postage & Fees	$ $10.10	11/29/2010

BRIDGEWATER NJ 08807 NOV 29 2010 USPS

Sent To Jeffrey Kindler
Street, Apt. No.; or PO Box No. 235 East 42nd St.
City, State, ZIP+4 New York, NY 10017-5755

PS Form 3800, August 2006 See Reverse for Instructions

7009 0820 0001 3390 8163


UNITED STATES POSTAL SERVICE
NNJ METRO P&DC
30 NOV 2010 PM 3 T
First-Class Mail
Postage & Fees Paid
USPS
Permit No. G-10
• Sender: Please print your name, address, and ZIP+4 in this box •
(b) (6)
Dr. Reddy's Laboratories, Inc.
200 Somerset Corp. Blvd.
Building 11, 7th Floor
Bridgewater, NJ 08807-2862

Search Results

Label/Receipt Number: **7009 0820 0001 3390 8170**
Expected Delivery Date: **November 30, 2010**
Class: **Priority Mail®**
Service(s): **Certified Mail™**
Return Receipt
Status: **Delivered**

Track & Confirm
Enter Label/Receipt Number.
Go >

Your item was delivered at 9:01 am on November 30, 2010 in MORRIS PLAINS, NJ 07950.

Detailed Results:

- **Delivered, November 30, 2010, 9:01 am, MORRIS PLAINS, NJ 07950**
- **Arrival at Unit, November 30, 2010, 8:27 am, MORRIS PLAINS, NJ 07950**
- **Acceptance, November 29, 2010, 4:31 pm, BRIDGEWATER, NJ 08807**

SENDER: COMPLETE THIS SECTION

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:
President
Warner-Lambert Co.
201 Tabor Road
Morris Plains, NJ 07950

COMPLETE THIS SECTION ON DELIVERY

A. Signature
X (b) (6) ☐ Agent ☐ Addressee

B. Received by (Printed Name) (b) (6) C. Date of Delivery

D. Is delivery address different from item 1? ☐ Yes
If YES, enter delivery address below: ☐ No

3. Service Type
☒ Certified Mail ☐ Express Mail
☐ Registered ☑ Return Receipt for Merchandise
☐ Insured Mail ☐ C.O.D.

4. Restricted Delivery? *(Extra Fee)* ☐ Yes

2. Article Number *(Transfer from service label)* 7009 0820 0001 3390 8170

PS Form 3811, February 2004 Domestic Return Receipt 102595-02-M-1540

7009 0820 0001 3390 8170

U.S. Postal Service™
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For delivery information visit our website at www.usps.com®
MORRIS PLAINS NJ 07950 OFFICIAL USE

Postage	$ $5.00	0607
Certified Fee	$2.80	07
Return Receipt Fee (Endorsement Required)	$2.30	Postmark Here
Restricted Delivery Fee (Endorsement Required)	$0.00	
Total Postage & Fees	$ $10.10	11/29/2010

BRIDGEWATER NJ 08807 NOV 29 2010 USPS

Sent To President, Warner-Lambert Co.
Street, Apt. No.; or PO Box No. 201 Tabor Road
City, State, ZIP+4 Morris Plains, NJ 07950

PS Form 3800, August 2006 See Reverse for Instructions

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, and WARNER-LAMBERT COMPANY LLC,	)	
Plaintiffs,	)	
v.	)	Civil Action No. _____
DR. REDDY'S LABORATORIES LTD., and DR. REDDY'S LABORATORIES INC.,	)	
Defendants.	)	

COMPLAINT

Pfizer Inc., Pfizer Ireland Pharmaceuticals, and Warner-Lambert Company LLC, formerly Warner-Lambert Company (collectively, "Pfizer"), by their attorneys, for their Complaint against Dr. Reddy's Laboratories Ltd. ("Dr. Reddy's Ltd.") and Dr. Reddy's Laboratories Inc. ("Dr. Reddy's Inc.") (collectively, "Defendants"), allege as follows:

1. This is an action by Pfizer against Defendants for infringement of U.S. Patent No. 5,969,156 and its Reexamination Certificate (collectively "the '156 patent"). A copy of the '156 patent with the '156 Reexamination Certificate is attached hereto as Exhibit A.

PATENTS IN SUIT

2. On October 19, 1999, the United States Patent and Trademark Office (the "USPTO") issued the '156 patent, entitled "Crystalline [R-(R*,R*)]-2-(4-Fluorophenyl)-ß,δ-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-1H-Pyrrole-1-Heptanoic Acid Hemicalcium Salt (Atorvastatin)", on an application filed by Christopher Briggs, *et al.*, and

assigned to Warner-Lambert Company. On September 26, 2006, the USPTO issued an Ex Parte Reexamination Certificate for the '156 patent.

PARTIES, JURISDICTION AND VENUE

3. Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017.

4. Warner-Lambert Company is a corporation formerly organized under the laws of the State of Delaware with offices for service of process at 235 East 42nd Street, New York, New York 10017. Warner-Lambert Company has been the owner of record of the '156 patent since its issuance.

5. Warner-Lambert Company became a wholly-owned subsidiary of Pfizer Inc. effective June 19, 2000.

6. Warner-Lambert Company was converted into a Delaware limited liability company and changed its name to Warner-Lambert Company LLC on December 31, 2002. Warner-Lambert Company LLC has offices located at 235 East 42nd Street, New York, New York 10017.

7. Pfizer Ireland Pharmaceuticals is a partnership, organized and existing under the laws of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. Pfizer Ireland Pharmaceuticals is a wholly-owned, indirect subsidiary of Pfizer Inc.

8. Pfizer Ireland Pharmaceuticals is the exclusive licensee of the '156 patent.

9. Pfizer has all the right, title, and interest in the '156 patent and the right to sue for infringement thereof.

10. Pfizer holds an approved New Drug Application for atorvastatin calcium formulations, including 10 mg, 20 mg, 40 mg, and 80 mg dosage strengths, which it sells under the registered name Lipitor®.

11. The '156 patent is identified pursuant to 21 U.S.C. § 355(b)(1) and (j)(7) by the United States Food and Drug Administration ("FDA") as covering Pfizer's Lipitor® product.

12. By letter dated November 29, 2010 (the "ANDA Notice Letter"), Defendants notified Pfizer that Defendants had filed Abbreviated New Drug Application ("ANDA") No. 202357 seeking approval to market atorvastatin calcium tablets in an 80 mg dosage strength, and that Defendants were providing information to Pfizer pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) and 21 C.F.R. § 314.95. A copy of the ANDA Notice Letter on Dr. Reddy's Inc. letterhead is attached hereto as Exhibit B.

13. On information and belief, Defendant Dr. Reddy's Ltd. is a corporation operating and existing under the laws of India with its principal place of business at 7-1-27, Ameerpet, Hyderabad, 500 016, India.

14. On information and belief, Dr. Reddy's Inc. is a corporation operating and existing under the laws of New Jersey with a principal place of business at 200 Somerset Corporate Boulevard, Bridgewater, NJ 08807.

15. On information and belief, Defendant Dr. Reddy's Inc. is a wholly-owned subsidiary of Dr. Reddy's Ltd., and is controlled by Dr. Reddy's Ltd.

16. On information and belief, both Dr. Reddy's Ltd. and Dr. Reddy's Inc. participated in the preparation and/or filing of ANDA No. 202357.

17. On information and belief and as stated in the ANDA Notice Letter, the FDA received ANDA No. 202357 from Dr. Reddy's Ltd. and Dr. Reddy's Inc.

18. This action arises under the Patent Laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to the provisions of Title 28, United States Code, Sections 1331 and 1338.

19. On information and belief, Defendants are subject to personal jurisdiction in this District.

20. On information and belief, Defendants are in the business of developing and manufacturing generic and branded pharmaceutical products.

21. On information and belief, Defendants directly, or indirectly through subsidiaries and/or licensed third-party distributors, market, distribute, and sell their generic and branded pharmaceutical products within and throughout the United States, including the State of Delaware.

22. On information and belief, Defendants have purposefully availed themselves of the privilege of doing business in the State of Delaware by continuously and systematically placing goods into the stream of commerce for distribution throughout the United States, including the State of Delaware, and/or by selling, directly or through their agents, pharmaceutical products in the State of Delaware.

23. On information and belief, Defendants maintain distribution and supply agreements to distribute Defendants' pharmaceutical products with companies that operate throughout the United States, including in the State of Delaware, including, *inter alia*, Caremark, Rite-Aid, CVS Distribution Inc., and/or Walgreens (d/b/a Happy Harry's Discount Drug Stores).

24. On information and belief, Defendant Dr. Reddy's Ltd.'s generic versions of Depakote®, Risperdal®, Altace®, Effexor®, Lamictal®, Keppra®, Cipro®, Vasotec®, Floxin®, Daypro®, Zocor®, Coreg®, Norvasc®, Zonegran®, Celexa®, Ambien®, Dynacin®,

and Aleve® are available for purchase, and have been purchased and used, in the State of Delaware.

25. On information and belief, Defendant Dr. Reddy's Inc.'s generic versions of Imitrex®, Prozac®, Zanaflex®, Zocor®, Pravachol®, Lamisil®, and Ibuprofen are available for purchase, and have been purchased and used, in the State of Delaware.

26. On information and belief, Defendants' generic versions of Accupril® and Meprobamate are also available for purchase, and have been purchased and used, in the State of Delaware.

27. On information and belief, Defendants derive substantial revenue from the sale of pharmaceutical products used and/or consumed in the State of Delaware.

28. On information and belief, from January 2009 to October 2009, approximately $1.8 million worth of Defendants' pharmaceutical products were sold and used within the State of Delaware.

29. On information and belief, the sales from January 2009 to October 2009 of Defendants' pharmaceutical products in Delaware represent a greater than two thousand percent (2000%) increase in revenue when compared to sales of Defendants' pharmaceutical products in Delaware in all of 2007.

30. On information and belief, Defendants' maintain a global distribution supply agreement with UPS Supply Chain Solutions to distribute their FDA-approved generic and/or branded drugs throughout the United States, including the State of Delaware.

31. On information and belief, UPS Supply Chain Solutions maintains active Pharmacy-Wholesale and Distributor/Manufacturer CSR licenses with the Delaware Board of

Pharmacy, which allow UPS Supply Chain Solutions to distribute manufactured pharmaceuticals and/or controlled substances within the State of Delaware.

32. On information and belief, personal jurisdiction over Defendants is also proper because Defendants have sought affirmative relief in this jurisdiction by answering complaints and filing counterclaims in at least four cases since 2004, and because Defendants have employed Delaware counsel to assist in obtaining that relief.

33. In one of those cases, *Merck & Co., Inc. v. Dr. Reddy's Labs., Ltd.*, No. 04-1313 (GMS), Defendants admitted that they are "subject to personal jurisdiction in this judicial district," *i.e.*, the District of Delaware.

34. In another case, *Pfizer Inc. et al. v. Dr. Reddy's Labs. Ltd. et al.*, No. 09-943-LPS, where Pfizer brought an action against Defendants for infringement of the '156 patent upon Defendant's notification to Pfizer that Defendants had filed an ANDA seeking approval to market atorvastatin calcium tablets in 10 mg, 20 mg, and 40 mg dosage strengths, Defendants stated that it "consents to personal jurisdiction for the limited purpose of this action only." That action is still pending before this Court and involves similar issues as those raised by the instant Complaint.

35. Personal jurisdiction over Defendants is also proper because, by filing their ANDA No. 202357 for generic atorvastatin calcium tablets, they have committed the tort of patent infringement pursuant to 35 U.S.C. § 271(e)(2)(A) and the location of that tort is where the patent holder, Pfizer, resides, *i.e.*, in Delaware.

36. Venue is proper in this District pursuant to the provisions of Title 28, United States Code, Sections 1391(c) and (d), and 1400(b).

FIRST CLAIM FOR RELIEF:
INFRINGEMENT OF THE '156 PATENT

37. The allegations of paragraphs 1-36 above are repeated and realleged as if set forth fully herein.

38. The expiration date for the ‘156 patent is July 8, 2016.

39. Patents associated with Lipitor®, including the ‘156 patent, have been granted a further period of pediatric exclusivity under section 505a of the Food, Drug and Cosmetic Act [21 U.S.C. § 355a].

40. The pediatric exclusivity period associated with the ‘156 patent will expire January 8, 2017.

41. The ANDA Notice Letter notified Pfizer that Defendants, by filing ANDA No. 202357, seek approval from the FDA to engage in the commercial manufacture, use, and sale of products containing the 80 mg strength of atorvastatin calcium prior to the expiration of the ‘156 patent.

42. The ANDA Notice Letter addressed the ’156 patent and asserted that the patent was not infringed by Defendants’ proposed ANDA No. 202357 atorvastatin calcium product.

43. The ANDA Notice Letter did not provide an explanation of any grounds supporting a contention that any claim of the ‘156 patent is invalid, as would be required by 21 CFR § 314.95(c)(6)(ii) if Defendants contended that any of the claims were invalid.

44. Defendants have infringed the ‘156 patent under 35 U.S.C. § 271(e)(2)(A) by filing their ANDA No. 202357 seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing atorvastatin calcium prior to the expiration of the ‘156 patent.

45. Pfizer will be irreparably harmed if Defendants’ ANDA No. 202357 is approved prior to the expiration date of the ‘156 patent.

46. Pfizer will be irreparably harmed if Defendants are not enjoined from infringing the ‘156 patent.

PRAYER FOR RELIEF

WHEREFORE, Pfizer requests the following relief:

A. A judgment providing that pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any FDA approval of Defendants’ ANDA No. 202357 be no earlier than January 8, 2017, the date of expiration of the ‘156 Patent, including the period of exclusivity granted to Lipitor® under section 505a of the Food, Drug and Cosmetic Act;

B. A judgment pursuant to 35 U.S.C. § 271(e)(4)(B) permanently enjoining Defendants, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with it or any of them, from making, using, selling, offering to sell, or importing the atorvastatin calcium product described in Defendants’ ANDA No. 202357 until January 8, 2017, the expiration date of the ‘156 patent including the period of exclusivity granted to Lipitor® under section 505a of the Food, Drug and Cosmetic Act;

C. Attorneys’ fees in this action pursuant to 35 U.S.C. § 285;

D. Costs and expenses in this action; and

E. Such further and other relief as this Court may deem just and proper.

RESPECTFULLY SUBMITTED,

/s/ Rudolf E. Hutz
Rudolf E. Hutz (#484)
Jeffery B. Bove (#998)
Mary W. Bourke (#2356)
Daniel C. Mulveny (#3984)
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899-2207
(302) 658-9141 (telephone)
(302) 658-5614 (telefax)

OF COUNSEL:
William E. McShane
CONNOLLY BOVE LODGE & HUTZ LLP
1875 Eye Street, NW
Suite 1100
Washington, DC 20006
(202) 572-0335
Attorneys for Plaintiffs Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company LLC, and Warner-Lambert Company

Dated: December 27, 2010
992088_1.DOC

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER, INC., PFIZER IRELAND PHARMACEUTICALS, WARNER -LAMBERT COMPANY, and WARNER -LAMBERT COMPANY LLC,	)	
Plaintiffs,	)	Civil Nos. 09-943-LPS and 10-01135-LPS
v.	)	
DR. REDDY'S LABORATORIES LTD, and DR. REDDY'S LABORATORIES INC.,	)	
Defendants.,	)	

ORDER

The Court having considered the Joint Motion to Dismiss submitted by the Parties in the above-captioned matter pursuant to Fed.R.Civ.P. 41(a)(2), hereby orders as follows:

1. All claims and counterclaims in this action are dismissed without prejudice, each Party to bear its own costs, expenses and attorneys' fees in connection with this action;

2. This dismissal shall not act as an adjudication on the merits;

3. The Protective Order entered by the Court in this action shall remain in full force and effect notwithstanding the dismissal by the court of this action;

4. The parties expressly waive any right of appeal from this Order; and

5. The Court reserves jurisdiction over this Order in the event of any dispute concerning it.

IT IS SO ORDERED, this 29th day of August, 2011.

The Honorable Leonard P. Stark
United States District Judge

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

April 11, 2012

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

Office of Generic Drugs,
Center for Drug Evaluation and Research,
Food and Drug Administration
Document Control Room,
Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

Reference: **ANDA # 091650, eCTD Seq 0011**
Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg
&
ANDA # 202357, eCTD Seq 0009
Atorvastatin Calcium tablets, 80mg
Telephone Amendment – LOA for DMF 25902
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 091650 for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg and ANDA # 202357, Atorvastatin Calcium tablets, 80mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a telephone amendment to include the LOA for DMF # (b) (4) for (b) (4).

Reference is made to the telephone amendment dated March 26, 2012 to include the LOA for DMF submitted on March 23, 2011 for (b) (4). We are resubmitting the LOA for (b) (4) with DMF number included (DMF # (b) (4)) in the LOA .The updated LOA is provided in **Module 1.4.1** of this submission.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify all files in the submission were checked and verified to be free of viruses, using McAfee® VirusScan® Enterprise, program version 8.7i and scan engine version 5400 with a virus definition date of April 10,2012 .

Please contact the undersigned at 908-203-4977 by phone or at 908-203-4980 by fax or by email at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi

Jaya Ayyagari,
Senior Manager - Regulatory Affairs as Designee for
Kimberly Ernst,
Director Regulatory Affairs

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and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

March 26, 2012

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

Office of Generic Drugs,
Center for Drug Evaluation and Research,
Food and Drug Administration
Document Control Room,
Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

Reference: **ANDA # 091650, eCTD Seq 0010**
Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg
&
ANDA # 202357, eCTD Seq 0008
Atorvastatin Calcium tablets, 80mg
Telephone Amendment
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 091650 for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg and ANDA # 202357, Atorvastatin Calcium tablets, 80mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a telephone amendment .This is in response to the telephonic conversation with Dr. Laxma Nagavelli and Dr. Khalid Khan on March 15, 2012.

As recommended by the agency the DMF 21125 is amended and is designated as Atorvastatin Calcium. The DMF holder has also confirmed that a separate DMF (new) is also submitted to agency on March 23, 2012 for [redacted] (b) (4). A copy of the Letter of Authorization for the new DMF for [redacted] (b) (4) is provided in **Module 1.4.1** of this submission.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify all files in the submission were checked and verified to be free of viruses, using McAfee® VirusScan® Enterprise, program version 8.7i and scan engine version 5400 with a virus definition date of March 26, 2012.

Please contact the undersigned at 908-203-4977 by phone or at 908-203-4980 by fax or by email at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi

Jaya Ayyagari,
Senior Manager - Regulatory Affairs as Designee for
Kimberly Ernst,
Director Regulatory Affairs

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

March 05, 2012

Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place,
Rockville, Maryland 20855

Reference: ANDA # 202357, eCTD Seq 0007
Atorvastatin Calcium Tablets, 80 mg
Gratuitous Labeling Amendment
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Gratuitous Labeling Amendment.

The package insert labeling is revised to be in accordance with the current version of the RLD labeling Lipitor® (atorvastatin calcium) tablets approved on February 28, 2012.

The following Labeling files are included in this submission.

1. Final container and [redacted] (b) (4) in ***Module 1 (1.14.2.1)***
2. Final Package Insert Labeling and final Patient Information Leaflet in ***Module 1 (1.14.2.2)***
3. Structured Product Labeling in XML format in ***Module 1 (1.14.2.2)***
4. Side by Side comparison of labeling in ***Module 1 (1.14.2.3)***

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of March 05, 2012.

Please contact the undersigned at 908-203-4977 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi

Jaya Ayyagari,
Senior Manager – Regulatory Affairs as Designee for
Kimberly Ernst
Director, Regulatory Affairs

This Letter Contains Confidential, Commercial and Trade Secret Information. Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-7022
Fax: (908) 203-4980

www.drreddys.com

February 07, 2012

Office of Generic Drugs,
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

Reference: ANDA # 202357, eCTD Seq 0006
Atorvastatin Calcium tablets, 80mg
Gratuitous Chemistry Amendment - Revision of drug product specification for impurities
Submitted via Electronic Submission Gateway

Dear Sir/Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium tablets, 80mg, Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Gratuitous Chemistry Amendment.

Reference is made to the following comment (FDA's comment no. 17 of minor chemistry deficiency dated: 7th October 2011), from agency with respect to impurity limits.

- *Your drug product release and stability specifications for impurities exceed qualification threshold based On ICH Q3B guideline, Please be informed that the Pharm-Tox Consult team has determined that the proposed specifications for six major degradation impurities between NMT (b)(4)% to NMT (b)(4)% are not supported by the tested levels of these impurities (b)(4)%) in toxicity studies, and therefore the proposed levels are not acceptable, Please provide the pharm-tox data for the proposed amounts of impurities present in the 80 mg dose of the drug product or the amounts that were tested in 300 and 1000 mg doses of the drug product administered in a 4-week toxicity study in rats.*

Reference is made to Quality minor amendment dated December 02,2011(eCTD Seq 0005) in which a response was provided to the above comment along with other comments . However, subsequent to this response, we have reviewed 24-months long term stability data of bottles and found that the impurity levels in bottle pack are in compliance with the impurity levels that were qualified in pharm-tox studies

The below table summarizes 24 months long term stability data, the qualified levels of each impurity and reference product data.

S. No.	Impurity	% Impurity in tox batch	Dr Reddys (24 Months)	RLD
1	[redacted]			
2				
3				
4				

Based on the above data, we propose to tighten the impurity limits of drug product at release and stability as shown below:

S. No	Impurity	Release Specification		Stability Specification	
		Existing	Proposed	Existing	Proposed
1	[redacted]	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%
2		NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%
3		NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%
4		NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%
5		NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%
6		NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%

* [redacted] A detailed justification report is provided in **Module 32P56** of response dated 02nd December, 2011. We have received an approval from [redacted] regulatory authority with the same justification for a limit of [redacted]%.

We would like to inform to the Agency that, we have reviewed the [redacted] stability data of [redacted] and as the data is not meeting the above proposed specification, Dr. Reddy's would like to withdraw the [redacted] from the ANDA.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also verify that all the files in the submission were checked and verified to be free of viruses using McAfee® VirusScan® Enterprise, Program Version 8.7i and scan engine 5400 with a virus definition dated February 07, 2012.

Please contact the undersigned at 908-203-4977 by phone or at 908-203-4980 by fax or by email at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi

Jaya Ayyagari
Senior Manager – Regulatory Affairs as Designee for
Kimberly Ernst
Director, Regulatory Affairs

Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4937
Fax: (908) 203-4980

www.drreddys.com

December 02, 2011

Office of Generic Drugs,
Center for Drug Evaluation and Research,
Food and Drug Administration
Document Control Room,
Metro Park North VII,
7620 Standish Place,
Rockville, Maryland 20855

Reference: **ANDA # 202357, eCTD Seq 0005**
Atorvastatin Calcium Tablets, 80 mg
Quality (CMC) Minor Amendment / Response to Information Request
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Minor Chemistry Amendment. This is in response to the deficiency letter dated October 07, 2011 which is provided along with this cover letter for the reviewer's convenience.

FDA Comment:

1. (b) (4)

RESPONSE:

(b) (4)

12 pages have been withheld as b4 (CCI/TS) immediately following this page

RESPONSE:

We acknowledge the agency's comment.

FDA Comment:

4. *When submitting future ANDA's please provide answers to all Question-based Review questions. If the question is not applicable, please provide a response that the question is not applicable and why it is not applicable. Please ensure that your response is specific to the question being asked.*

RESPONSE:

We acknowledge the agency's comment.

FDA Comment:

5. *When submitting future ANDA's please provide optimization studies as part of Pharmaceutical Development, which should support that the formulation is robust to nominal process/material variations.*

RESPONSE:

We acknowledge the agency's comment.

FDA Comment:

6. *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.*

RESPONSE:

We acknowledge the agency's comment.

FDA Comment:

7. *Please submit all available stability data based on the revised specifications.*

RESPONSE:

The updated stability data is provided as ***Module 3.2.P.8.3.***

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify all files in the submission were checked and verified to be

free of viruses, using McAfee® VirusScan® Enterprise, program version 8.7i and scan engine version 5400 with a virus definition date of December 02, 2011.

Please contact the undersigned at 908-203- 4977 by phone or at 908-203-4980 by fax or by email at jayalakshmia@drreddys.com if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi.

Jaya Ayyagari,
Senior Manager - Regulatory Affairs as Designee for
Kimberly Ernst,
Associate Director Regulatory Affairs

QUALITY DEFICIENCY - MINOR

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Dr. Reddy's Laboratories Limited TEL: 908-203-7022

ATTN: Kimberly Ernst FAX: 908-203-4980

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 27, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 80 mg.

Reference is also made to your amendments dated October 20, 2010 and March 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 5 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review,** nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

Office of Generic Drugs, 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: 202357 **APPLICANT:** Dr. Reddy's Laboratories, Ltd.

DRUG PRODUCT: Atorvastatin calcium Tablets 80 mg

The deficiencies presented below represent MINOR deficiencies:

(b) (4)

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

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

/s/

LEIGH A SEARS
10/06/2011

LAXMA R NAGAVELLI
10/06/2011
Signed for Vilayat A Sayeed, PhD

QUALITY DEFICIENCY - MINOR

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Dr. Reddy's Laboratories Limited TEL: 908-203-7022

ATTN: Kimberly Ernst FAX: 908-203-4980

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 27, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 80 mg.

Reference is also made to your amendments dated October 20, 2010 and March 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 **5** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

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III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202357 **APPLICANT:** Dr. Reddy's Laboratories, Ltd.

DRUG PRODUCT: Atorvastatin calcium Tablets 80 mg

The deficiencies presented below represent MINOR deficiencies:

(b) (4)

[redacted]

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

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/s/

LEIGH A SEARS
10/06/2011

LAXMA R NAGAVELLI
10/06/2011
Signed for Vilayat A Sayeed, PhD

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4937
Fax: (908) 203-4980

www.drreddys.com

March 31, 2011

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7620 Standish Place,
Rockville, Maryland 20855

Reference: ANDA # 202357, eCTD Seq 0004
Atorvastatin Calcium Tablets, 80 mg
Labeling Amendment
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Labeling Amendment. This is in response to the deficiency letter dated March 15, 2011 which is provided along with this cover letter for reviewer's convenience.

FDA COMMENT:

1. *CONTAINER (30s, 60s, 90s, and 500s)*
   Acceptable in final print.

RESPONSE:

We acknowledge the agency's comment.

FDA COMMENT:

(b) (4)

RESPONSE:

We acknowledge the agency's comment.

FDA COMMENT:

(b) (4)

DR. REDDY'S

RESPONSE:

[redacted] (b) (4)

FDA COMMENT:

4. *INSERT*
   11 DESCRIPTION: You may delete " [redacted] (b) (4) *" and just state the composition of the* [redacted] (b) (4) *.*

RESPONSE:

We acknowledge the agency's comment. The Package Insert Labeling is revised as recommended by the agency. The revised package insert labeling along with structured product labeling (SPL) is provided in ***Module 1.14.2.2.*** Side by Side comparison of revised package insert labeling with previously submitted package insert labeling is provided in ***Module 1.14.2.3***.

FDA COMMENT:

5. *PATIENT INFORMATION SHEET:*
   Please refer to INSERT comment.

RESPONSE:

We acknowledge the agency's comment. The Patient Information Sheet is revised as recommended by the agency. The revised patient information sheet is provided in **Module 1.14.2.2**

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of March 30, 2011.

Please contact the undersigned at 908-203.4937 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi.

Kumara Sekar, Ph.D
Sr. Director, Regulatory Affairs

LABELING COMMENTS

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8991

TO: Dr. Reddy's Laboratories, Inc.
U.S. Agent for Actavis
Dr. Reddy's Laboratories Ltd.

TEL: 908-203-4937

FAX: 908-203-4980

ATTN: Kumara Sekar

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, 80 mg.

Pages (including cover): 3

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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

ANDA Number: 202357 Date of Submission: September 27, 2010

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

Labeling Deficiencies:

1. CONTAINER (30s, 60s, 90s, and 500s)

   Acceptable in final print.

[redacted] (b) (4)

4. INSERT

   11 DESCRIPTION: You may delete [redacted] (b) (4) " and just state the composition of the [redacted] (b) (4).

3. PATIENT INFORMATION SHEET:

   Please refer to INSERT comment.

Submit label and labeling electronically.

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

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

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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
03/14/2011
for Wm Peter Rickman

This Letter Contains Confidential, Commercial and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4937
Fax: (908) 203-4980

www.drreddys.com

March 18, 2011

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7620 Standish Place,
Rockville, Maryland 20855

Reference: ANDA # 202357, eCTD Seq 0003
Atorvastatin Calcium Tablets, 80 mg
Bioequivalence Dissolution Acknowledgement / Response to Information Request and QUALITY (CMC) Amendment
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Bioequivalence Amendment. This is in response to the deficiency letter dated March 09, 2011 which is provided along with this cover letter for reviewer's convenience.

The amendment is also marked as a quality (CMC) amendment to provide the revised dissolution specifications of the drug product to the chemistry division.

FDA COMMENT:

- *Your dissolution testing data are acceptable. However, your proposed specification of "NLT (b)(4)% (Q) in 30 minutes" is not acceptable. Based on the dissolution data, the DBE recommends a more appropriate specification for your Atorvastatin Calcium Tablets, 80 mg. Please acknowledge your acceptance of the following FDA recommended dissolution method and specification:*

  The dissolution should be conducted in 900 ml 0.05 M Phosphate Buffer pH 6.8; using USP apparatus II (paddle) at 75 rpm at 37 ± (b)(4)° C.

  The product should meet the following specification:

  NLT (b)(4)% (Q) of labeled amount of atorvastatin in the dosage form should be dissolved in 30 minutes.

Atorvastatin Calcium Tablets, 80 mg
ANDA # 202357

RESPONSE:

We acknowledge the agency's comment. As per the agency's recommendation, the Specification is revised from 'NLT (b)(4)% (Q) in 30 minutes' to 'NLT (b)(4)% (Q) in 30 minutes'.

The revised specification and test method of drug product is provided in **Module 3.2.P.5.1** and Module **3.2.P.5.2** respectively.

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of March 18, 2011.

Please contact the undersigned at 908-203.4937 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalekshmi

Kumara Sekar, Ph.D
Sr. Director, Regulatory Affairs

Agency's Letter

BIOEQUIVALENCE AMENDMENT

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (908) 203-4937

ATTN: Kumara Sekar FAX: (908) 203-4980

FROM: Nam Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on September 27, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

Reference is also made to your amendment dated February 21, 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 2 page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** 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:

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 DEFICIENCY

ANDA: 202357

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable. However, your proposed specification of "NLT (b)(4)% (Q) in 30 minutes" is not acceptable. Based on the dissolution data, the DBE recommends a more appropriate specification for your Atorvastatin Calcium Tablets, 80 mg. Please acknowledge your acceptance of the following FDA recommended dissolution method and specification:

The dissolution should be conducted in 900 ml 0.05 M Phosphate Buffer pH 6.8, using USP apparatus II (paddle) at 75 rpm at 37 ± 5° C.

The product should meet the following specification:

NLT (b)(4)% (Q) of labeled amount of atorvastatin in the dosage form should be dissolved in **30 minutes.**

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

DALE P CONNER
03/08/2011

LABELING COMMENTS

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8991

TO: Dr. Reddy's Laboratories, Inc.
U.S. Agent for Actavis
Dr. Reddy's Laboratories Ltd.

TEL: 908-203-4937

FAX: 908-203-4980

ATTN: Kumara Sekar

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, 80 mg.

Pages (including cover): 3

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Document Control Room
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Rockville, Maryland 20855

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

ANDA Number: 202357 Date of Submission: September 27, 2010

Applicant's Name: Dr. Reddy's Laboratories Ltd.

Established Name: Atorvastatin Calcium Tablets, 80 mg

Labeling Deficiencies:

1. CONTAINER (30s, 60s, 90s, and 500s)

   Acceptable in final print.

[redacted] (b) (4)

4. INSERT

   11 DESCRIPTION: You may delete "[redacted] (b) (4)" and just state the composition of the [redacted] (b) (4).

3. PATIENT INFORMATION SHEET:

   Please refer to INSERT comment.

Submit label and labeling electronically.

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

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

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JOHN F GRACE
03/14/2011
for Wm Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 202357

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (908) 203-4937

ATTN: Kumara Sekar FAX: (908) 203-4980

FROM: Nam Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on September 27, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 80 mg.

Reference is also made to your amendment dated February 21, 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 **1** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** 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.

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Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 202357

APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be done at a later date. The following deficiency has been identified:

Your dissolution testing data are acceptable. However, your proposed specification of "NLT (b)(4)% (Q) in 30 minutes" is not acceptable. Based on the dissolution data, the DBE recommends a more appropriate specification for your Atorvastatin Calcium Tablets, 80 mg. Please acknowledge your acceptance of the following FDA recommended dissolution method and specification:

The dissolution should be conducted in 900 ml 0.05 M Phosphate Buffer pH 6.8, using USP apparatus II (paddle) at 75 rpm at 37 ± 5° C.

The product should meet the following specification:

NLT (b)(4)% (Q) of labeled amount of atorvastatin in the dosage form should be dissolved in **30 minutes**.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

DALE P CONNER
03/08/2011

This Letter Contains Confidential, Commercial and Trade Secret Information. Do Not Disclose Under FOI.

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4937
Fax: (908) 203-4980

www.drreddys.com

February 21, 2011

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7620 Standish Place,
Rockville, Maryland 20855

Ref: ANDA # 202357, Seq no. 0002
Atorvastatin Calcium Tablets 80 mg
Gratuitous Bioequivalency Amendment – Long term Stability data for plasma
Submitted via Electronic Submission Gateway

Dear Sir/ Madam,

With reference to ANDA # 202357 for Atorvastatin calcium tablets 80 mg, Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Gratuitous Bioequivalency Amendment.

The fasting long term stability data of Atorvastatin and its metabolites 2-hydroxy atorvastatin & 4-hydroxy atorvastatin in human plasma are provided in **Module 5.3.1.4**

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® Virus Scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of February 21, 2011.

Please contact the undersigned at 908-203-4937 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,
DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi.

Kumara Sekar Ph.D.,
Sr. Director, Global Regulatory Affairs

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 #: 202357 **FIRM NAME**: DR. REDDY'S LABORATORIES 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, 80 MG

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC3 TM 34 ☒ ***Activity***	***Bio Team 4: Nilufer Tampal*** ☒ ***Activity***
ANDA/Quality RPM: Leigh Ann Bradford ☒ ***FYI***	Bio PM: Diana Solana ☐ ***FYI***
Quality Team Leader: Nagavelli, Laxma No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☐ ***Activity***
Labeling Reviewer: Ann Vu ☒ ***Activity***	***Micro Review (No)*** ☐ ***Activity***

*****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: SEPTEMBER 27, 2010 **Received Date**: SEPTEMBER 27, 2010

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Rebekah Granger **Date 10/25/2010**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

10/19 – Kumara Sekar (908) 203-4937

Form 3455 submitted , please check box Firm's response: Form 3455 submitted in error, Form 3454 submitted
Schematic diagram for (b) (4)

DBE Contact Entered 10/25

Per correspondence submitted by sponsor dated 10/20 the above is adequate for filing

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** YES (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: SEPTEMBER 27, 2010 YES	☒
1.2.1	**Form FDA 3674** **(PDF)** YES – Box B	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☐
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) SAME	☒
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 – '893, '995 and '667 PIV – '104, '156 and '971 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☐ 3. Expiration of Patent(s): 1/8/2017 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES Will not market prior to expiration of "893, '995 and '667	☒

Patent and Exclusivity Search Results from query on Appl No 020702 Product 004 in the OB_Rx list.

<>

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020702	004	4681893	Sep 24, 2009	Y	Y	U - 161	
N020702	004	4681893*PED	Mar 24, 2010			U - 161	
N020702	004	5273995	Dec 28, 2010	Y	Y	U - 162	
N020702	004	5273995*PED	Jun 28, 2011			U - 162	
N020702	004	5686104	Nov 11, 2014		Y	U - 213	
N020702	004	5686104*PED	May 11, 2015			U - 213	
N020702	004	5969156	Jul 8, 2016	Y			
N020702	004	5969156*PED	Jan 8, 2017				
N020702	004	6126971	Jan 19, 2013		Y		
N020702	004	6126971*PED	Jul 19, 2013				
N020702	004	RE40667	Dec 28, 2010	Y	Y	U - 162	
N020702	004	RE40667*PED	Jun 28, 2011				

<>

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N020702	004	I - 523	Mar 2, 2010

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U - 161	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT
U - 162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA
U - 213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
I - 523	USE IN ADULT PATIENTS WITH CLINICALLY EVIDENT CORONARY HEART DISEASE TO REDUCE THE RISK OF NONFATAL MYOCARDIAL INFARCTION, FATAL AND NONFATAL STROKE, ANGINA, REVASCULARIZATION PROCEDURES AND HOSPITALIZATION FOR CONGESTIVE HEART FAILURE

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES Type II DMF No. 21125 b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒
1.12.11	**Basis for Submission** NDA# : 20-702 Ref Listed Drug: LIPITOR Firm: PFIZER ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use 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): NA	☐

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 (b) (4) 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 of 80 mg are white to off-white, oval shaped, biconvex, film coated tablets debossed 'RDY' on one side and '124' on other side and are supplied in bottles of 30's, 60's, 90's, 500's and (b) (4) Bottles of 30 NDC 55111-124-30 Bottles of 60 NDC 55111-124-60 Bottles of 90 NDC 55111-124-90 Bottles of 500 NDC 55111-124-05 (b) (4)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

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** YES **3.2.S.1.2 Structure** YES **3.2.S.1.3 General Properties** YES	☒
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 – DMF #21125 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** YES	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) **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** YES	☒
3.2.S.5	**Reference Standards or Materials** YES	☒
3.2.S.6	**Container Closure Systems** YES	☒
3.2.S.7	**Stability** YES	☒

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 **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 YES (no more than 10x pilot batch) with equipment specified 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** YES **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) **PROPOSED COMMERCIAL BATCH SIZE:** **Exhibit Batch size** (b) (4) [redacted] **Intended Commercial Batch size** (b) (4) [redacted]	☒
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** YES **3.2.P.4.3 Validation of Analytical Procedures** USP/NF Testing **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: 1. Finished Dosage Form YES 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** YES **3.2.P.5.6 Justification of Specifications** YES	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 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 YES – Lot # EC9156	☒

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)** Refer to DMF **3.2.R.2.S Comparability Protocols** N/A **3.2.R.3.S Methods Validation Package** YES in Module 3.2.S.4.3 Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES – See Attached **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** RLD: Lot # 04568V ANDA: Lot # EC9156 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. Summary Bioequivalence tables: Table 10. Study Information YES Table 12. Dropout Information YES Table 13. Protocol Deviations YES **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information YES Table 16. Composition of Meal Used in Fed Bioequivalence Study YES **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples YES Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES **5.3.7** **Case Report Forms and Individual Patient Listing**	☒
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: YES 3. In-Vitro Dissolution: YES in Module 3.2.P.2 and 5.3.1.3	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009

Table 03: Statistical Summary of the Bioequivalence Data of Atorvastatin (Fed Study)

Atorvastatin Calcium 80 mg Tablets Ln-transformed Geometric Least Squares Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 09-VIN-105)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	260.848	294.379	88.61%	85.35% - 91.99%
AUC_{0-inf}	263.997	298.056	88.57%	85.33% - 91.93%
C_{max}	49.111	54.387	90.30%	84.57% - 96.41%

Table 03: Statistical Summary of the Bioequivalence Data of Atorvastatin (Fasting Study)

Atorvastatin Calcium 80 mg Tablets Geometric Least Squares Means, it's Ratio, and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. : 10-VIN-095)				
Parameter	**Test (A)**	**Reference (B)**	**Ratio**	**90% C.I.**
AUC_{0-t}	121.240	109.102	111.13%	105.58% - 116.96%
AUC_{0-inf}	125.074	113.024	110.66%	105.26% - 116.34%
C_{max}	36.549	33.490	109.14%	99.85% - 119.28%

Table 06: Formulation Data

S. No.	Component	Quantity per Unit (mg)	% (w/w)	Pharmaceutical Function
				(b) (4)
1.	Atorvastatin calcium (b) (4)			
2.	Basic butylated methacrylate copolymer (b) (4) (b) (4)			
3.	Lactose monohydrate (b) (4)			
4.	Microcrystalline cellulose (b) (4)			
5.	Methanol (b) (4)			
				(b) (4)
6.	Atorvastatin calcium (b) (4)			
7.	Lactose monohydrate (b) (4)			
8.	Sodium bicarbonate (b) (4)			
9.	Sodium lauryl sulphate (b) (4)			
10.	(b) (4)			
				(b) (4)
11.	Crospovidone (b) (4)			
12.	Hydroxy propyl cellulose (b) (4)			
13.	Magnesium Stearate (b) (4)			
Total Weight				
				(b) (4)
14.	(b) (4)			(b) (4)
15.	Talc (b) (4)			
16.	(b) (4)			
Total Weight				

(b) (4)

INACTIVE INGREDIENTS SEARCH FOR ANDA [redacted]
DR REDDY'S LAB LTD – ATORVASTATIN CALCIUM TABLETS, 80 MG

LACTOSE MONOHYDRATE					
CELLULOSE, MICROCRYSTALLINE					
SODIUM BICARBONATE					
SODIUM LAURYL SULFATE	ORAL; TABLET	[redacted]	N022024	5/12/2009	[redacted]
CROSPOVIDONE					
HYDROXYPROPYL CELLULOSE					
MAGNESIUM STEARATE					
TALC					

JUSTIFICATION FOR BASIC BUTYLATED METHACRYLATE COPOLYMER

[redacted]

Reference [redacted]

COMPOSITION OF (b) (4)

POLYVINYL ALCOHOL	(b) (4)
TITANIUM DIOXIDE	(b) (4)
TALC	(b) (4)
LECITHIN	(b) (4)
XANTHAN GUM	(b) (4)

Atorvastatin calcium tablets 80mg

Process Step	Batch No. EC9156
(b) (4	(b) (4)
Theoretical Yield	
Actual Yield	
Percentage of Theoretical Yield	
Sample quantity for analysis	
Rejects	
Others	
Reconciliation	
(b) (4	
Theoretical Yield	
Actual Yield	
Percentage of Theoretical Yield	
Sample quantity for analysis	
Rejects	
Others	
Reconciliation	
(b) (4	
Theoretical Yield	
Actual Yield	
Percentage of Theoretical Yield	
Sample quantity for analysis	
Rejects	
Others	
Reconciliation	

Please refer Module 3.2.R Regional information (Drug product) for Executed batch records (Manufacturing and packaging) and further details.

Summary of Reconciliation for Atorvastatin Calcium Tablets 80mg

Batch # : EC9156 **Actual Yield :** (b) (4)

Batch Size : (b) (4) **Quantity Packed :** (b) (4)

Count	*Quantity Packed (Tablets)*	*Reserve Samples (Tablets)*	*Stability Samples (Tablets)*	*Quantity transferred to Ware house (Tablets)*	*R&D Samples*	*Bio Samples*
30's	(b) (4)					
60's						
90's						
500's						
	(b) (4)					
Total Quantity Packed	(b) (4)					

(b) (4)

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

/s/

REBEKAH P GRANGER
10/27/2010

MARTIN H Shimer
11/09/2010

Food and Drug Administration
Rockville, MD 20857

ANDA 202357

Dr. Reddy's Laboratories, Inc.
US Agent for Dr. Reddy's Laboratories Limited
Attention: Kumara Sekar, Ph.D.
200 Somerset Corporate Boulevard
7th Floor
Bridgewater, NJ 08807

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversations dated October 19, 2010 and your correspondence dated October 20, 2010.

NAME OF DRUG: Atorvastatin Calcium Tablets, 80 mg

DATE OF APPLICATION: September 27, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 27, 2010

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 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) 276-8675.

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:

Leigh Ann Bradford
Project Manager
240-276-8453

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

MARTIN H Shimer
11/09/2010
Signing for Wm Peter Rickman

This Letter Contains Confidential, Commercial
and Trade Secret Information Do Not Disclose Under FOI

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4937
Fax: (908) 203-4980

www.drreddys.com

October 19, 2010

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
7620 Standish Place,
Rockville, Maryland 20855

Reference: ANDA # 202357, eCTD Seq 0001
Atorvastatin Calcium Tablets, 80 mg
Telephone Amendment (Response to Screening Information Request)
Submitted Via Electronic Submission Gateway

Dear Sir/ Madam:

With reference to ANDA # 202357 for Atorvastatin Calcium Tablets, 80 mg Dr. Reddy's Laboratories Inc., U.S. agent for Dr. Reddy's Laboratories Limited, herewith submits a Telephone Amendment (Response to Screening Information Request). This is in response to the telephonic query received from agency on October 19, 2010.

FDA COMMENT:

1. *In the financial disclosure forms, check the appropriate column.*

RESPONSE:

A certification of "Financial interests and arrangements of clinical investigators" Form 3454 is provided in **Module 1.3.4.**

We request the agency, to disregard the form 3455 included in the original submission since the investigators at Nuvisan Pharma Services (Fasting study) and (b) (4) (FED study) were not involved in any financial arrangements and have no proprietary interest in the product tested in the covered study.

FDA COMMENT:

2. *Provide the structural drawing for the* (b) (4).

RESPONSE:

As requested by the agency, the structural drawing for the (b) (4) is provided in **Module 3.2.P.7.2.**

DR. REDDY'S

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all the files included in this submission were checked and verified to be free of viruses using McAfee® virus scan® Enterprise, program version 8.7i and scan engine 5400 with a virus definition date of October 19, 2010.

Please contact the undersigned at 908-203-4937 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalekhme.

Kumara Sekar, Ph.D
Sr. Director, Global Regulatory Affairs

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
Regulatory Affairs

200 Somerset Corporate Boulevard
Building II, 7th Floor
Bridgewater, NJ 08807-2862

Tel: (908) 203-4937
Fax: (908) 203-4980

www.drreddys.com

September 27, 2010

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
7620 Standish Place,
Rockville, Maryland 20855

Re: Pre-assigned ANDA # 202357, eCTD Seq: 0000
Atorvastatin Calcium Tablets, 80mg
ANDA Original application
Submitted via electronic Submission Gateway

Dear Sir/ Madam:

Dr. Reddy's Laboratories Inc., U.S. agent to Dr. Reddy's Laboratories Ltd., herewith submits an abbreviated new drug application (ANDA) for Atorvastatin Calcium Tablets, 80 mg pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

Basis for Submission

This ANDA refers to the listed drug, Lipitor® (Atorvastatin Calcium) Tablets, 80mg manufactured by Pfizer, USA, the holder of the approved application listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).

Chemistry, Manufacturing and Controls

Atorvastatin Calcium Tablets, 80 mg will be manufactured and supplied by (b) (4) , manufacturing facility, in accordance with 21 CFR § 210 and 211.

Atorvastatin Calcium (b) (4) manufactured by (b) (4) is used to produce the ANDA / Bio batch of this product.

Dr. Reddy's Laboratories Limited, Generics division, located at Bachepalli – 502 325, Andhra Pradesh, India provided the purchasing, research and development, production planning, pilot production, as well as the stability testing and other operations.

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION & HOW SUPPLIED) for Dr. Reddy's Laboratories Limited's Atorvastatin Calcium Tablets 80 mg are same as those for Pfizer's Lipitor ® (Atorvastatin calcium) Tablets 80 mg.

Atorvastatin Calcium Tablets 80mg are stable and 24-months expiration date is requested. The 24 months expiration dating of this product is supported by three months accelerated stability data (40°C ± 2°C/ 75% ± 5% Relative Humidity) in the smallest and largest fill size of the container / closure system proposed for marketing. The stability studies were conducted under a stability protocol.

Bioequivalence

The required bioavailability/ bioequivalence studies were conducted at Nuvisan GmbH, Wegenerstraße 13, 89231 Neu-U1m, Germany (For clinical study) and (b) (4) (b) (4) (For bioanalytical study) and (b) (4) (For FED study) This study supports the conclusion that Dr. Reddy's Laboratories Limited's Atorvastatin Calcium Tablets 80 mg is bioequivalent to Pfizer's Lipitor ® 80 mg.

The in vitro dissolution profiles of Atorvastatin Calcium Tablets 80 mg are comparable to that of Pfizer's Lipitor ® (Atorvastatin calcium) Tablets 80 mg respectively. The dissolution profiles for these products are included in the Module 5.3.1.3 of this ANDA.

Administrative Information

The original ANDA is provided as a complete Electronic Submission. The Amendment of ANDA has been organized in accordance with the following FDA guidance documents:

- "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations" (January 1999).
- Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related submissions using the eCTD Specifications (04/19/2006).
- Providing Regulatory Submissions in Electronic Format - General Considerations (10/22/2003)

Also please note that Dr. Reddy's Laboratories has submitted a letter of non repudiation to the agency to allow submission of electronically signed document or documents with scanned signatures in lieu of paper signatures.

Also please note that Dr. Reddy's Laboratories has submitted a letter of non repudiation to the agency to allow submission of electronically signed document or documents with scanned signatures in lieu of paper signatures

DR. REDDY'S

This submission is provided as an electronic copy only and is submitted through electronic submission gateway. We also certify that all files included in the submission were checked and verified to be free of viruses using McAfee® VirusScan® Enterprise, program version 8.5.0i and scan engine version 5400 with a virus definition date of September 27, 2010.

Please contact the undersigned at 908-203-4937 or by fax at 908-203-4980 if you have any questions regarding this submission.

Sincerely,

DR. REDDY'S LABORATORIES, INC.

A. Jayalakshmi

Kumara Sekar Ph.D.,
Sr. Director, Global Regulatory Affairs

See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 10-31-2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
   Dr. Reddy's Laboratories Limited

2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

3. ADDRESS *(Number, Street, State, and ZIP Code)*
   Mailing Address: Bachepalli,Post Bag No. 15,Kukatpally P.O. , Hyderabad-500 072, India
   Factory Address: Bachepalli 502 325, India

4. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
   (Tel.) 0091-40-23045206
   (Fax) 0091-40-23045238

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
   FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
   (Attach extra pages as necessary)
   Atorvastatin Calcium Tablets 80mg

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
   ☐ IND ☐ NDA ☒ ANDA ☐ BLA ☐ PMA ☐ HDE ☐ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*
   202357

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
   0000

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*
   ☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.
   ☒ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.
   ☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*
    NCT Number(s):

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)
    A. Jayalakshmi

12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11
    (Name) Kumara Sekar, Ph.d
    (Title) Sr. Director, Global Regulatory Affairs

13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)*
    Dr. Reddy's Laboratories, Inc.
    200 Somerset Corporate Blvd, 7th floor,
    Bridgewater, NJ08807

14. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
    (Tel.) 908-203-4937
    (Fax) 908-203-4980

15. DATE OF CERTIFICATION
    Sep 27, 2010