CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 91650

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

Sponsor: Dr. Reddy's Laboratories Inc.

Approval Date: July 17, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091650

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 July 15, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), and 40 mg (base).

Reference is also made to your amendments dated February 9, and August 26, 2010; May 13, and November 16, 2011; and February 8, March 5 and 26, April 11, May 17, 21, and 23, 2012.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), and 40 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, 10 mg (base), 20 mg (base), and 40 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. 09-943-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.

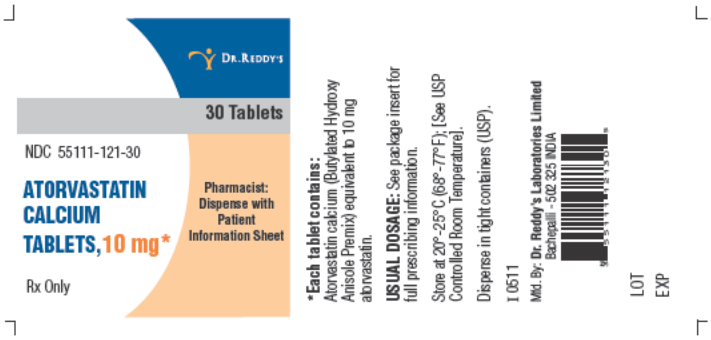
CENTER FOR DRUG EVALUATION AND RESEARCH

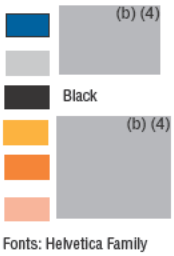
APPLICATION NUMBER:

ANDA 91650

LABELING

Final Container Label for Atorvastatin Calcium Tablets, 10 mg
10 mg - 30's Count
Label Size: 90mm x 40mm





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10 mg - 60's Count
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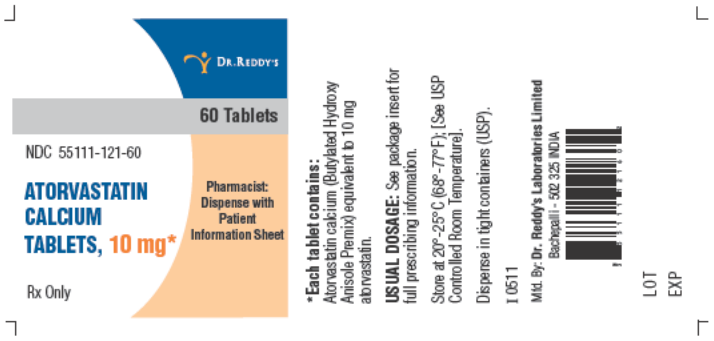

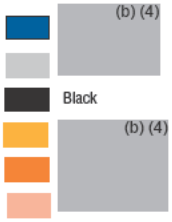

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Final Container Label for Atorvastatin Calcium Tablets, 10 mg
10 mg - 90's Count
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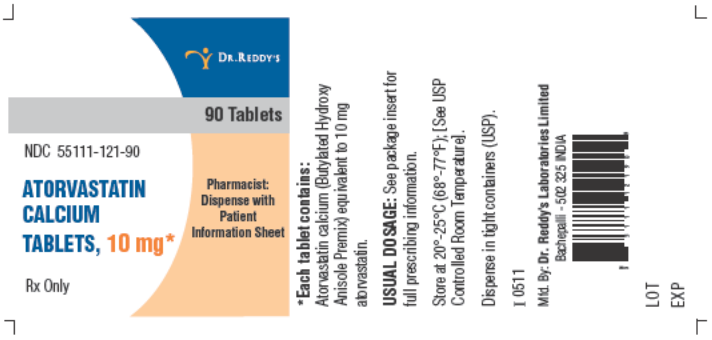

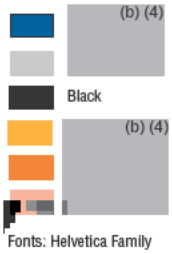

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10 mg - 500's Count
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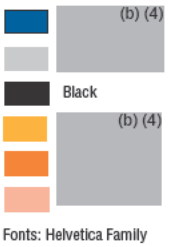

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20 mg - 30's Count
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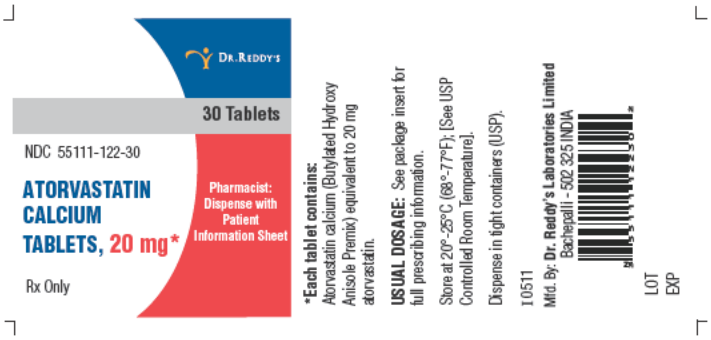

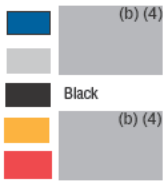

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20 mg - 60's Count
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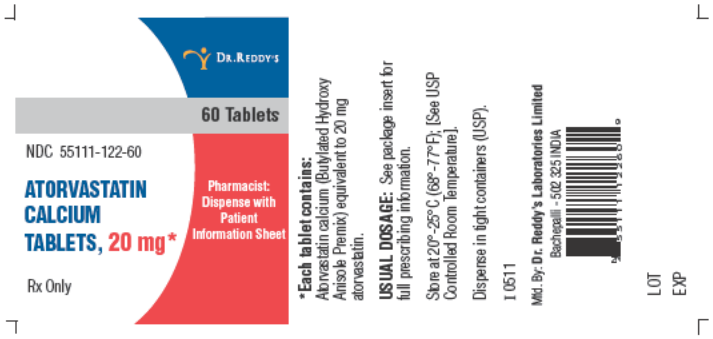

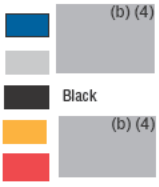

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20 mg - 90's Count
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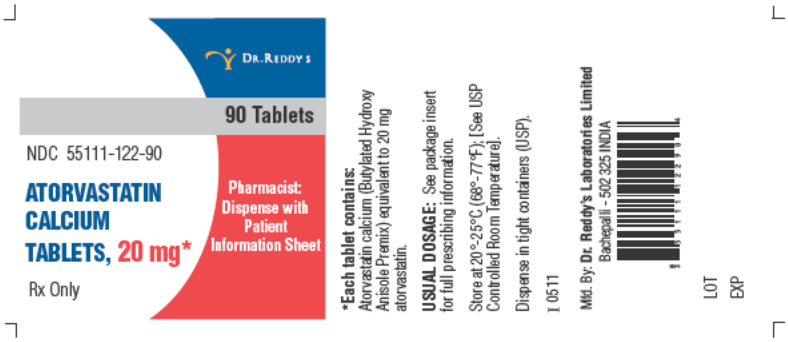

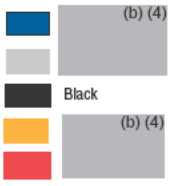

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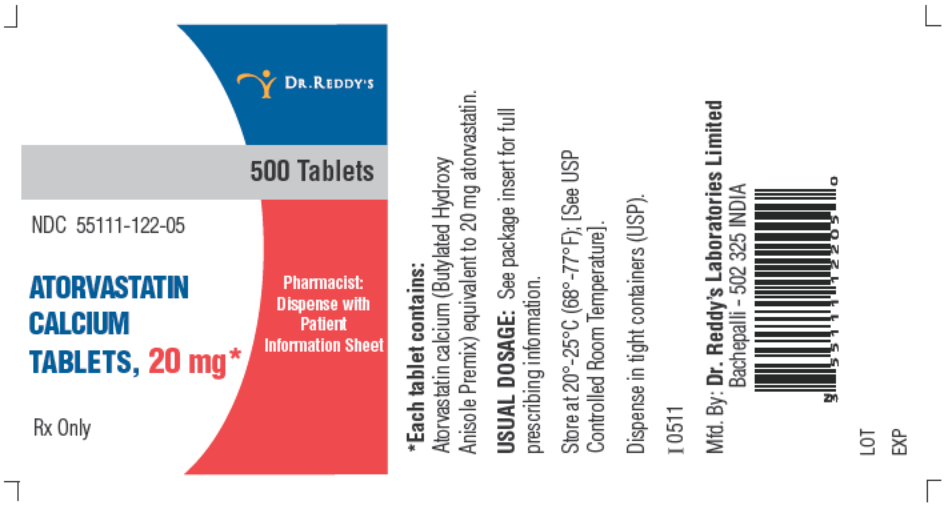
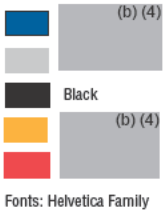
Final Container Label for Atorvastatin Calcium Tablets, 20 mg
20 mg - 500's Count
Label Size: 120mm x 60mm





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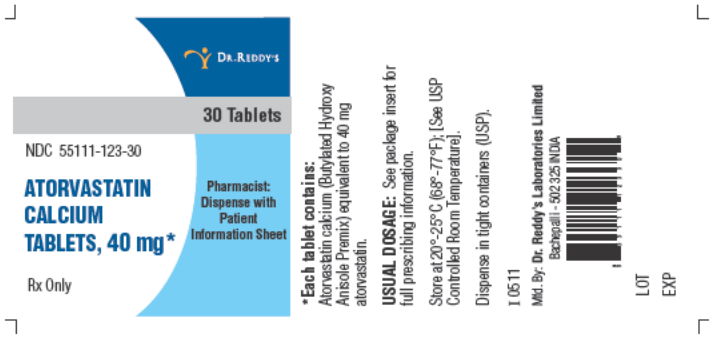
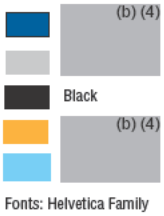
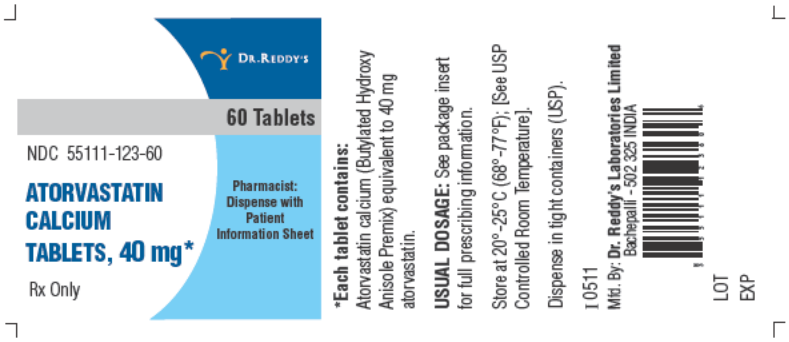
40 mg - 30's Count
Label Size: 90mm x 40mm

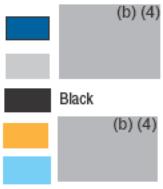




Fonts: Helvetica Family

Final Container Label for Atorvastatin Calcium Tablets, 40 mg
40 mg - 60's Count
Label Size: 100mm x 40mm





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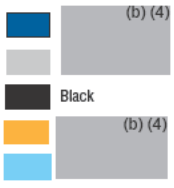
Final Container Label for Atorvastatin Calcium Tablets, 40 mg
40 mg - 90's Count
Label Size: 120mm x 50mm



Final Container Label for Atorvastatin Calcium Tablets, 40 mg
40 mg - 500's Count
Label Size: 150mm x 70mm

DR. REDDY'S

500 Tablets

NDC 55111-123-05

ATORVASTATIN CALCIUM TABLETS, 40 mg*

Rx Only

Pharmacist: Dispense with Patient Information Sheet

***Each tablet contains:** Atorvastatin calcium (Butylated Hydroxy Anisole Premix) equivalent to 40 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 0511

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

LOT

EXP

(b) (4)

Black

(b) (4)

Fonts: Helvetica Family

Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg
Rx only
I 0312
55111-121-02

Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg
Rx only
I 0312
55111-121-02

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-------

10, 20 and 40 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 10 mg are white to off-white capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '121'on other side.

Atorvastatin calcium tablets of 20 mg are white to off-white capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '122' on other side.

Atorvastatin calcium tablets of 40 mg are white to off-white capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '123' 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.

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

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

6.3 Pediatric Patients (ages 10-17 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)-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.

(b) (4)

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 isopropyl alcohol, methylene chloride and coloring agent opadry OY-58900 white contains polyethylene glycol, titanium dioxide and hypromellose.

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

Rx Only

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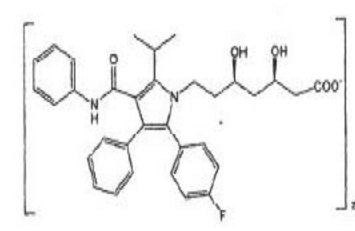


Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in dimethyl sulphoxide, slightly soluble in alcohol, very slightly soluble in water, in pH 7.4 phosphate buffer and in acetonitrile and practically insoluble in aqueous solutions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

Atorvastatin calcium tablets for oral administration contain 10, 20 and 40 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 isopropyl alcohol, methylene chloride and coloring agent opadry OY-58900 white contains polyethylene glycol, titanium dioxide and hypromellose.

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

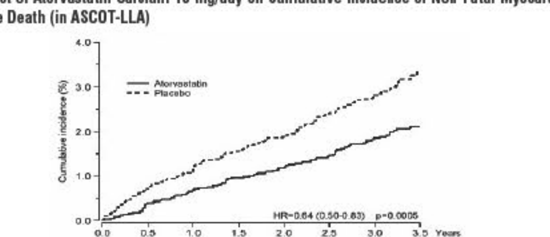
14.1 Prevention of Cardiovascular Disease

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.

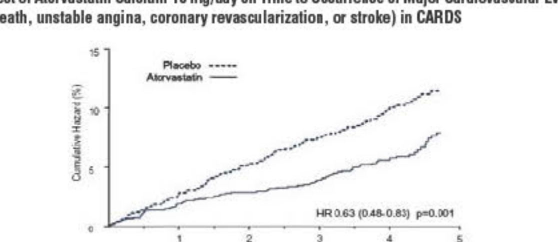
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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)

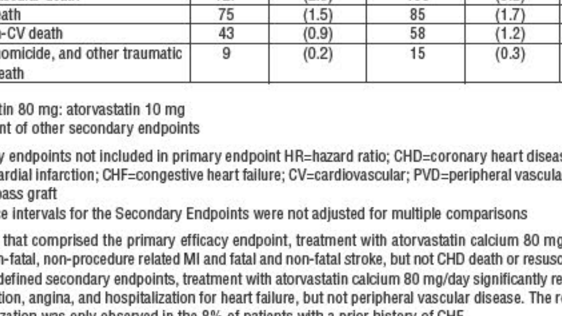


TABLE 5. Overview of Efficacy Results in TNT

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 10 mg are white to off-white, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '121' on other side and are supplied in bottles of 30's, 60's, 90's and 500's.

Bottles of 30	NDC 55111-121-30
Bottles of 60	NDC 55111-121-60
Bottles of 90	NDC 55111-121-90
Bottles of 500	NDC 55111-121-05

Atorvastatin calcium tablets of 20 mg are white to off-white, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '122' on other side and are supplied in bottles of 30's, 60's, 90's and 500's.

Bottles of 30	NDC 55111-122-30
Bottles of 60	NDC 55111-122-60
Bottles of 90	NDC 55111-122-90
Bottles of 500	NDC 55111-122-05

Atorvastatin calcium tablets of 40 mg are white to off-white, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '123' on other side and are supplied in bottles of 30's, 60's, 90's and 500's.

Bottles of 30	NDC 55111-123-30
Bottles of 60	NDC 55111-123-60
Bottles of 90	NDC 55111-123-90
Bottles of 500	NDC 55111-123-05

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 isopropyl alcohol, methylene chloride and coloring agent opadry OY-58900 white contains polyethylene glycol, titanium dioxide and hypromellose.

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

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PATIENT INFORMATION

Atorvastatin Calcium Tablets

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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.

(Continued on other side)

(Continued from previous side)

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 isopropyl alcohol, methylene chloride and coloring agent opadry OY-58900 white contains polyethylene glycol, titanium dioxide and hypromellose.

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
Reference ID: 3132949

DR.REDDY'S

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

LABELING REVIEWS

****** (This AP Summary supersedes the review dated 5/15/2012) *****

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

ANDA Number: 091650

Date of Submission: May 13, 2011, March 5, 2012 and May 17, 2012

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

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

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REMS required?

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

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

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

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

CONTAINER LABELS: (all strengths in bottles of 30s, 60s, 90s and 500s): Final Printed Labels acceptable in 5/13/2011 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 (b) (4)

(b) (4)

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 [redacted] (b) (4)" 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
[redacted] (b) (4)

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 2/28/12.

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,

(b) (4)

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.

(b) (4)

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 (b) (6)
Fax : 908-203-4980
jayalakshmia@drreddys.com

From: "Turner, Betty" <Betty.Turner@fda.hhs.gov>
To: "'jayalakshmia@drreddys com'" <jayalakshmia@drreddys.com>,
Date: 05/16/2012 11:14 AM
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

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Good morning Jaya,

After discussing this with the Chemistry Division, it was decided that your label is incorrect [redacted] (b) (4) and must be revised prior to approval.

Thank you,

Betty
(240) 276-8728

From: Nagavelli, Laxma
Sent: Wednesday, May 16, 2012 10:45 AM
To: Turner, Betty
Cc: Vera, Matthew; Gill, Devinder; Sayeed, Vilayat A
Subject: FW: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Attachments: Picture (Enhanced Metafile)

Hi Betty,

[redacted] (b) (4)

Thanks,
Laxma

From: Turner, Betty
Sent: Wednesday, May 16, 2012 10:39 AM
To: Nagavelli, Laxma
Cc: Vera, Matthew; Khan, Khalid
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Good morning Laxma,

I understand there was a T-Con with the firm and Khalid on 3/15/12 regarding [redacted] (b) (4) . Can you discuss with your team and provide your comments as to whether this is acceptable for approval. Would you allow this change to be made post-approval?

Your comments are greatly appreciated.

Thanks,

Betty

From: Nagavelli, Laxma
Sent: Monday, May 14, 2012 5:55 PM
To: Turner, Betty
Cc: Vera, Matthew; Khan, Khalid
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Betty
As Khalid mentioned in his e-mail, we have recently asked the firm to (b) (4) [redacted] Hope, this clarified your questions. Please let us know if you have any further comments.

Thanks,
Laxma

From: Turner, Betty
Sent: Monday, May 14, 2012 3:40 PM
To: Khan, Khalid
Cc: Nagavelli, Laxma
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Hi Khalid,

Thank you very much for your quick response.

I have one question and maybe Laxma could comment (b) (4) [redacted]

Thanks

Betty

From: Khan, Khalid
Sent: Monday, May 14, 2012 3:10 PM
To: Turner, Betty
Cc: Nagavelli, Laxma
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Hello Betty,

This application has been transferred to another colleague of mine in our Division. Laxma, who is our team leader can help you with any inquiries for the future.

(b) (4)

Laxma, could you please comment?

Thanks.

Khalid

Email to K. Khan on August 2, 2011:

Good afternoon,

I'm the labeling reviewer for 91650 (Reddy's atorvastatin). Could you answer my question when you pick up 91650 for review?

In the last chemistry deficiencies, Dr. Reddy's was instructed to revise their labels (b) (4) . I attached the chemistry comment, the firm's revised label and section 11 DESCRIPTION from the insert.

Thanks
Ann

Email from Weiqin Jiang on 8/19/10:

Sorry, Ann: the pasted file was disrupted. (b) (4) weiqin

From: Jiang, Weiqin
Sent: Thursday, August 19, 2010 2:39 PM
To: Vu, Thuyanh (Ann)
Cc: Iser, Robert
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Ann: I checked with Bob. Here is what we found.

(b) (4)

Hope this helps.

weiqin

From: Vu, Thuyanh (Ann)
Sent: Thursday, August 19, 2010 1:59 PM
To: Jiang, Weiqin
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Here's the original email.

Thanks!

From: Vu, Thuyanh (Ann)
Sent: Thursday, March 11, 2010 2:02 PM
To: Jiang, Weiqin
Cc: Vu, Thuyanh (Ann)
Subject: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Weiquin,

When you get to this application, could you answer these two questions?

Dr. Reddy's labeling is different from the RLD's. Please see below. I asked Dr. Reddy's why it was so different and in the labeling amendment dated 2/9/2010, the firm stated "

<< OLE Object: Picture (Enhanced Metafile) >>
Is this acceptable? Please see below for Dr. Reddy's labeling and the RLD, Lipitor.

(b) (4)

Thanks
Ann

Dr. Reddy's labeling from DESCRIPTION section:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-
1Hpyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of atorvastatin calcium is C66H68CaF2N4O10 and its
molecular weight is 1155.36. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>

Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in
dimethyl sulphoxide.

Lipitor labeling:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, ð-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O and its molecular weight is 1209.42. Its structural formula is:
<< OLE Object: Picture (Enhanced Metafile) >>
Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol

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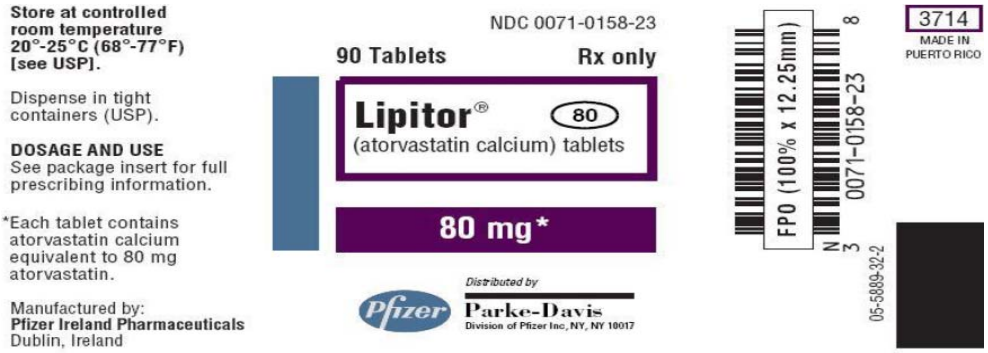
FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the last reviews dated 8/3/2011 and 5/15/2012 in DARRTS.

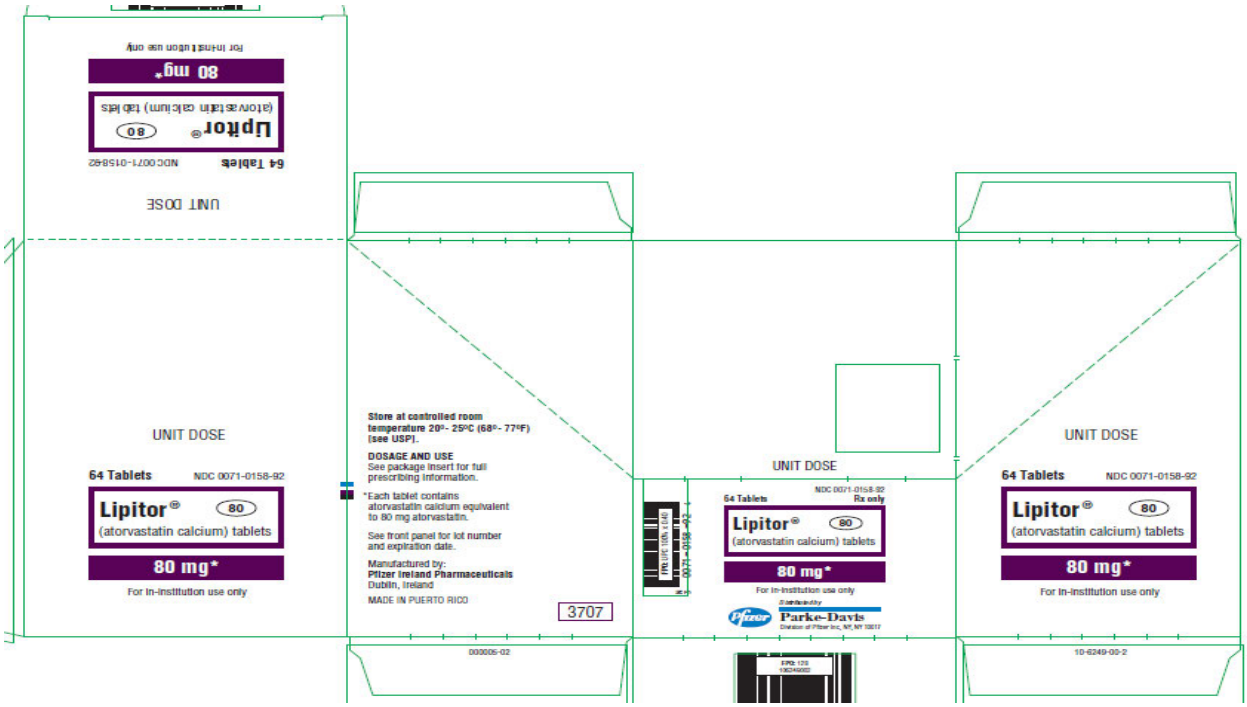
1. MODEL LABELING: This review was based on the labeling of the RLD, Lipitor, 020702/S-060; approved February 28, 2012.

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

CONTAINER



CARTON



BLISTER :

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent	Patent	Use	Description	How Filed	Labeling Impact

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

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

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

The original ANDA submission for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg dated July 15, 2009 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 in (Case No . 09-943-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.

[Per Reg Support review]

3. INACTIVE INGREDIENTS

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

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:

Basic Butylated methacrylate copolymer (b) (4)
Microcrystalline cellulose NF (b) (4)
Lactose monohydrate NF (b) (4)
Methanol NF
Crospovidone NF
Sodium bicarbonate USP
Hydroxy propyl cellulose NF (b) (4)
Magnesium stearate NF
(b) (4)
Sodium lauryl sulphate NF
(b) (4)

Film coating contains: isopropyl alcohol, methylene chloride, and Opadry White OY-58900. Opadry white OY-58900 contains: hypromellose, titanium dioxide, polyethylene glycol (b) (4)
[2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.2.1-original submission]

Dr. Reddy's Laboratories Ltd.
Bachepalli 502325
Andhra Pradesh, India

5. FINISHED DOSAGE FORM

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

RLD:

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

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

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

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

(b) (4)

ANDA:

10 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “121” on the other side. (b) (4)

20 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “122” on the other side. (b) (4)

40 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “123” on the other side. (b) (4)

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

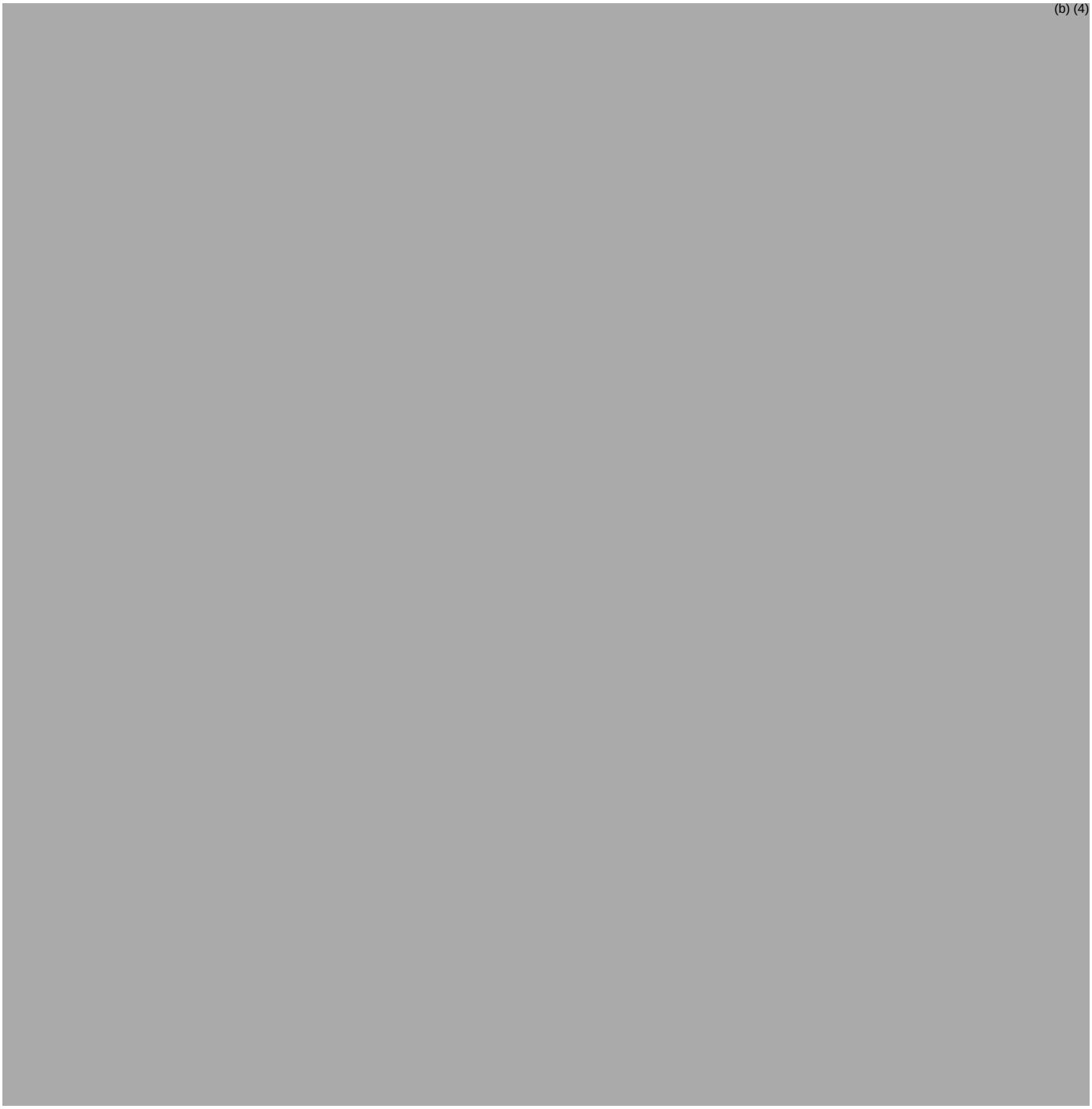
Bottle packs

10 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE Container (b) (4)

20 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE container ((b) (4)

40 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE container (b) (4)

(b) (4)



6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Drug Substance only. (checked May 14, 2012)

Atorvastatin Calcium

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, and store at room temperature.

RLD: store at CRT 20-25°C (68-77°F) [see USP].

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

7. DISPENSING STATEMENTS COMPARISON

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

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO Dissolution is deficient as of 12/18/09.

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

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

ANDA: All strengths in bottles of 30s, 60s, 90s and 500s.
(b) (4)

11. SPL:

SPL was submitted in the amendment dated 3/5/2012. Data elements are acceptable. (b) (4)
(b) (4)

(b) (4).

12. Patient Package Insert: Per AF dated 2/9/2010:

(b) (4)

13. Container colors:

10 mg: strength is yellow text against white background

20 mg: strength is red text against white background

40 mg: strength is blue text against white background

14. Firm submitted combined chemistry and labeling amendment dated 5/13/2011 to revise their labels in accordance to chemistry's request.

(b) (4)

15. REMS:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Date of Review: May 18, 2012 Date of Submission: May 13, 2011, March 5, 2012 & May 17, 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
05/18/2012

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

****** (Supersedes LBL AP SUM #2 dated 08/03/2011)*****
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091650 Date of Submission: March 5, 2012

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

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

---

LABELING DEFICIENCIES:

1. CONTAINER:

Revise the "*Each tablet contains…" statement to read [redacted (b) (4)].

2. CARTON:

i. Revise "[redacted (b) (4)]

ii. See comment 1.

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 [redacted (b) (4)]" 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
[redacted (b) (4)]

Basis of Approval

Was this approval based upon a petition? No

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

NDA Number: 020702
NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

From: Nagavelli, Laxma
Sent: Monday, May 14, 2012 5:55 PM
To: Turner, Betty
Cc: Vera, Matthew; Khan, Khalid
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Betty
As Khalid mentioned in his e-mail, [redacted] (b) (4)
.
Hope, this clarified your questions. Please let us know if you have any further comments.

Thanks,
Laxma

From: Turner, Betty
Sent: Monday, May 14, 2012 3:40 PM
To: Khan, Khalid
Cc: Nagavelli, Laxma
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Hi Khalid,

Thank you very much for your quick response.

I have one question and maybe Laxma could comment. [redacted] (b) (4)

Thanks

Betty

From: Khan, Khalid
Sent: Monday, May 14, 2012 3:10 PM
To: Turner, Betty
Cc: Nagavelli, Laxma
Subject: RE: ANDA 091650 Atorvastatin Calcium (Dr. Reddy's)

Hello Betty,

This application has been transferred to another colleague of mine in our Division. Laxma, who is our team leader can help you with any inquiries for the future.

(b) (4)

Laxma, could you please comment?

Thanks.

Khalid

Email to K. Khan on August 2, 2011:

Good afternoon,

I'm the labeling reviewer for 91650 (Reddy's atorvastatin). Could you answer my question when you pick up 91650 for review?

In the last chemistry deficiencies, Dr. Reddy's was instructed to revise their labels (b) (4) I attached the chemistry comment, the firm's revised label and section 11 DESCRIPTION from the insert.

Thanks
Ann

Email from Weiqin Jiang on 8/19/10:

Sorry, Ann: the pasted file was disrupted. (b) (4) weiqin

From: Jiang, Weiqin
Sent: Thursday, August 19, 2010 2:39 PM
To: Vu, Thuyanh (Ann)
Cc: Iser, Robert
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Ann: I checked with Bob. Here is what we found.

(b) (4)

Hope this helps.

weiqin

From: Vu, Thuyanh (Ann)
Sent: Thursday, August 19, 2010 1:59 PM
To: Jiang, Weiqin
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Here's the original email.

Thanks!

From: Vu, Thuyanh (Ann)
Sent: Thursday, March 11, 2010 2:02 PM
To: Jiang, Weiqin
Cc: Vu, Thuyanh (Ann)
Subject: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Weiquin,

When you get to this application, could you answer these two questions?

Dr. Reddy's labeling is different from the RLD's. Please see below. I asked Dr. Reddy's why it was so different and in the labeling amendment dated 2/9/2010, the firm stated "

<< OLE Object: Picture (Enhanced Metafile) >>
Is this acceptable? Please see below for Dr. Reddy's labeling and the RLD, Lipitor.

(b) (4)

Thanks
Ann

Dr. Reddy's labeling from DESCRIPTION section:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-
1Hpyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of atorvastatin calcium is C66H68CaF2N4O10 and its
molecular weight is 1155.36. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>

Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in
dimethyl sulphoxide.

Lipitor labeling:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O and its molecular weight is 1209.42. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>

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

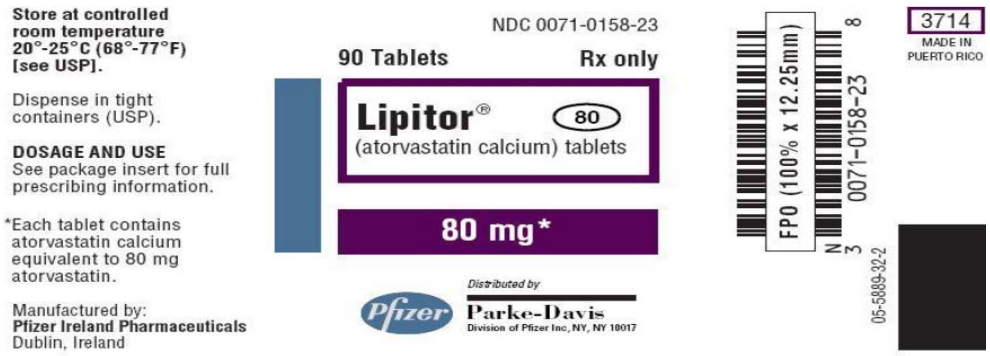
---

FOR THE RECORD: Please note that the previous review cycles were completed by labeling reviewer, Thuyanh Vu. Portions of this review were taken from the review dated 8/3/2011 in DARRTS.

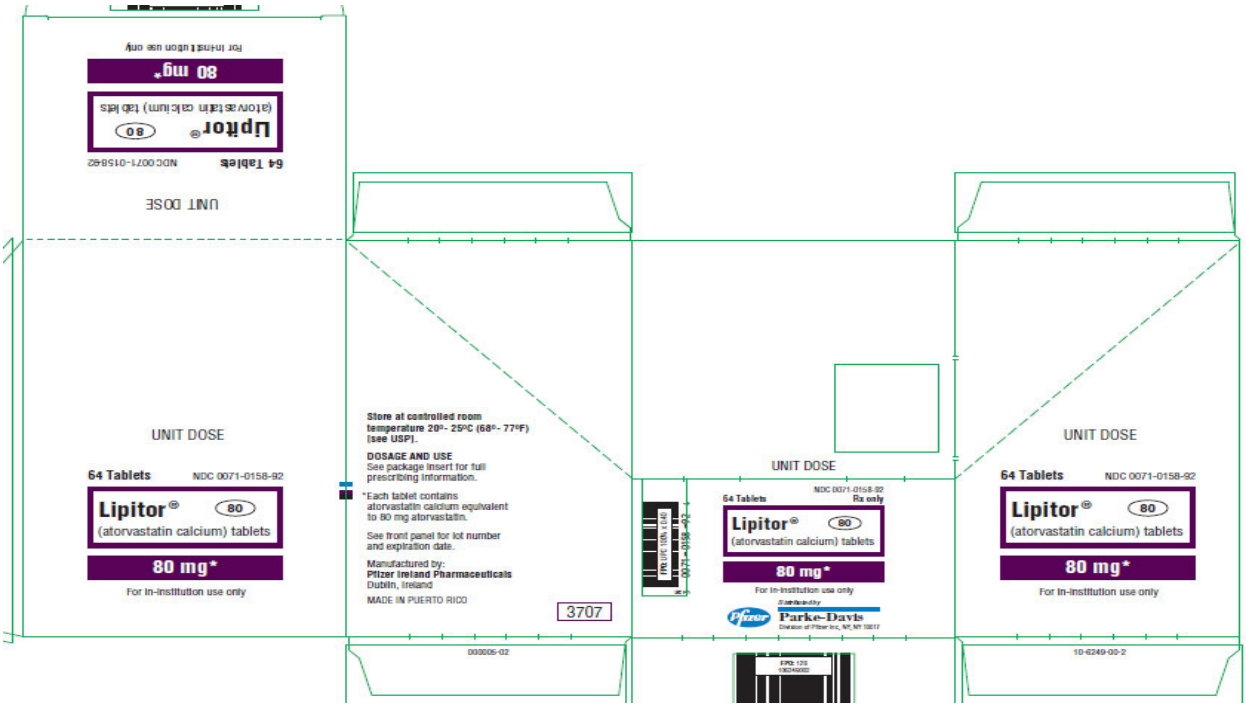
1. MODEL LABELING: This review was based on the labeling of the RLD, Lipitor, 020702/S-060; approved February 28, 2012.

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

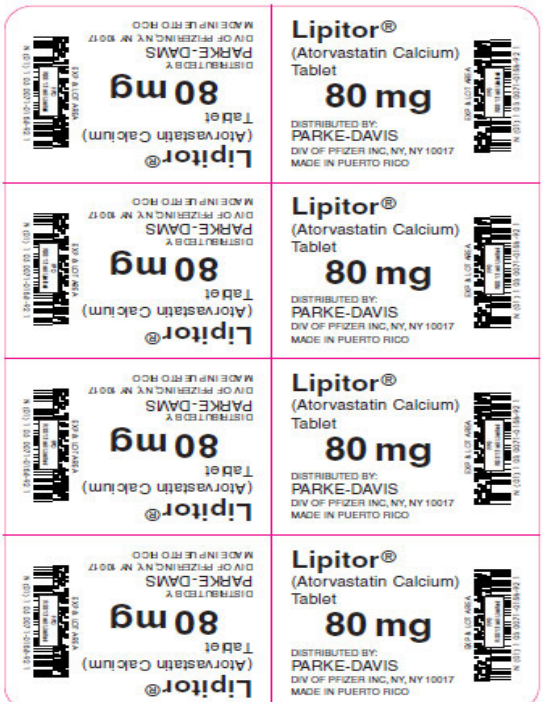
CONTAINER



CARTON



BLISTER :



2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent	Patent	Use	Description	How Filed	Labeling Impact

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

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

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

The original ANDA submission for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg dated July 15, 2009 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 in (Case No . 09-943-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.

[Per Reg Support review]

3. INACTIVE INGREDIENTS

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

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:

Basic Butylated methacrylate copolymer [redacted]
Microcrystalline cellulose NF [redacted]
Lactose monohydrate NF [redacted]
Methanol NF
Crospovidone NF
Sodium bicarbonate USP
Hydroxy propyl cellulose NF [redacted]
Magnesium stearate NF
[redacted]
Sodium lauryl sulphate NF
[redacted]

Film coating contains: isopropyl alcohol, methylene chloride, and Opadry White OY-58900. Opadry white OY-58900 contains: hypromellose, titanium dioxide, polyethylene glycol [redacted] [2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.2.1-original submission]

Dr. Reddy's Laboratories Ltd.
Bachepalli 502325
Andhra Pradesh, India

5. FINISHED DOSAGE FORM

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

RLD:

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

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

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

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

[redacted]

ANDA:

10 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "121" on the other side. [redacted]

20 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "122" on the other side. [redacted]

40 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "123" on the other side. [redacted]

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

Bottle packs

10 mg:
30's: HDPE container
60's: HDPE container
90's: HDPE container
500's: HDPE Container
[redacted]

20 mg:
30's: HDPE container [redacted]
60's: HDPE container
90's: HDPE container
500's: HDPE container

40 mg:
30's: HDPE container [redacted]
60's: HDPE container
90's: HDPE container
500's: HDPE container

[redacted]

[redacted]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Drug Substance only. (checked May 14, 2012)

Atorvastatin Calcium

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, and store at room temperature.

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

7. DISPENSING STATEMENTS COMPARISON

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

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO Dissolution is deficient as of 12/18/09.

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

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

ANDA: All strengths in bottles of 30s, 60s, 90s and 500s.
(b) (4)

11. SPL:

SPL was submitted in the amendment dated 3/5/2012. Data elements are acceptable. (b) (4)
(b) (4)

12. Patient Package Insert: Per AF dated 2/9/2010:

(b) (4)

13. Container colors:

10 mg: strength is yellow text against white background

20 mg: strength is red text against white background

40 mg: strength is blue text against white background

14. Firm submitted combined chemistry and labeling amedment dated 5/13/2011 to revise their labels in accordance to chemistry's request.

15. REMS:
REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

Date of Review: May 14, 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#2****
(Superceds LBL AP SUM #1 dated 9/9/2010)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091650 Date of Submission: May 13, 2011

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

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

---

BASIS OF APPROVAL:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (all strengths in bottles of 30s, 60s, 90s and 500s): Final Printed Labels submitted on 5/13/2011 e-submission

Carton Labels: Final Printed Labels submitted on 5/13/2011 e-submission

(b) (4)

Professional Package Insert Labeling: Final Printed Labeling acceptable in the 2/9/10 e-submission

Patient Information Sheet: Final Printed Labels submitted on 2/9/2010 e-submission

Revisions needed before full approval: No

Was this approval based upon a petition? No

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

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

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

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

Email to K. Khan on August 2, 2011:

Good afternoon,

I'm the labeling reviewer for 91650 (Reddy's atorvastatin). Could you answer my question when you pick up 91650 for review?

In the last chemistry deficiencies, Dr. Reddy's was instructed to revise their labels (b) (4) [redacted]. I attached the chemistry comment, the firm's revised label and section 11 DESCRIPTION from the insert.

Thanks
Ann

Email from Weiqin Jiang on 8/19/10:

Sorry, Ann: the pasted file was disrupted. (b) (4) [redacted]

weiqin

From: Jiang, Weiqin
Sent: Thursday, August 19, 2010 2:39 PM
To: Vu, Thuyanh (Ann)
Cc: Iser, Robert
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Ann: I checked with Bob. Here is what we found.

(b) (4) [redacted]

Hope this helps.

weiqin

From: Vu, Thuyanh (Ann)
Sent: Thursday, August 19, 2010 1:59 PM
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Here's the original email.

Thanks!

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Subject: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

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When you get to this application, could you answer these two questions?

Dr. Reddy's labeling is different from the RLD's. Please see below. I asked Dr. Reddy's why it was so different and in the labeling amendment dated 2/9/2010, the firm stated "

<< OLE Object: Picture (Enhanced Metafile) >>
Is this acceptable? Please see below for Dr. Reddy's labeling and the RLD, Lipitor.

(b) (4)

Thanks
Ann

Dr. Reddy's labeling from DESCRIPTION section:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-
1Hpyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of atorvastatin calcium is C66H68CaF2N4O10 and its
molecular weight is 1155.36. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>

Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in
dimethyl sulphoxide.

Lipitor labeling:
Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of

atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O and its molecular weight is 1209.42. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>

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

---

FOR THE RECORD:

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

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

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

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

[Per Reg Support review]

3. INACTIVE INGREDIENTS

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

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:
Basic Butylated methacrylate copolymer (b) (4)
Microcrystalline cellulose NF (b) (4)
Lactose monohydrate NF (b) (4)
Methanol NF
Crospovidone NF
Sodium bicarbonate USP
Hydroxy propyl cellulose NF (b) (4)
Magnesium stearate NF
(b) (4)
Sodium lauryl sulphate NF
(b) (4)

Film coating contains: isopropyl alcohol, methylene chloride, and Opadry White OY-58900. Opadry white OY-58900 contains: hypromellose, titanium dioxide, polyethylene glycol (b) (4) [2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.2.1-original submission]

Dr. Reddy's Laboratories Ltd.
Bachepalli 502325
Andhra Pradesh, India

5. FINISHED DOSAGE FORM

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

RLD:

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

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

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

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

ANDA:

10 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “121” on the other side.

20 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “122” on the other side.

40 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “123” on the other side.

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

Bottle packs

10 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE Container (b) (4)

20 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE container (b) (4)

40 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE container (b) (4)

(b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

7. DISPENSING STATEMENTS COMPARISON

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

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO Dissolution is deficient as of 12/18/09.

9. SCORING

   RLD: Not scored

ANDA: Not scored

10. PACKAGE CONFIGURATION

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

ANDA: All strengths in bottles of 30s, 60s, 90s and 500s.
(b) (4)

11. SPL

Since this drug product could not be fully approved until 2011, SPL is not neccessary at this moment.

12. Patient Package Insert: Per AF dated 2/9/2010:

(b) (4)

13. Container colors:

10 mg: strength is yellow text against white background

20 mg: strength is red text against white background

40 mg: strength is blue text against white background

14. Firm submitted combined chemistry and labeling amedment dated 5/13/2011 to revise their labels in accordance to chemistry's request.

(b) (4)

Date of Review: August 2, 2011 Date of Submission: May 13, 2011

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Following this page, 22 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

THUYANH VU
08/03/2011

JOHN F GRACE
08/03/2011

LABELING APPROVAL SUMMARY

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

ANDA Number: 091650 Date of Submission: February 9, and August 26, 2010

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

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

---

BASIS OF APPROVAL:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (all strengths in bottles of 30s, 60s, 90s and 500s): Final Printed Labels submitted on 2/9/2010 e-submission

Carton Labels: Final Printed Labels submitted on 2/9/2010 e-submission

(b) (4)

Professional Package Insert Labeling: Final Printed Labeling acceptable in the 2/9/10 e-submission

Patient Information Sheet: Final Printed Labels submitted on 2/9/2010 e-submission

Revisions needed before full approval: Yes

(b) (4)

Was this approval based upon a petition? No

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

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

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

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

Email from Weiqin Jiang on 8/19/10:

Sorry, Ann: the pasted file was disrupted. (b) (4)

weiqin

From: Jiang, Weiqin
Sent: Thursday, August 19, 2010 2:39 PM
To: Vu, Thuyanh (Ann)
Cc: Iser, Robert
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Ann: I checked with Bob. Here is what we found.

(b) (4)

Hope this helps.

weiqin

From: Vu, Thuyanh (Ann)
Sent: Thursday, August 19, 2010 1:59 PM
To: Jiang, Weiqin
Subject: FW: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Here's the original email.

Thanks!

From: Vu, Thuyanh (Ann)
Sent: Thursday, March 11, 2010 2:02 PM
To: Jiang, Weiqin
Cc: Vu, Thuyanh (Ann)
Subject: Dr. Reddy's atorvastatin 91-650 DESCRIPTION section is different than RLD's

Weiquin,

When you get to this application, could you answer these two questions?

Dr. Reddy's labeling is different from the RLD's. Please see below. I asked Dr. Reddy's why it was so different and in the labeling amendment dated 2/9/2010, the firm stated "

<< OLE Object: Picture (Enhanced Metafile) >>
Is this acceptable? Please see below for Dr. Reddy's labeling and the RLD, Lipitor.

(b) (4)

Thanks
Ann

Dr. Reddy's labeling from DESCRIPTION section:

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-
1Hpyrrole-1-heptanoic acid, calcium salt (2:1). The molecular formula of atorvastatin calcium is C66H68CaF2N4O10 and its
molecular weight is 1155.36. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>

Atorvastatin calcium is a white to off-white colored powder free from visible extraneous matter. Atorvastatin calcium is soluble in
dimethyl sulphoxide.

Lipitor labeling:
Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C33H34 FN2O5)2Ca•3H2O and its molecular weight is 1209.42. Its structural formula is:

<< OLE Object: Picture (Enhanced Metafile) >>
Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol

Email to Weiqin on March 11, 2010:

Weiquin,

When you get to this application, could you answer these two questions?

Dr. Reddy's labeling is different from the RLD's. Please see below. I asked Dr. Reddy's why it was so different and in the labeling amendment dated 2/9/2010, the firm stated "

(b) (4)

Is this acceptable? Please see below for Dr. Reddy's labeling and the RLD, Lipitor.

(b) (4)

Thanks
Ann

Dr. Reddy's labeling from DESCRIPTION section:

Following this page, 1 Page of Draft Labeling have been Withheld in Full as (b)(4)

FOR THE RECORD:

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

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

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

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None

I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[Per Reg Support review]

3. INACTIVE INGREDIENTS

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

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:
Basic Butylated methacrylate copolymer (b) (4)
Microcrystalline cellulose NF (b) (4)
Lactose monohydrate NF (b) (4)
Methanol NF
Crospovidone NF
Sodium bicarbonate USP
Hydroxy propyl cellulose NF (b) (4)
Magnesium stearate NF
(b) (4)
Sodium lauryl sulphate NF
(b) (4)

Film coating contains: isopropyl alcohol, methylene chloride, and Opadry White OY-58900. Opadry white OY-58900 contains: hypromellose, titanium dioxide, polyethylene glycol (b) (4) [2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.2.1-original submission]

Dr. Reddy's Laboratories Ltd.
Bachepalli 502325
Andhra Pradesh, India

5. FINISHED DOSAGE FORM

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

RLD:

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

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

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

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

ANDA:

10 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "121" on the other side.

20 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "122" on the other side.

40 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed “RDY” on one side and “123” on the other side.

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

Bottle packs

10 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE Container (b) (4)

20 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE container (b) (4)

40 mg:
30’s: HDPE container (b) (4)
60’s: HDPE container
90’s: HDPE container
500’s: HDPE container (b) (4)

(b) (4)

(b) (4)

(b) (4)

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

7. DISPENSING STATEMENTS COMPARISON

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

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO Dissolution is deficient as of 12/18/09.

9. SCORING

   RLD: Not scored
   ANDA: Not scored

10. PACKAGE CONFIGURATION

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

    ANDA: All strengths in bottles of 30s, 60s, 90s and 500s.
    (b) (4)

11. SPL

    Since this drug product could not be fully approved until 2011, SPL is not neccessary at this moment.

12. Patient Package Insert: Per AF dated 2/9/2010:

(b) (4)

(b) (4)

13. Container colors:

10 mg: strength is yellow text against white background

20 mg: strength is red text against white background

40 mg: strength is blue text against white background

Date of Review: September 8, 2010 Dates of Submission: February 9, and August 26, 2010

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Following this page, 41 Pages of Draft Labeling have been Withheld in Full as (b)(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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

/s/

THUYANH VU
09/08/2010

JOHN F GRACE
09/09/2010

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

ANDA Number: 091650 Date of Submission: July 15, 2009

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

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

---

Labeling Deficiencies:

1. CONTAINER (all strengths in bottles of 30s, 60s, 90s and 500s):

   Revise (b) (4) to "USUAL DOSAGE".

2. (b) (4)

3. CARTON

   (b) (4)

4. INSERT

   11 DESCRIPTION

   The third paragraph of this subsection is significantly different than the RLD's. Please provide an explanation as to why the physical properties of your drug product differ significantly from the RLD's.

5. PATIENT INFORMATION SHEET:

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

Submit labels and labeling electronically.

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

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

BASIS OF TENTATIVE APPROVAL:

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

Do you have 12 Final Printed Labels and Labeling? No

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

Professional Package Insert Labeling: No

Patient Information Sheet: No

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

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

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

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

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

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

FOR THE RECORD:

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

2. PATENTS/EXCLUSIVITIES:

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	III	Same As
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Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-523	Mar 2, 2010	Use in adult patients with clinically evident coronary heart disease to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, angina, revascularization procedures and hospitalization for congestive heart failure	None
I-471/S-035	**SEP 21,2008**	INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE	None

[Per Reg Support review]

3. INACTIVE INGREDIENTS

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

Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients:

Basic Butylated methacrylate copolymer (b) (4)
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Lactose monohydrate NF (b) (4)
Methanol NF
Crospovidone NF
Sodium bicarbonate USP
Hydroxy propyl cellulose NF (b) (4)
Magnesium stearate NF
(b) (4)
Sodium lauryl sulphate NF
(b) (4)

Film coating contains: isopropyl alcohol, methylene chloride, and Opadry White OY-58900. Opadry white OY-58900 contains: hypromellose, titanium dioxide, polyethylene glycol (b) (4) [2.3.P.1-original submission]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM [2.3.P.2.1-original submission]

Dr. Reddy's Laboratories Ltd.
Bachepalli 502325
Andhra Pradesh, India

5. FINISHED DOSAGE FORM

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

RLD:

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

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

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

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

ANDA:

10 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "121" on the other side.

20 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "122" on the other side.

40 mg: white to off white, capsule shaped, biconvex, film coated tablets, debossed "RDY" on one side and "123" on the other side.

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

Bottle packs

10 mg:
30's: HDPE container (b) (4)
60's: HDPE container

90's: HDPE container [redacted]
500's: HDPE Container [redacted]

20 mg:
30's: HDPE container [redacted]
60's: HDPE container
90's: HDPE container
500's: HDPE container [redacted]

40 mg:
30's: HDPE container [redacted]
60's: HDPE container
90's: HDPE container
500's: HDPE container [redacted]

[redacted]:

[redacted]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

7. DISPENSING STATEMENTS COMPARISON

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

8. BIOAVAILABILITY/BIOEQUIVALENCE: BIO Dissolution is deficient as of 12/18/09.

9. SCORING

RLD: Not scored
ANDA: Not scored

10. PACKAGE CONFIGURATION

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

ANDA: All strengths in bottles of 30s, 60s, 90s and 500s.
(b) (4)

11. SPL

Since this drug product could not be fully approved until 2011, SPL is not neccessary at this moment.

Date of Review:January 19, 2010 Date of Submission: July 15, 2009

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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

/s/

THUYANH VU
01/19/2010

JOHN F GRACE
01/25/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

CHEMISTRY REVIEWS

ANDA 091650

Addendum #1 to Review #4

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

Dr. Reddy's Laboratories Limited

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

Background:

When review #4 was finalized on June 29, 2012, Type II DMFs 21125 and 25902 had been reviewed and found Adequate with additional information requested.

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

The purpose of this review addendum is to reflect the current status of DMF 21125 and 25902 as fully adequate.

An updated replacement table for Item #17 in Review #4 is 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 (no BHA Premix)	1	Adequate	10-July-2012	M. Vera
25902	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium with BHA	1	Adequate	10-July-2012	M. Vera
(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		
(b) (4)							
(b) (4)	III	(b) (4)		4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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

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

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

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

B. Other Documents: None

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: (None).

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

C:\Documents and Settings\veram\My Documents\Reviews in progress\ANDA 091650 Atrovastatin calcium\091650R04_Addendum1.doc

TYPE OF LETTER: Approvable

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
07/11/2012

VILAYAT A SAYEED
07/12/2012

ANDA 091650

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

Dr. Reddy's Laboratories Limited

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 091650

2. REVIEW #: 4

3. REVIEW DATE: 5/15/2012
4. REVIEWER: Matthew D. Vera, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	15-JULY-2009 (09-JULY-2009 EDR date)
Amendment	19-FEB-2010
Amendment	27-AUG-2010
Amendment	13-MAY-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD #8)	16-NOV-2011
Amendment (SD #9)	08-FEB-2012
Amendment (SD #11)	26-MAR-2012
Amendment(SD #12)	11-APR-2012
Amendment (SD #15)	21-MAY-2012
Amendment (SD #16)	23-MAY-2012
Amendment (SD #17)	31-MAY-2012
Amendment (SD #18)	14-JUN-2012
Amendment (SD #19)	25-JUN-2012
Amendment (SD #20)	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 (b) (4)
U.S. Representative:	Jaya Ayyagari Dr. Reddy's Laboratories, Inc. 200 Somerset Corporate Blvd., 7th Fl., Bridgewater, NJ 08807
Telephone:	908-203-4977
Fax:	908-203-4980

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

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

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.(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 (no BHA Premix)	1	Adequate-IR	25-May-2012	M. Vera
25902	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium with BHA	1	Adequate-IR	25-May-2012	M. Vera
(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		
(b) (4)							
(b) (4)	III	(b) (4)		4	N/A		
	III			4	N/A		
	III			4	N/A		

(b) (4)		(b) (4)				
	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		

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

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

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	28-APR-2010	E. Johnson
Methods Validation	Not Applicable		
Labeling	Acceptable	03-Aug-2011	Vu, Thuyanh
Bioequivalence	Acceptable	20-Jul-2011	J. Walters
Dissolution	Acceptable	20-Jul-2011	J. Walters
EA	Categorical Exclusion Requested	07-Feb-2009	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

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

CMC Approvable

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

II. Summary of Chemistry Assessments

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

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is (b) (4) oral, (b) (4) tablets. It is indicated for lipid regulation. 10 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '121'on other side. 20 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '122'on other side. 40 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '123'on other side.

Critical Attributes of the Formulation: The manufacturing process is a (b) (4)

(b) (4)

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

The DP is intended for long term use. Thus, it is packaged in bottles, with CRC, in 30's, 60's, 90's, 500's count, (b) (4). Based on three month accelerated and 24 month CRT stability data an expiration period of 24 months is requested. Note in Review #4: (b) (4)

The MDD for adults is 80 mg. (b) (4) (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review, other disciplines and/or EES. This CMC review may require an addendum based on recommendations made by other review disciplines.

Following this page, 74 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

R REGIONAL INFORMATION- **Satisfactory in CR # 2**

R1 Executed Batch Records: Provided

	Strength	Batch	Batch Size	Manufacturing Yield	Packaging Yield
(b) (4)					
[redacted]					

(b) (4)

[redacted]

R2 Comparability Protocols: N/A

Reviewer's Comment:	**Satisfactory per Review #1**
CR1: (b) (4) [redacted] This is adequate.	

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: (None).

B. Endorsement Block
HFD-630 / M. Vera / 05/24/2012; 6/19/2012; 6/25/2012; 6/27/2012
HFD-630 / L. Nagavelli /5/25/2012; 6/20/2012; 6/26/2012; 6/28/2012
HFD-617 / L. A. Sears /6/28/2012

C:\Documents and Settings\veram\My Documents\Reviews in progress\ANDA 091650 Atrovastatin calcium\091650R04.doc

TYPE OF LETTER: Approvable

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
06/28/2012

LAXMA R NAGAVELLI
06/28/2012
CMC Approvable at Team Level

LEIGH A SEARS
06/29/2012

ANDA 091650

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

Dr. Reddy's Laboratories Limited

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

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 091650

2. REVIEW #: 3

3. REVIEW DATE: 7/13/2011; 8/17/2011; 9/6/2011; 9/28/2011

4. REVIEWER: Khalid M. Khan

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	15-JULY-2009 (09-JULY-2009 EDR date)
Amendment	19-FEB-2010
Amendment	27-AUG-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	13-MAY-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 (b) (4)
U.S. 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: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets

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

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.(2.3.S)

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
Raw materials							
21125	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium	1	Inadequate	Sep 30, 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		
(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		
	III			4	N/A		
	III			4	N/A		

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

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

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

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	28-APR-2010	E. Johnson
Methods Validation	Not Applicable		
Labeling	Acceptable	03-Aug-2011	Vu, Thuyanh
Bioequivalence	Acceptable	20-Jul-2011	J. Walters
Dissolution	Acceptable	20-Jul-2011	J. Walters
EA	Categorical Exclusion Requested	07-Feb-2009	K. Khan
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Pending	03-Aug-2011	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

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

NA-Minor deficiencies (Review #3)

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

II. Summary of Chemistry Assessments

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

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is (b) (4) oral, (b) (4) tablets. It is indicated for lipid regulation. 10 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '121'on other side. 20 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '122'on other side. 40 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '123'on other side.

The DP is manufactured by (b) (4)

Pharm-tox study for (b) (4)

Inadequate. (b) (4)

See Rev.#2 for details.

The firm provided additional data on composition and quantities of impurities evaluated in toxicological studies. The data is under review by Pharm-Tox team under consult No. 2011-0542 (DARRTS 07/11/2011). The consult has been completed and based on the submitted data, the impurity specifications could not be qualified. See Rev. # 3 for updated details.

(b) (4) DMF# (b) (4) has been reviewed. The Pharma-tox consult has been finished. The recommendation is: *"The firm should submit complete study reports including individual animal data, if available, for any pharmacokinetic (all species) and repeat-dose rat toxicity studies of* (b) (4) *In addition, the DMF holder should provide nonclinical safety pharmacology data, and nonclinical studies of reproductive effects. A careful review of the safety of* (b) (4) *in nonclinical studies or clinical trials may be helpful as well."* -Inadequate. However, the reviewer finds (b) (4) (b) (4). See Rev.#2 for details.

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

Drug Substance: The DS is atorvastatin calcium (b) (4) [redacted]

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 CRC, in 30's, 60's, 90's, 500's count, (b) (4) [redacted] (b) (4) [redacted]. 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.

(b) (4) [redacted]

C. Basis for Approvability or Not-Approval Recommendation

The application is not approved due to few CMC related minor deficiencies.

Following this page, 71 Pages Withheld in Full as (b)(4)

(b) (4)

R REGIONAL INFORMATION- **Satisfactory in CR # 2**

R1 Executed Batch Records: Provided

	Strength	Batch	Batch Size	Manufacturing Yield	Packaging Yield
(b) (4)					

R2 Comparability Protocols: N/A

Reviewer's Comment: **Satisfactory per Review #1**

CR1: (b) (4)

. This is adequate.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091650 APPLICANT: Dr. Reddy's Laboratories Limited

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

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.

(b) (4)

B. Please acknowledge and respond to the following comments:

1. Please provide all available long-term stability data with updated stability specifications.

(b) (4)

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

B. Endorsement Block
HFD-630 / K. Khan/CR/7/13/2011; 8/17/2011; 9/6/2011; 9/28/2011
HFD-630 / Nagavelli, L./TL/9/16/2011;9/30/2011
HFD-617 / Sears, L.A./PM/9/19/2011

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TYPE OF LETTER: NOT APPROVABLE – NA-Minor

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
10/06/2011
ANDA 091650R03 is NA-Minor

LEIGH A SEARS
10/06/2011

LAXMA R NAGAVELLI
10/06/2011

ANDA 091650

Atorvastatin Calcium Tablets
10 mg, 20 mg and 40 mg

Dr. Reddy's Laboratories, Inc.

Weiqin Jiang, Ph. D.
Division of Chemistry
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 091650

2. REVIEW #: 2

3. REVIEW DATE: 10-JAN-2011

4. REVIEWER: Weiqin Jiang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
Original	09-JULY-2009 (EDR date), 15-JULY-2009 (DARRTS date)
Amendment	19-FEB-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	27-AUG-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Dr. Reddy's Laboratories Ltd.
	Bachepalli, Post Bag No. 15, Kukatpally P.O., Hyderabad – 500 072, India
	Contact person: Zoher T. Sihorwala
Address:	Head-Global Regulatory Affairs & Compliance (India Operations)
	Tel. No. (040) 2304 4971; Fax No. (040) 2304 5238
	(b) (4)
U.S.	Kumara Sekar
Representative:	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: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets

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

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

16. CHEMICAL NAME, STRUCTURAL & MOLECULAR FORMULA, MOLECULAR Wt.(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	Inadequate	April 2011	by W. Jiang
(b) (4)	III	(b) (4)		4			
	III			4			
(b) (4)							
(b) (4)	III	(b) (4)		4			
	III			4			
	III			4			
(b) (4)							
(b) (4)	III	(b) (4)		4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)	III	(b) (4)	4			
	III		4			
	III		4			
	III		4			

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

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

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	28-APR-2010	E. Johnson
Methods Validation	Not Applicable		
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Pending	6-May-2010	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

___x_ Yes ____ No

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

NA-Minor deficiencies (Review #2)

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

II. Summary of Chemistry Assessments

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

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is (b) (4) oral, (b) (4) tablets. It is indicated for lipid regulation. 10 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '121'on other side. 20 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '122'on other side. 40 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '123'on other side.

Pharm-tox study for (b) (4)

Inadequate. (b) (4)

See Rev.#2 for details.

(b) (4)

(b) (4). DMF# (b) (4) has been reviewed. The Pharma-tox consult has been finished. The recommendation is: *"The firm should submit complete study reports including individual animal data, if available, for any pharmacokinetic (all species) and repeat-dose rat toxicity studies of* (b) (4) *In addition, the DMF holder should provide nonclinical safety pharmacology data, and nonclinical studies of reproductive effects. A careful review of the safety of* (b) (4) *in nonclinical studies or clinical trials may be helpful as well."* -Inadequate. (b) (4)

(b) (4) See Rev.#2 for details.

Critical Attributes of the Formulation: The manufacturing process is a (b) (4)

Drug Substance: The DS is atorvastatin calcium (b) (4)

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

The DP is intended for long term use. Thus, it is packaged in bottles, with CRC, in 30's, 60's, 90's, 500's count, (b) (4)

(b) (4)

The DP is manufactured by

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.

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The application is not approved due to few CMC related minor deficiencies.

Following this page, 57 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

R REGIONAL INFORMATION- Unsatisfactory in Rev.#2

R1 Executed Batch Records: Provided

	Strength	Batch	Batch Size	Manufacturing Yield	Packaging Yield
(b) (4) [redacted]					

R2 Comparability Protocols: N/A

Reviewer's Comment CR1: (b) (4) [redacted] This is adequate.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091650 APPLICANT: Dr. Reddy's Laboratories, Ltd.

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

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10

(b) (4)

[redacted]

B. Please acknowledge and respond to the following comments:

1. Please provide all available long-term stability data with updated stability specifications.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

B. Endorsement Block
HFD-630 / W. Jiang/CR/10-JAN-2011, revised Mar. 2, 2011; 3/24/2011; 4/20/2011
HFD-630 / Nagavelli, L./TL/3/11/2011; 3/25/2011; 4/22/2011
HFD-617 / Sears, L.A./PM/4/22/2011

V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\ANDA\91650R02.doc

TYPE OF LETTER: NOT APPROVABLE – NA-Minor

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

/s/

WEIQIN JIANG
04/25/2011

LEIGH A SEARS
04/26/2011

LAXMA R NAGAVELLI
04/28/2011

ANDA 091650

Atorvastatin Calcium Tablets
10 mg, 20 mg and 40 mg

Dr. Reddy's Laboratories, Inc.

Weiqin Jiang, Ph. D.
Division of Chemistry III
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. ANDA 091650

2. REVIEW #: 1

3. REVIEW DATE: 22-MAR-2010

4. REVIEWER: Weiqin Jiang

5. PREVIOUS DOCUMENTS:

Previous Documents:	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	09-JULY-2009 (EDR date) 15-JULY-2009 (DARRTS date)
Amendment	19-FEB-2010

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 (b) (4)
U.S. 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: Proprietary Name: Not Available
Non-Proprietary Name: Atorvastatin Calcium Tablets

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

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

11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg, 20 mg and 40 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed __X___Not a SPOTS product

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

17. RELATED/SUPPORTING DOCUMENTS: A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)							
21125	II	Dr. Reddy's Laboratories Ltd.	Atorvastatin Calcium Tablets	1	Not Adequate	16-MAR-2010	by W. Jiang
(b) (4)	III	(b) (4)		4			
	III			4			
(b) (4)							
(b) (4)	III	(b) (4)		4			
	III			4			
	III			4			
	s (Child r						
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)	III	(b) (4)	4			
	III		4			
(b) (4)	III	(b) (4)	4			
(b) (4)	III	(b) (4)	4			
(b) (4)	III		4			
(b) (4)	III	(b) (4)	4			

[1] Action codes for DMF Table: 1 – DMF Reviewed.

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

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

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	28-APR-2010	E. Johnson
Methods Validation	Not Applicable		
Labeling	Pending		
Bioequivalence	Pending		
EA	Adequate	10-APR-2010	W. Jiang
Radiopharmaceutical	Not Applicable		
Pharm/Tox	Pending	6-May-2010	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No

If no, explain reason(s) below:

The Executive Summary

I. Recommendations

1. Recommendation and Conclusion on Approvability

NA-Minor deficiencies (Review #1)

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

II. Summary of Chemistry Assessments

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

10 mg	White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '121'on other side
20 mg	White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '122'on other side
40mg	White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '123'on other side

Description of Drug Product: The proposed DP, Atorvastatin Calcium tablets, is (b) (4), oral, (b) (4) tablets. It is indicated for lipid regulation. 10 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '121'on other side. 20 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '122'on other side. 40 mg strength is White to off white capsule shaped , biconvex , film coated tablets debossed 'RDY' on one side and '123'on other side.

Pharm-tox study for (b) (4) (b) (4) is under consult with Pharm-tox review. The report is pending.

(b) (4) . DMF# (b) (4) has been reviewed. The Pharma-tox consult has been submitted. The report is pending.

Critical Attributes of the Formulation: The manufacturing process is a (b) (4)

(b) (4)

Drug Substance: The DS is atorvastatin calcium (b) (4) The MDD for adults is 80 mg. (b) (4) (b) (4) Revision for 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 CRC, in 30's, 60's, 90's, 500's count, [redacted] (b) (4). The DP is manufactured by [redacted] (b) (4) Based on the 3-month accelerated studies, the firm has requested an expiration period of 24 months at room conditions

C. Basis for Approvability or Not-Approval Recommendation

The application is not approved due to few CMC related minor deficiencies.

Following this page, 95 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

A	APPENDICES	
A.1	Facilities and Equipment (biotech only)	N/A
A.2	Adventitious Agents Safety Evaluation	N/A
A.3	Novel Excipients	N/A

R REGIONAL INFORMATION

R1 Executed Batch Records: Provided

	Strength	Batch	Batch Size	Manufacturing Yield	Packaging Yield
[redacted]					

(b) (4)

R2 Comparability Protocols: N/A

Reviewer's Comment: [redacted]. This is adequate.

(b) (4)

R3 Methods Validation Package: Provided

Sample availability:

(b) (4)

[redacted]

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091650 APPLICANT: Dr. Reddy's Laboratories, Ltd.

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

A. The deficiencies presented below represent MINOR deficiencies.

1

(b) (4)

2

3

4

a

Following this page, 3 Pages Withheld in Full as (b)(4)

25. (b) (4)

26.

B. Please acknowledge and respond to the following comments:

1. (b) (4)

2. Please provide all available long-term stability data.

3. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

B. Endorsement Block

HFD-630 / W. Jiang - CR 05/06/10, 5/7/2010, 5/26/2010
HFD-630 / R. Iser - TL 5/13/2010, 5/27/2010
HFD-617 / Leigh Ann Bradford - PM 6/01/2010

TYPE OF LETTER: NOT APPROVABLE - Minor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

WEIQIN JIANG
06/02/2010

LEIGH A BRADFORD
06/02/2010

ROBERT L ISER
06/02/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

PHARM/TOX REVIEWS

Signed off in DARRTS on 5/29/12

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

ANDA number: ANDA 91-650
Drug Names: Atorvastatin Calcium (RLD Lipitor), 10, 20, 40, 80 mg from Dr. Reddy's Laboratories Inc.

Consult #: **2012-0668 (*previous one** 2012-0625). Previous consult on this ANDA were signed off in DARRTS on 9/7/2010 (consult # 2010-0429), on 7/27/11 (consult # 2011-0542), and on 4/11/12 (consult # 2012-0625)

Consult from: **Matthew Vera, OGD/DCIII**.

Request date: 5/21/12. Desired completion date: 5/25/12

Date of submission: 2/8/12.

Drug class: Statins. Indication: Lipid lowering.

Subject of Consult: See the OGD comments below.

OGD is requesting a pharmacology /toxicology review of information submitted by the Applicant to qualify a revised specified limit of (b) (4) ***impurity.*** (b) (4) ***The sponsor previously submitted 4-week rat toxicity data and an Ames test for genotoxicity, which had been reviewed in consults 2010-0429, 2011-0542 and 2012-0625 (Indra Antonipillai). Through several amendments provided, the Applicant has*** (b) (4) ***impurity limits and provided additional information. OGD has attached a summary of the pertinent information for the convenience of the consult reviewer. Please review and comment if the*** (b) (4) ***impurity can be considered as qualified at the revised level of*** (b) (4) ***The drug product Maximum Daily Dose is 80 mg. For additional information or clarification, please contact Matthew Vera, 240-276-8493 or matthew.vera@fda.hhs.gov. Please provide an electronic copy of the review to the requestor by email (matthew.vera@fda.hhs.gov) and cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) when it is being checked into DARRTS. Thank you***

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.

Division: Division of Metabolism and Endocrinology products.

Review completion date: 5/25/12

Introduction and drug history: Dr. Reddys Laboratories Inc. had submitted an ANDA 91-650 dated 7/9/09 for atorvastatin calcium as 505 (j) application to OGD. The company had stated that their (b) (4) atorvastatin tablets (strengths at 10, 20 & 40, 80 mg) are same as approved 10-80 mg tablets of Lipitor from Pfizer's, USA.

Dr. Reddys Laboratories Inc. had stated in the original application that the current drug substance is manufactured (b) (4)

(b) (4) To qualify the impurities, they had conducted a 4-week

toxicity study in rats and a geno-toxicity study [redacted] which have *been reviewed in consults 2010-0429, 2011-0542*. However the tested limits of impurities (percentages) [redacted] in the toxicity studies than the proposed specification limits in the drug product. The sponsor was asked to clarify the levels of impurities. Sponsor had responded to these comments; and these were reviewed in consult # 2012-0625, signed off in DARRTS on 4/11/12.

In the review signed off in DARRTS (4/11/12), the sponsor had provided the actual concentrations of impurities [redacted] in the atorvastatin amorphous drug batch administerd at 300 and 1000 mg/kg/day to rats, in a 4-week study. The toxicity profile in this subchronic rat toxicity study was comparable between atorvastatin [redacted].

Among [redacted] impurities tested by the sponsor, [redacted]

A (Q)SAR consult from CDER CompTox was requested for [redacted] Since atorvastatin is a chronic use drug, the longterm effects of the presence of these [redacted] impurities [redacted] were a concern.

[redacted]

The OGD points out that the Firm has [redacted] OGD has requested the current consult from pharmacology/toxicology to determine if these levels are acceptable. Therefore these data are being reviewed here.

OGD wants us to consider the items 1 to 4 listed below, to determine if the [redacted] impurity is [redacted] is qualified?

OGD points out that all the impurities listed in this application for DP release and stability are satisfactory, "meeting either RLD limits or limits qualified for other Atorvastatin applications, [redacted]

[redacted]

Following this page, 9 Pages Withheld in Full as (b)(4)

The Table below shows the safety margins of different impurities in rats to humans, based on the **revised impurity specification of** (b) (4)

(b) (4)

Safety evaluation

In this submission (2/8/12), the sponsor has provided the actual concentrations of impurities present in the Ames assay (requested in a prior reviews signed off in DARRTS on 9/7/2010, and 4/11/12). Sponsor has (b) (4) the impurities in their atorvastatin calcium drug product (submissions dated 2/8/12 and 5/21/12).

As previously stated that (b) (4) are (b) (4) impurities not seen in the RLD. Qualifications of the proposed specifications for known impurities as well as adequate qualification for (b) (4) impurities are needed.

In the earlier submission (see DARRTs review signed off on 4/11/12), the proposed specifications for the described impurities were (b) (4) The tested levels of each impurity in the toxicity study were (b) (4) see Table 8 (columns 1 & 2).

In the subsequent submissions by the sponsor (dated 2/6/12 and 5/21/12), the proposed specifications for the described impurities were (b) (4) The tested levels of each impurity in the toxicity study were (b) (4) see Table 9 (columns 1 & 2), this is because sponsor had (b) (4) the proposed impurity specifications in their drug product. Note that calculations and safety factors are based on the proposed specifications of each impurity, i.e. amounts of each impurity present in the final drug product.

Sponsor in the current submission has provided the impurities present in the genotoxicity testing in an Ames assay which show the specified amounts of impurities present; they had not provided this information previously. [redacted], see consult signed off in DARRTS on 9/7/10).

The recommended doses of the current drug product (atorvastatin) are up to 80 mg/day Therefore, 80 mg/day of atorvastatin will contain [redacted]

As far the ICH Q3(A) & ICH Q3(B) guidance, qualification of an impurity requires a sub-chronic toxicity study and in vitro genotoxicity assays. The 4-week rat general toxicity study with [redacted] impurities shows comparable toxicity profiles [redacted] drug batches. [redacted], see Table 11 in this review based on the 4-week rat toxicity study.

As stated in the previous consult, a (Q)SAR consult from CDER CompTox was requested for the [redacted] The consult also indicated that the databases are incomplete for some of these impurities, so a prediction could not be reliably rendered. Since atorvastatin is a chronic use drug, the long term effects of the presence of these [redacted] impurities [redacted].

Thus, the sponsor has provided the required information in this submission, and have further [redacted] the impurity specifications [redacted] in the drug product, including of [redacted] this impurity showed positive Ames potential in (Q)SAR consult.

We had recommend that sponsor [redacted]

We acknowledge that the sponsor has stated that [redacted] The OGD states that all the impurities listed in this application for DP release and stability are satisfactory, "meeting either RLD limits or limits qualified for other Atorvastatin applications, [redacted]

OGD requests a response in the consult to the following question: Is the proposed limit for [redacted] impurity [redacted] qualified based on the firm's response through amendments listed in background information items 1-4?

Our response: NO.

[redacted]

3. CDER does not use proprietary data from one sponsor to support that of another, so OGD's position that the [redacted] are "qualified" based on information on impurity profiles of other atorvastatins (that are not the listed drug i.e. Lipitor) are not considered "qualified" or safe by CDER standards.

(b) (4)

[redacted]

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/Antonipillai/Leigh Ann Sears/Tran Trang / Nagavelli, Laxma/ Vera, Matthew/ Marchick, J/Ripper, L
File name: AND91650-0512 consult (atorvastatin, Reddy lab)

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/s/

INDRA ANTONIPILLAI
05/29/2012
Please see the safety evaluation and summary recommendations on this consult.

KAREN L DAVIS BRUNO
05/29/2012

Signed off in DARRTS on 4/11/12

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

ANDA number: ANDA 91-650
Drug Names: Atorvastatin Calcium (RLD Lipitor), 10, 20, 40 mg from Dr. Reddy's Laboratories Inc.

Consult #: 2012-0625. Previous consult on this ANDA were signed off in DARRTS on 9/7/2010 (consult # 2010-0429), and on 7/27/11 (consult # 2011-0542).

Consult from: Leah Ripper.

Request date: 3/13/2012. Desired completion date: 4/12/2012

Date of submission: 11/16/2011.

Drug class: Statins. Indication: Lipid lowering.

Subject of Consult: Sponsor had conducted 4-week toxicity studies in rats to qualify the impurities in their atorvastatin (b) (4) drug product (consult # 2010-0429), however the firm did not indicate the levels of impurities tested in the 4-week toxicity study in rats. OGD had communicated the pharmacology/toxicology comments to the sponsor, and asked them to provide the proposed amounts of impurities present in the 80 mg dose of the drug and the amounts tested in 300 and 1000 mg/kg/day doses in the 4-week rat study. On 11/16/11, sponsor has responded to these comments; OGD is therefore requesting that we review their submitted response. **See the OGD comments below.**

OGD is requesting a Pharm/Tox Review (b) (4), as a follow up to the previous consult No. 2011-0542. The firm has responded to the deficiency letter dated 10/06/2011, which was written in light of the Pharm-Tox Consult Report by Dr. Indra Antonipillai, DARRTS dated 07/27/2011. By initiating this consult, review of the response, specifically to the deficiency No. 11 is requested. Please review the data provided by the firm and recommend if the specifications for individual and total impurities in the drug product are acceptable.

Previous Phar-Tox Consult Nos. are 2011-0542 and 2010-0429 by Dr. Antonipillai.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.

Division: Division of Metabolism and Endocrinology products.

Review completion date: 4/11/12

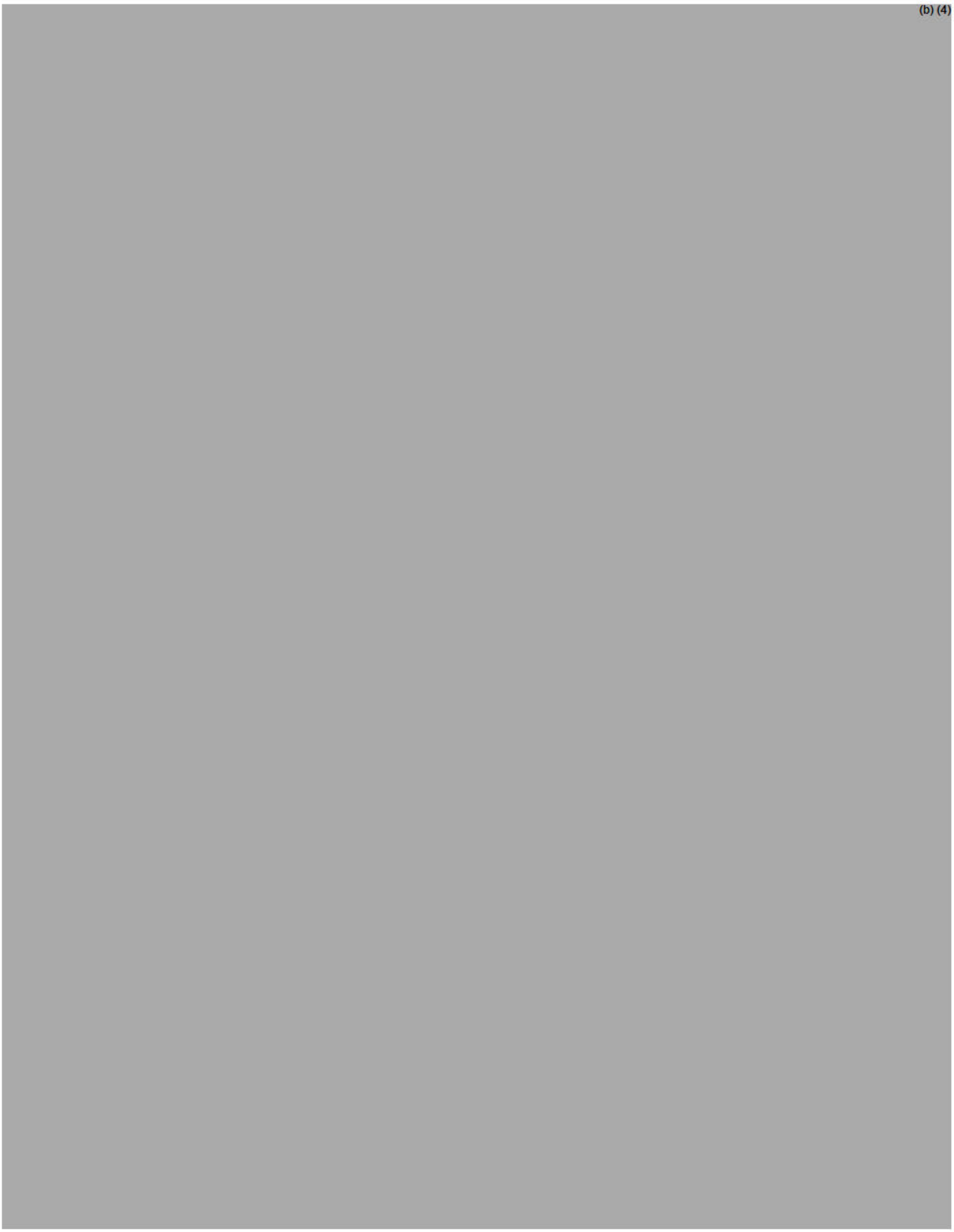
Introduction and drug history: Dr. Reddys Laboratories Inc. had submitted an ANDA 91-650 dated 7/9/09 for atorvastatin calcium as 505 (j) application to OGD. The company had stated that their (b) (4) atorvastatin tablets (strengths at 10, 20 & 40 mg) are same as approved 10-40 mg tablets of Lipitor from Pfizer's, USA.

Dr. Reddys Laboratories Inc. had stated in the original application that the current drug substance is manufactured (b) (4)

(b) (4) . To qualify the impurities, they had conducted a 4-week toxicity study in rats and a geno-toxicity study (b) (4) (b) (4). However the tested limits of impurities (percentages) (b) (4) in the toxicity studies than the proposed specification limits in the drug product. The sponsor was asked to clarify the levels of impurities. Sponsor has responded to these comments; and therefore these data are being reviewed here.

As stated before, the proposed acceptance criteria of these impurities are stated below.

(b) (4)



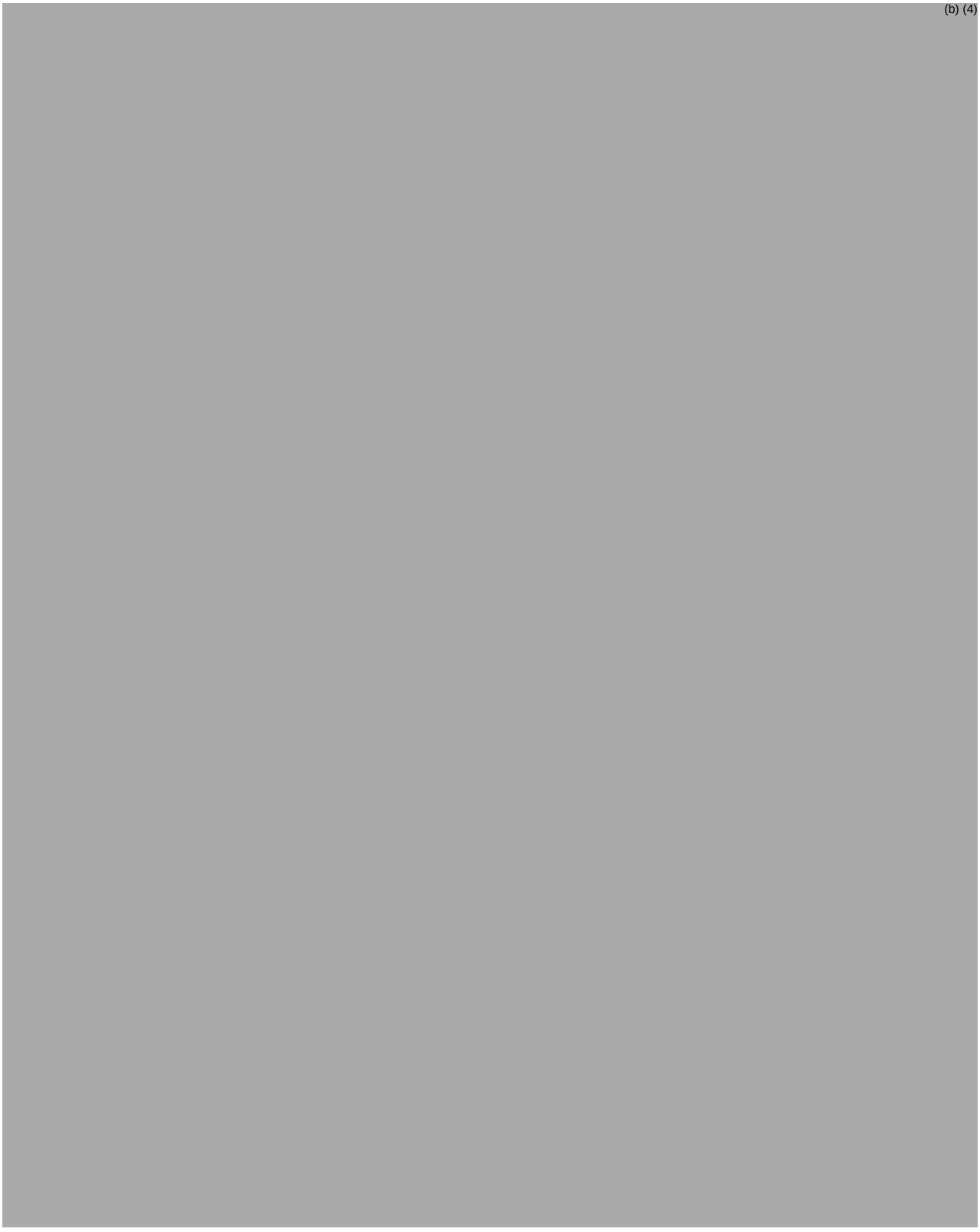
(b) (4)

So far the only genotoxicity testing has been in an Ames assay with unspecified amounts of impurities present.

In the current submission, sponsor has provided the information requested, i.e. actual amounts of each impurity present in the batch of drug used in the 4-week toxicity study. The proposed specifications for the described impurities are (b) (4)

(b) (4)

(b) (4)



(b) (4)

However, the histopathological changes observed in the liver and stomach were generally similar (i.e. without or with impurities in the drug). Sponsor did not test the reference listed drug to see how the toxicity of the original drug differs compared to the current one. They also did not determine the exposures of the drug with and without impurities.

The sponsor was also asked to provide the levels of impurities present in the drug product used for the geno-toxicity (AMES) assay, which they have still not provided in the current submission. Note that different batch number of atorvastatin (b) (4) (b) (4) than for the 4-week toxicity study in rats (batch number AVS T10080-F390).

Information provided by the OGD chemist shows that the RLD has some of these impurities (b) (4) (b) (4)

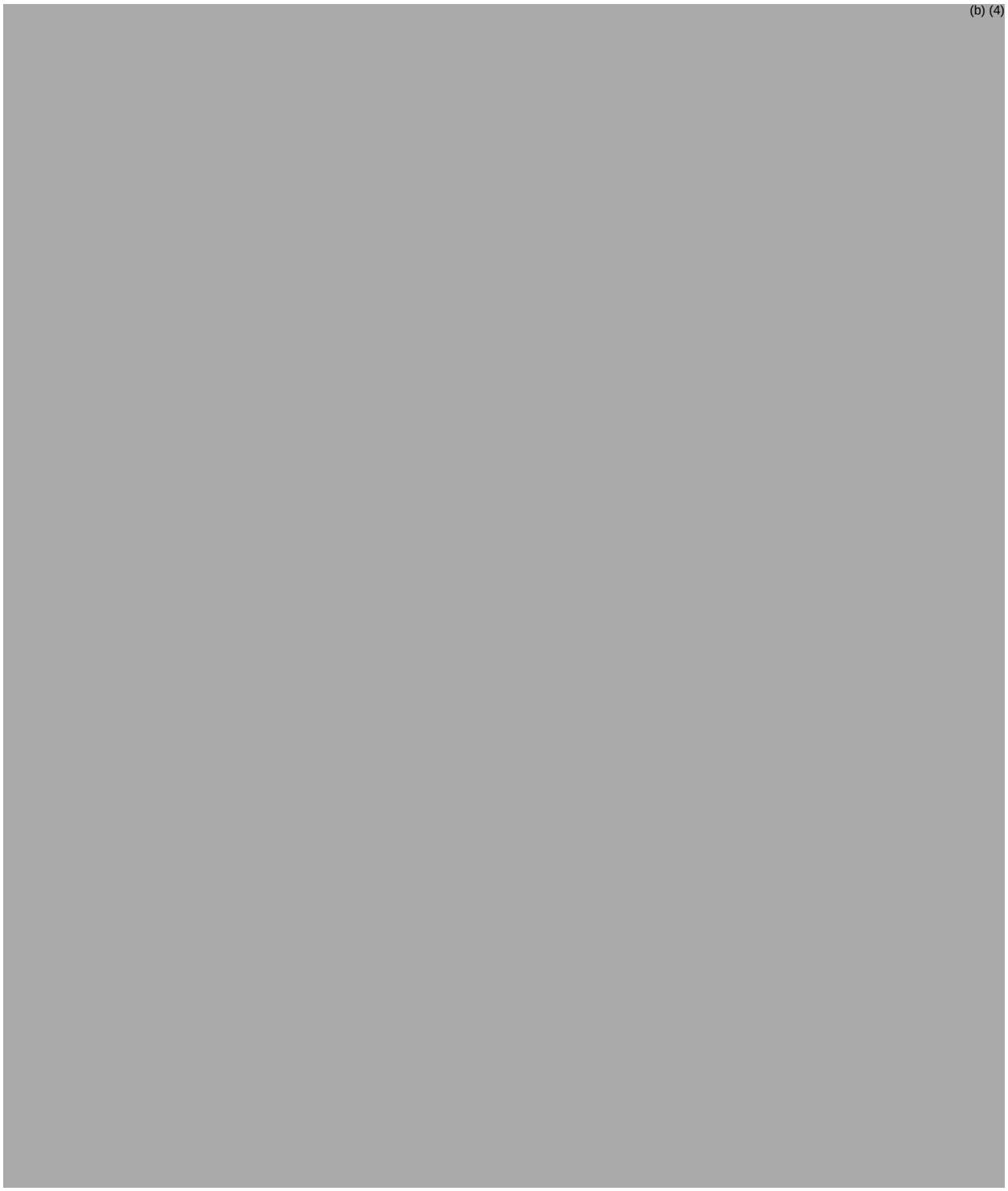
(b) (4)

(b) (4)

Summary and safety evaluation

In this submission, the sponsor has provided the actual concentrations of impurities (b) (4) (b) (4) in the atorvastatin (b) (4) drug batch given at 300 and 1000 mg/kg/day to rats, in a 4-week study. The proposed acceptance criteria set by the sponsor for each impurity (b) (4)

(b) (4)


(b) (4)

(b) (4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/Antonipillai/Leigh Ann Sears/Tran Trang / Khan, Khalid/ Marchick, J/Ripper, L
File name: AND91650-11 consult (atorvastatin, Reddy lab)

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/s/

INDRA ANTONIPILLAI
04/11/2012
Please see the Pharmacology/Toxicology recommendations on this ANDA 91650 consult.

KAREN L DAVIS BRUNO
04/11/2012

Signed off in DARRTS on 7/27/11

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

ANDA number: ANDA 91-650
Drug Names: Atorvastatin Calcium (RLD Lipitor), 10, 20, 40 mg.

Consult #: 2011-0542 (previous consult # on this ANDA was 2010-0429, it was signed off in DARRTS on 9/7/2010).

Consult from: Leigh Ann Sears.

Request date: 7/11/11. Desired completion date: 8/10/2011

Date of submission: 5/13/2011.

Drug class: Statins. Indication: Lipid altering, hypolipidemic.

Subject of Consult: Previously we had done a pharmacology/toxicology consult on ANDA 91-650 when it was originally submitted on 7/9/2009 from Dr. Reddy's laboratories Inc. This consult was requested by OGD, (b) (4) In that submission, sponsor had provided a 4-week toxicity study and a geno-toxicity study to qualify the impurities (b) (4) (b) (4). We had asked the sponsor to clarify what concentrations and composition of impurities were tested (b) (4) before an assessment of qualification of these impurity levels and safety of the proposed generic atorvastatin could be determined. The firm has responded to our request on 05/13/2011, and OGD is requesting that we review their submitted response. **See the OGD comments below.**

COMMENTS
OGD is requesting a Pharm/Tox Review. (b) (4) Please evaluate the toxicological studies performed by the firm including the additional information requested in response to the previous Phar-Tox Consult No. 2010-0429 by Dr. Antonipillai.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrinology products.

Review completion date: 7/21/2011

Introduction and drug history: Dr. Reddys Laboratories Inc. had submitted an ANDA 91-650 dated 7/9/09 for atorvastatin calcium as 505 (j) application to OGD. The company had stated that their tablets (strengths at 10, 20 & 40 mg) are same as approved 10-40 mg tablets of Lipitor from Pfizer's, USA. On 6/1/10, OGD requested a pharmacology/toxicology consult on the impurities present in the generic drug product, (b) (4) (b) (4)

Dr. Reddys Laboratories Inc. had stated in the original application that the current drug substance is manufactured (b) (4)

(b) (4) . To qualify the impurities, they had conducted a 4-week toxicity study in rats and a geno-toxicity study (b) (4) (b) (4). However they had not stated the levels of impurities in their drug product tested in a 4-week toxicity study in rats and we had asked them to provide that data.

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Summary and safety evaluation

In summary, it is unclear to this reviewer what percentage of impurities (b) (4) were present in the final concentration of 300 and 1000 mg/kg/day of atorvastatin (b) (4) tested in a 4-week study in rats. The proposed acceptance criteria set for each impurity is (b) (4)

(b) (4)

Sponsor needs to clearly state 1) what are the amounts of impurities present in the 80 mg dose of the drug product that will be marketed? 2) What are the amounts that were tested in a 300 and 1000 mg doses of the drug product administered in a 4-week toxicity study in rats.

From the pharmacology/toxicology point of view, the above studies at this time are considered inadequate. The sponsor has provided the data for CMC clarification, but has not clarified the pharmacology/toxicology concerns.

(b) (4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/Antonipillai/Leigh Ann Sears/Tran Trang,/Khan Khalid/
Marchick, J/Ripper, L
File name: AND91650-11 consult (atorvastatin, Reddy lab)

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/s/

INDRA ANTONIPILLAI
07/27/2011
Please see the pharmacology/toxicology internal recommendations.

KAREN L DAVIS BRUNO
07/27/2011

Signed off in DARRTS on 9/7/10

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: ANDA 91-650
Drug Names: Atorvastatin Calcium (RLD Lipitor), 10, 20, 40 mg.

Consult #: 2010-0429.

Consult from: Leigh Ann Bradford.

Request date: 6/1/10. Desired completion date: 8/30/2010

Date of submission: 7/9/2009.

Drug class: Statins. Indication: Lipid altering, hypolipidemic (to lower cholesterol).

Subject of Consult: In the current consult, OGD has requested a pharmacology/toxicology consult on the impurities present in the generic product (submission date 7/9/2009 from Dr. Reddy's laboratories Inc.). They state that impurities listed are (b) (4) than RLD (atorvastatin from Pfizer), review module 3.2. See the comments below.

COMMENTS
OGD is requesting a Pharm/Tox Review. (b) (4) Please evaluate the original ANDA in EDR Module 3.2.P.5.6 pgs. 4-5 and pgs. 49-334. Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) and Leigh Ann Bradford, HFD-617 (Leigh.Bradford@fda.hhs.gov) on the review when it is being checked into DARRTS. Thank you.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrinology products.

Review completion date: 10/2/2006

Introduction and drug history: Dr. Reddys Laboratories Inc. has submitted an ANDA 91-650 (dated 7/9/09) for atorvastatin calcium to OGD as 505 (j) application. They state that their tablets (strengths at 10, 20 & 40 mg) are same as approved 10-40 mg tablets of Lipitor from Pfizer's, USA. On 6/1/10, OGD requested a pharmacology/toxicology consult on the impurities present in the generic drug product, (b) (4) (b) (4)

Dr. Reddys Laboratories Inc. states that the current drug substance is manufactured (b) (4) (b) (4) , therefore they have conducted a 4-week toxicity study and geno-toxicity studies (b) (4)

They state the following:

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Safety Evaluation:

(b) (4)

Above toxicity study conducted has limited value, as the reference listed drug was not examined to see if the toxicities were different between these products and no toxicokinetic (TK) parameters were examined. (b) (4) .

(b) (4)

However it is unclear to this reviewer what percentage of impurities/ (b) (4) were present in the drug. Sponsor needs to clearly indicate the levels of impurities tested and provide the safety margins in rats vs humans of these impurities/ (b) (4) and determine what is the maximum possible consumption of the impurities in clinical situation. Similarly, sponsor needs to provide what levels of impurities were present in the drug product used for the geno-toxicity (AMES) assay.

From the pharmacology/toxicology point of view, the above studies at this time are considered inadequate. However, the proposed levels of different impurities may be considered qualified, after the above information provided by the sponsor is reviewed.

Internal Recommendations:

Sponsor needs to clarify what concentrations and composition of impurities they were testing in batch (b) (4) before an assessment of qualification of these impurity levels and safety of the proposed generic atorvastatin can be determined.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/Antonipillai/Bradford leigh/Galliers/aljuburi/Ripper, L
File name: AND91650-OGD consult (atorvastatin consult)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

INDRA ANTONIPILLAI
09/07/2010
Please see the internal pharmacology/toxicology recommendations.

KAREN L DAVIS BRUNO
09/07/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091650		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	10 mg, 20 mg, and 40 mg		
Applicant Name	Dr. Reddy's Laboratories Limited		
Address	Bachepalli, Post Bage No. 15, Kukatpally P.O., Hyderabad – 500 072, India Factory Address: Bachepalli 502 325, India		
Applicant's Point of Contact	200 Somerset Corporate Blvd, 7th Floor Bridgewater, NJ 08807		
Contact's Telephone Number	(908) 203 – 4900		
Contact's Fax Number	(908) 203 – 4937		
Original Submission Date(s)	09 July 2009		
Submission Date(s) of Amendment(s) Under Review	09 February 2010		
Reviewer	Johnetta F. Walters, Ph.D.		
Study Number (s)	01621/09-10	09-VIN-057	
Study Type (s)	Fasting	Fed	
Strength (s)	40 mg	40 mg	
Clinical Site	Clinical Research Division	(b) (4)	
Clinical Site Address	Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA Tel: 91-40-27264141 Extn: 107		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
DSI INSPECTION RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**

1, 2	**Fasting**	**40 mg**	**ADEQUATE**
1, 2	**Fed**	**40 mg**	**ADEQUATE**
1, 2	**Dissolution**	**40 mg**	**ADEQUATE**
1, 2	**Dissolution**	**20 mg**	**ADEQUATE**
1, 2	**Dissolution**	**10 mg**	**ADEQUATE**
2	**Amendment**	**10 mg, 20 mg, and 40 mg**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting (01621-09-10) and fed (09-VIN-057) bioequivalence (BE) studies comparing a test product, Dr. Reddy's Atorvastatin Calcium Tablets, 40 mg to the corresponding reference product, Pfizer's Lipitor® (atorvastatin calcium) Tablets, 40 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The fasting and fed BE studies are **adequate**. The results are summarized in the tables below.

Atorvastatin, 1 X 40 mg Fasting Bioequivalence Study No. 01621-09-10, N=69 (Male=69) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	125.94	130.62	0.96	92.74	100.24
AUC∞ (ng·hr/mL)	129.25	135.96	0.95	91.33	98.96
Cmax (ng/mL)	28.71	30.24	0.95	85.33	105.60

Atorvastatin, 1 X 40 mg Fed Bioequivalence Study No. 09-VIN-057, N=71 (Male=71) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	107.03	113.44	0.94	90.94	97.88
AUC∞ (ng·hr/mL)	110.65	116.60	0.95	91.52	98.41
Cmax (ng/mL)	13.89	15.17	0.92	85.69	97.88

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin as submitted by the firm, were comparable.

The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA - recommended dissolution method, (DARRTS: ANDA 091650. REV-BIOEQ-02(Dissolution Review) 12/18/2009. On 09 February 2010, the firm has acknowledged the FDA – recommended dissolution method and specification. The dissolution test is acceptable.

The DBE grants the waiver requests for *in vivo* BE study requirements for the 10 mg and 20 mg strength tablets.

A routine inspection was completed under ANDA (b) (4) for the Clinical site (Clinical Research Division, Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA) (also used for the fasting study of the current ANDA) on (b) (4) The outcome was Voluntary Action Indicated (VAI). (DARRTS, Search: ANDA (b) (4) CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review). (b) (4) The reviewer

reviewed the DSI findings and concludes that the DSI findings for ANDA [redacted] do not have impact on the outcome of the current application.

A routine inspection was completed under NDA [redacted] for the Analytical Site [redacted] (also used for the fasting study of the current ANDA) on [redacted]. The outcome was Voluntary Action Indicated (VAI). (DARRTS, Search: NDA [redacted] CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review). [redacted]. The reviewer reviewed the DSI findings and concludes that the DSI findings for ANDA [redacted] do not have impact on the outcome of the current application.

A routine inspection was completed under ANDA [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).

A routine inspection was completed 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). (DARRTS, Search: NDA [redacted] CONSULT REV-BIOEQ-01(General Consult Review). [redacted]) The reviewer reviewed the DSI findings and concludes that the DSI findings for ANDA [redacted] do not have impact on the outcome of the current application.

Please see sections 3.10 and 3.11 for further details regarding the DSI inspections status of all sites.

The application is **adequate.**

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Atorvastatin Calcium Tablets, EQ. 10 mg, 20 mg, and 40 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** LIPITOR® is indicated: • as an adjunct to diet to reduce elevated total-C, LDL-C, apo B,

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

	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

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

		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 (for details, see Appendix Error! Reference source not found.**):**	There are currently no approved generic drug products[Error! Bookmark not defined]. The DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets[5]: (3) ANDA 076477 (Ranbaxy Labs) (4) ANDA 078773 (Teva) (5) ANDA 077575 (Sandoz) (6) ANDA 091226 (Matrix Labs) (7) ANDA 090548 (Apotex) (8) ANDA 091624 (Kudco) (9) 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	Yes	2

[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.

BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

3.5.1 Fasting Study Number 01621/09-10: Atorvastatin

Information Requested	Data
Report Location	**Study Report No.:** 01621/09-10 ; **Section**-16.4
Analyte	**Atorvastatin**
Internal standard (IS)	(b) (4)
Method description	Refer Method Validation Report No. 23/MVR/ATORVASTATIN, 2-OH ATORVASTATIN AND 4-OH ATORVASTATIN/029, Page No. 19 of 105 Analytical Method :LC-MS/MS
Limit of quantitation	0.250 ng/mL
Average recovery of drug (%)	91.40 %
Average recovery of IS (%)	90.32 %
Standard curve concentrations (ng/mL)	0.249, 0.499, 2.495, 9.980, 19.959, 49.898, 99.795 & 199.590 ng/mL.
QC concentrations (ng/mL)	LQC= 0.749 ng/mL GMQC= 7.992 ng/mL MQC= 79.923 ng/mL HQC= 159.846 ng/mL
QC Intra-batch precision range (%)	LQC= 1.77% to 4.04% GMQC= 1.42% to 3.39% MQC= 2.41% to 3.76% HQC= 1.67% to 3.77%
QC Intra-batch accuracy range (%)	LQC= 98.78% to 101.20% GMQC= 100.18% to 101.76% MQC= 97.15% to 100.81% HQC= 92.70% to 98.56%
QC Inter-batch precision range (%)	LQC= 2.82% GMQC= 2.60% MQC= 3.32% HQC= 3.66%
QC Inter-batch accuracy range (%)	LQC= 99.98% GMQC= 100.91% MQC= 99.05% HQC= 95.12%
Bench-top stability (hrs)	21.00 hours at room temperature % Stability for LQC=97.64%, % Stability for HQC=103.94%
Stock stability (hrs)	Found to be stable at room temperature up to 07.00 hours % Stability for LQC=100.00%, % Stability for HQC=96.49% % Stability for ISTD=98.05%
Processed stability (hrs)	**a) In-Injector stability** : 27.00 hours @ 5°C % Stability for LQC=99.69%, % Stability for HQC=104.04%

	b) **Wet extract stability** : 20.00 hours @ ambient temperature % Stability for LQC=97.17%, % Stability for HQC=102.91% **c)** **Dry extract stability** : 20.00 hours @ ambient temperature % Stability for LQC=98.91%, % Stability for HQC=103.17%
Freeze-thaw stability (cycles)	Stability was estimated for three cycles **d)** % Stability for LQC=96.93%, % Stability for HQC=104.09%
Long-term storage stability (days)	54 days @ -70ºC % Stability for LQC=106.48%, % Stability for HQC=95.32%
Long-term Stock stability (days)	58 days @ -20ºC % Stability for LQC=107.07%, % Stability for HQC=92.50% and % Stability for ISTD=99.33%
Dilution integrity	1.6 times of CC8 concentration diluted in 1:5 ratio CV% for 1:5 dilution = 2.67% and % Accuracy for 1:5 dilution = 94.24%
Selectivity	No interfering peaks noted in blank plasma samples

3.5.2 Fasting Study Number 01621/09-10: 2-Hydroxy Atorvastatin

Information Requested	**Data**
Report Location	**Study Report No.:** 01621/09-10 ; **Section**-16.4
Analyte	**2-Hydroxy Atorvastatin**
Internal standard (IS)	(b) (4)
Method description	Refer Method Validation Report No. 23/MVR/ATORVASTATIN, 2-OH ATORVASTATIN AND 4-OH ATORVASTATIN/029, Page No. 19 of 105 Analytical Method :LC-MS/MS
Limit of Quantitation	0.250 ng/mL
Average recovery of drug (%)	90.59 %
Average recovery of IS (%)	89.81 %
Standard curve concentrations (ng/mL)	0.250, 0.500, 2.498, 9.993, 19.987, 49.967, 99.934 & 199.868 ng/mL.
QC concentrations (ng/mL)	LQC= 0.750 ng/mL GMQC= 8.003 ng/ mL MQC= 80.032 ng/mL HQC= 160.064 ng/mL
QC Intra-batch precision range (%)	LQC= 2.71% to 3.19% GMQC= 1.27% to 2.32% MQC= 2.56% to 3.54% HQC= 0.63% to 4.04%
QC Intra-batch accuracy range (%)	LQC= 98.22% to 103.24% GMQC= 99.93% to 102.91% MQC= 98.04% to 102.79% HQC= 97.73% to 104.46%
QC Inter-batch precision range (%)	LQC= 3.47% GMQC= 2.24% MQC= 3.56% HQC= 3.98%

QC Inter-batch accuracy range (%)	LQC= 100.94% GMQC= 101.09% MQC= 99.86% HQC= 100.11%
Bench-top stability (hrs)	21.00 hours at room temperature % Stability for LQC=100.89%, % Stability for HQC=106.12%
Stock stability (hrs)	Found to be stable at room temperature up to 07.00 hours % Stability for LQC=99.84%, % Stability for HQC=96.69% % Stability for ISTD=98.59%
Processed stability (hrs)	a) **In-Injector stability** : 27.00 hours @ 5°C % Stability for LQC=100.16%, % Stability for HQC=106.24% b) **Wet extract stability** : 20.00 hours @ ambient temperature % Stability for LQC=100.04%, % Stability for HQC=104.90% c) **Dry extract stability** : 20.00 hours @ ambient temperature % Stability for LQC=100.27%, % Stability for HQC=106.26%
Freeze-thaw stability (cycles)	Stability was estimated for three cycles % Stability for LQC=99.76%, % Stability for HQC=105.81%
Long-term stability in matrix samples (days)	54 days @ -70ºC % Stability for LQC=107.62%, % Stability for HQC=96.83%
Long-term Stock stability (days)	58 days @ -20ºC % Stability for LQC=105.23%, % Stability for HQC=94.89% and % Stability for ISTD=99.09%
Dilution integrity	1.6 times of CC8 concentration diluted in 1:5 ratio CV% for 1:5 dilution = 4.29% and % Accuracy for 1:5 dilution = 94.96%
Selectivity	No interfering peaks noted in blank plasma samples

3.5.3 Fasting Study Number 01621/09-10: 4-Hydroxy Atorvastatin

Information Requested	Data
Report Location	**Study Report No.:** 01621/09-10 **; Section**-16.4
Analyte	**4-Hydroxy Atorvastatin**
Internal standard (IS)	(b) (4)
Method description	Refer Method Validation Report No. 23/MVR/ATORVASTATIN 2-OH ATORVASTATIN AND 4-OH ATORVASTATIN/029 Page No. 19 of 105 Analytical Method :LC-MS/MS
Limit of Quantitation	0.100 ng/mL
Average recovery of drug (%)	93.90 %
Average recovery of IS (%)	93.19 %
Standard curve concentrations (ng/mL)	0.100, 0.200, 0.501, 1.002, 2.003, 4.006, 7.011 & 10.016 ng/mL.
QC concentrations (ng/mL)	LQC= 0.301 ng/mL GMQC= 1.202 ng/ mL MQC= 5.009 ng/mL HQC= 8.014 ng/mL
QC Intra-batch precision range (%)	LQC= 2.77% to 8.16% GMQC= 1.67% to 4.66% MQC= 2.83% to 3.60%

	HQC= 1.30% to 3.27%
QC Intra-batch accuracy range (%)	LQC= 96.73% to 108.25% GMQC= 95.90% to 106.79% MQC= 95.23% to 106.20% HQC= 90.08% to 102.75%
QC Inter-batch precision range (%)	LQC= 7.10% GMQC= 5.84% MQC= 5.93% HQC= 6.85%
QC Inter-batch accuracy range (%)	LQC= 102.86% GMQC= 100.08% MQC= 99.26% HQC= 94.48%
Bench-top stability (hrs)	21.00 hours at room temperature % Stability for LQC=99.50%, % Stability for HQC=101.97%
Stock stability (hrs)	Found to be stable at room temperature up to 07.00 hours % Stability for LQC=100.33%, % Stability for HQC=95.67% % Stability for ISTD=96.95%
Processed stability (hrs)	**a) In-Injector stability** : 27.00 hours @ 5°C % Stability for LQC=103.38%, % Stability for HQC=103.08% **b) Wet extract stability** : 20.00 hours @ ambient temperature % Stability for LQC=100.61%, % Stability for HQC=102.14% **c) Dry extract stability** : 20.00 hours @ ambient temperature % Stability for LQC=102.27%, % Stability for HQC=103.38%
Freeze-thaw stability (cycles)	Stability was estimated for three cycles **d)** % Stability for LQC=102.46%, % Stability for HQC=102.48%
Long-term stability in matrix samples (days)	54 days @ -70°C % Stability for LQC=108.19%, % Stability for HQC=98.37%
Long-term Stock stability (days)	58 days @ -20°C % Stability for LQC=106.68%, % Stability for HQC=94.43% and % Stability for ISTD=101.22%
Dilution integrity	1.6 times of CC8 concentration diluted in 1:5 ratio CV% for 1:5 dilution = 4.70% and % Accuracy for 1:5 dilution = 108.70%
Selectivity	No interfering peaks noted in blank plasma samples

3.5.4 Fed Study Number 09-VIN-057

Information Requested	**Analyte**
Bioanalytical method validation report location	Section 16.5 Appendix 17 C of 09-VIN-057 Bioanalytical report.
Drug	**Atorvastatin**
Metabolite-1	**2-Hydroxy Atorvastatin**
Metabolite-2	**4-Hydroxy Atorvastatin**
Internal standard-1	(b) (4)
Internal standard-2	

Internal standard-3	(b) (4)
Type of Method	Liquid-Liquid Extraction
Limit of quantitation for Drug	0.100ng/mL
Limit of quantitation for Metabolite-1	0.100ng/mL
Limit of quantitation for Metabolite-2	0.0500ng/mL
Average recovery of Drug (%)	88.44%
Average recovery of Metabolite-1 (%)	82.57%
Average recovery of Metabolite-2 (%)	66.82%
Average recovery of ISTD-1 (%)	89.42%
Average recovery of ISTD-2 (%)	92.77%
Average recovery of ISTD-3 (%)	85.41%
Standard curve concentrations for Drug (ng/mL)	100, 50.0, 25.0, 12.0, 6.00, 3.00, 1.20, 0.480, 0.200 and 0.100ng/mL
Standard curve concentrations for Metabolite-1 (ng/mL)	100, 50.0, 25.0, 12.0, 6.00, 3.00, 1.20, 0.480, 0.200 and 0.1004ng/mL
Standard curve concentrations for Metabolite-2 (ng/mL)	50, 25.0, 12.5, 6.00, 3.00, 1.50, 0.60, 0.240, 0.100 and 0.050ng/mL
QC concentrations for Drug (ng/mL)	HQC (90.0ng/mL), MQC (3.60ng/mL), LQC (0.300ng/mL) and LLOQ QC (0.100ng/mL).
QC concentrations for Metabolite-1 (ng/mL)	HQC (90.0ng/mL), MQC (3.60ng/mL), LQC (0.300ng/mL) and LLOQ QC (0.100ng/mL)
QC concentrations for Metabolite-2 (ng/mL)	HQC (45.0ng/mL), MQC (1.80ng/mL), LQC (0.150ng/mL) and LLOQ QC (0.0500ng/mL).
QC Intraday precision range for Drug (%)	1.79 to 9.98%% (HQC, MQC and LQC) and 4.12 to 7.32%for LLOQ QC
QC Intraday precision range for Metabolite-1 (%)	0.92 to 3.87% (HQC, MQC and LQC) and 8.95 to 11.80% for LLOQ QC
QC Intraday precision range for Metabolite-2 (%)	1.03 to 5.18% (HQC, MQC and LQC) and 10.31 to16.08 for LLOQ QC
QC Intraday accuracy range for Drug (%)	92.22 to 108.93% (HQC, MQC and LQC) and 93.18 to 102.96% for LLOQ QC
QC Intraday accuracy range for Metabolite-1 (%)	95.18 to 109.80% (HQC, MQC and LQC) and93.28 to 97.22% for LLOQ QC
QC Intraday accuracy range for Metabolite-2 (%)	90.56 to 104.93% (HQC, MQC and LQC) and 89.68 to 94.68% for LLOQ QC
QC Interday precision range for Drug (%)	4.13 to 6.57% (HQC, MQC and LQC) and 7.00% for LLOQ QC
QC Interday precision range for Metabolite-1 (%)	3.20 to 5.67% (HQC, MQC and LQC) and 9.62%% for LLOQ QC
QC Interday precision range for Metabolite-2 (%)	4.41 to 6.06% (HQC, MQC and LQC) and 11.82 for LLOQ QC

QC Interday accuracy range for Drug (%)	97.11 to 104.78% (HQC, MQC and LQC) and 98.05% for LLOQ QC
QC Interday accuracy range for Metabolite-1 (%)	100.02 to 105.09% (HQC, MQC and LQC) and 95.31% for LLOQ QC
QC Interday accuracy range for Metabolite-2 (%)	95.59 to 101.91% (HQC, MQC and LQC) and 91.60% for LLOQ QC
Wet Extract Stability	For 28 hours 43 minutes at 5°C ± 3°C.
Dry Extract Stability	For 28 hours 57 minutes at -20°C ±5°C.
Freeze Thaw Stability	3 Cycles at -20°C ± 5°C and at -78°C + 8°C.
Bench Top Stability	For 10 hours 07 minutes at ambient temperature.
Autosampler Re-Injection Reproducibility	For 37 hours 52 minutes at 5°C ± 3°C.
Short Term Stock Solution Stability for Drug, Metabolite-1, Metabolite-2, ISTD-1, ISTD-2 and ISTD-3	For Drug and metabolite-1 15 hours 32 minute at ambient temperature; For Metabolite-2, 15 hours 34 minutes at ambient temperature For ISTD-1 and ISTD-2 15 hours 34 minutes at ambient temperature. For ISTD-3 15 hours 35 minutes at ambient temperature.
Long Term Stock Solution Stability Drug, Metabolite-1, Metabolite-2, ISTD-1, ISTD-2 and ISTD-3	For 33 days at 5°C ± 3°C
Long Term Stability of Drug in Plasma For (Drug -1, Drug -2 and Metabolite-2)	Not performed at the time of report preparation
Dilution integrity	1/2 and 1/10 times diluted.
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes SOP Number: VIN-BRD-MS-210 Title: Simulataneous Estimation of Atorvastatin and its Metabolites 2-Hydroxy Atorvastatin, 4-Hydroxy Atorvastatin in K_3EDTA Human Plasma by Using LC-ESI-MS/MS Effective Date: 26 April 2009
Bioanalytical method is acceptable	No

Comments on the Pre-Study Method Validation:

1. Di-potassium ethylenediaminetetraacetic acid, K_2EDTA was used as the anticoagulant for both the pre-study and during study method validation in the fasting study. Di-potassium ethylenediaminetetraacetic acid, K_2EDTA was also used as the anticoagulant for harvesting of biological fluids during the study assay.

2. Tri- potassium ethylenediaminetetraacetic acid, K_3EDTA was used as the anticoagulant for both the pre-study and during study method validation in the fed

study. Tri-potassium ethylenediaminetetraacetic acid, K_3EDTA was also used as the anticoagulant for harvesting of biological fluids during the study assay.

3. In an amendment dated 09 February 2010, the firm has submitted acceptable long-term storage stability (LTSS) data to cover a storage period of 48 days at -70°C. The firm previously provided LTSS data for 58 days at -20°C in its original submission. The study samples were stored for the fasting study from May 28, 2009 to July 03, 2009 (37 days). In this same submission, the firm has submitted acceptable LTSS data to cover a storage period of 75 days at -70°C. The samples were stored for the fed study from March 21, 2009 to May 26, 2009 (67 days), therefore, the firm's data is adequate.

4. The pre-study bioanalytical method validation is **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) C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$T½$ (hr)	K_{el} (hr-1)	Study Report Location
01621/09-10	An open-label, randomized, single oral dose, two way crossover bioequivalence study to compare Atorvastatin Calcium 40 mg Tablets of Dr.Reddy's Laboratories Limited, India with Lipitor® 40 mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland pharmaceuticals in 74 healthy, adult, human study participants under fasting conditions.	Open label, balanced, randomized two-treatment, two-period, two-sequence, two-way crossover bioequivalence study with 14 days washout period between each administration under fasting conditions.	**Test** Atorvastatin Calcium 40 mg Tablets Single dose of Atorvastatin Calcium 40 mg Tablets of Dr.Reddy's Laboratories Limited, India administered orally with 240 mL of drinking water at room temperature. Batch No.: EC8308 **Reference** Lipitor® (containing Atorvastatin calcium) 40 mg tablets Single dose of Lipitor® 40 mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland pharmaceuticals administered orally with 240 mL of	74 healthy male subjects Mean age: 26.2 Years Range: 18 – 42	32.674 (57.23) 35..251 (56.84)	0.83 (0.33-4.00) 0.67 (0.33-4.00)	134.917 (37.40) 140.660 (40.33)	139.192 (36.79) 145.182 (39.58)	7.378 (37.46) 7.916 (39.30)	0.107 (37.85) 0.099 (34.38)	Module 5.3.1.2, Final Report

			drinking water at room temperature. Lot No.: 0982068								
09-VIN-057	To assess the bioequivalence between Atorvastatin calcium 40 mg Tablets of Dr. Reddy's Laboratories Limited, India and Lipitor® 40mg Tablets manufactured by Pfizer Ireland pharmaceuticals in healthy, adult, human subjects under fed condition	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study in healthy, adult, human subjects under fed condition. .	**Test Product:** Atorvastatin calcium 40 mg Tablets administered orally. [Batch No./Lot No: EC8308] **Reference Product:** Lipitor® 40mg Tablets administered orally [Batch No./Lot No.: 0982068]	71completing (71M) Healthy subjects mean age 29.75 years (Range: 20 to 42 years)	15.160 ± 6.4442 16.923 ± 8.0035	4.500 (0.50 – 8.00 4.500 (0.75 – 5.00)	115.411 ± 46.7923 124.165 ± 53.7665	119.146 ± 47.7439 127.576 ± 54.7091	10.683 ± 3.5057 10.658 ± 3.4599	0.0717 ± 0.02258 0.0719 ± 0.02322	Module 5.3.1.2, Final Report

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Atorvastatin Dose (1 x 40 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. 01621/09-10)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·h/mL)	125.94	130.62	0.96	92.74	100.24
AUC∞ (ng·h/mL)	129.25	135.96	0.95	91.33	98.96
Cmax (ng/mL)	28.71	30.24	0.95	85.33	105.60

Atorvastatin Dose (1 x 40 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (Study No. 09-VIN-057)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·h/mL)	107.03	113.44	0.94	90.94	97.88
AUC∞ (ng·h/mL)	110.65	116.60	0.95	91.52	98.41
Cmax (ng/mL)	13.89	15.17	0.92	85.69	97.88

Table 3. Reanalysis of Study Samples

Fasted Study, Study No. 01621/09-10 (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**
Anomalous value*	0	6	0.00	0.33	0	5	0.00	0.28
Concentration of Subject sample more than the highest CC point	2	4	0.11	0.22	2	4	0.11	0.22
Pre-dose sample (0.00+ISTD) concentration, if any is more than the 5% Cmax from the same period	1	1	0.06	0.06	1	1	0.06	0.06
ISTD area variation	2	1	0.11	0.06	2	1	0.11	0.06
Total	**5**	**12**	**0.28**	**0.67**	**5**	**11**	**0.28**	**0.61**

Fasted Study, Study No. 01621/09-10 (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**
QC results not within the acceptance criteria	52	52	2.90	2.90	52	52	2.90	2.90
Anomalous value*	0	2	0.00	0.11	0	2	0.00	0.11
ISTD area variation	0	1	0.00	0.06	0	1	0.00	0.06
Total	**52**	**55**	**2.90**	**3.07**	**52**	**55**	**2.90**	**3.07**

Fasted Study, Study No. 01621/09-10 (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**
Anomalous value*	1	0	0.056	0.000	0	0	0.000	0.000
ISTD area variation	1	1	0.056	0.056	1	1	0.056	0.056
Total	**2**	**1**	**0.111**	**0.056**	**1**	**1**	**0.056**	**0.056**

*Sample was analyzed in duplicate and its mean was considered. **Total assays:** test product – 1794, reference product - 1794

Fed Study, Study No. 09-VIN-057 (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
Analytical Batch Failure	161	162	4.20	4.23	161	162	4.20	4.23
Improper / Inconsistent Internal Standard (IIS) Area	5	3	0.13	0.08	5	3	0.13	0.08
Sample Lost during Processing/Analysis (SLP)	1	0	0.03	0.00	1	0	0.03	0.00
Total	167	165	4.36	4.31	167	165	4.36	4.31

Fed Study, Study No. 09-VIN-057 (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
Analytical Batch Failure	216	216	5.64	5.64	216	216	5.64	5.64
Improper / Inconsistent Internal Standard (IIS) Area	0	3	0.00	0.08	0	3	0.00	0.08
Sample Lost during Processing/Analysis (SLP)	1	0	0.03	0.00	1	0	0.03	0.00
Total	217	219	5.66	5.72	217	219	5.66	5.72

Fed Study, Study No. 09-VIN-057 (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
Analytical Batch Failure	54	54	1.41	1.41	54	54	1.41	1.41
Improper / Inconsistent Internal Standard (IIS) Area	19	18	0.50	0.47	19	18	0.50	0.47
Sample Lost during Processing/Analysis (SLP)	0	1	0.00	0.03	0	1	0.00	0.03
Total	73	73	1.91	1.91	73	73	1.91	1.91

Did use of recalculated plasma concentration data change study outcome?

No.

Comments from the Reviewer:

- The standard operating procedure (SOP) number 23/13, Repeat Analysis of Samples & Reintegration of Chromatograms, effective date: 30 April 2008 (for fasting study no. 01621/09-10), allows for the following bioanalytical repeats: *(1) Unacceptable calibration curve, (2) Instrument malfunction, (3) QC acceptance criteria, (4) Extraction/processing error, (5) Internal standard area variation, (6) Acquisition error, (7) Samples lost during processing, (8) Poor chromatography, (9) Concentration of a subject sample is more than the highest CC point, (10) BLQ in the middle of the profile, (11) Pre-dose sample concentration, and (12) Anomalous value*.

- The standard operating procedure (SOP) number VIN-BRD-016, Repeat Analysis, effective date: 25 April 2008 (for fed study no. 09-VIN-057), 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 criterion and agrees that it is objective. The reviewer agrees that firm conducted its repeat analysis for the fasting study (01621/09-10) and fed study (09-VIN-057) in accordance with its SOPs. The reviewer also agrees with the firm's reasons for reanalysis.

- For the fasting study (01621/09-10), the firm reassayed a total of eight [5[6] atorvastatin, 2 orthohydroxy atorvastatin, and 1 parahydroxy atorvastatin (Per the table and report, the reanalyzed values were not used in analysis)] PK repeats from subjects under the reason code Anomalous Value. The reassays are indentified as follows:

    - Atorvastatin
        - Subject 8, period I, 1.25 hours, reference product
        - Subject 8, period I, 4.00 hours, reference product
        - Subject 35, period II, 2.50 hours, reference product
        - Subject 36, period I, 8.00 hours, reference product
        - Subject 37, period I, 36.00 hours, reference product

    - Orthohydroxy Atorvastatin
        - Subject 8, period I, 1.25 hours, reference product

[6] NOTE: There were only five (5) actual recalculated values used in the firm's calculation after reanalysis.

- Subject 8, period I, 4.00 hours, reference product

- The reviewer has reanalyzed the data using the original concentration values for all samples which were reported as anomalous values (as outlined above). Recalculation of the primary pharmacokinetic parameters using original data does not alter the outcome of the study.

As a result, the study repeat analysis is **adequate**.

3.7 Formulation

Location in appendix	Section **Error! Reference source not found.**
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 091650. REV-BIOEQ-02(Dissolution Review). 12/18/2009.
Source of Method (USP, FDA or Firm)	FDA
Medium	0.05 M Phosphate Buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
DBE-recommended specification	NLT (b) (4) (Q) in 15 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving drug product
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.9 Waiver Request(s)

Strengths for which waivers are requested	10 mg and 20 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS GRANTED**
If not then why?	N/A

3.10 Review of DSI Inspection Reports – Fasting Study (01621/09-10)

3.10.1 Review of DSI Inspection Reports – Clinical Site for the Fasting Study

A routine inspection was completed for the clinical site (Clinical Research Division, Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA) on (b) (4) for ANDA (b) (4) The outcome was Voluntary Action Indicated (VAI).

Following this page 2, pages withheld in full (b)(4)

3.12 Deficiency Comments

None

3.13 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (01621/09-10) conducted by Dr. Reddy's Laboratories on its Atorvastatin 40 mg Tablets (lot # EC8308) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 40 mg Base (lot # 0982068).

2. The Division of Bioequivalence accepts the fed BE study (09-VIN-057) conducted by Dr. Reddy's Laboratories on its Atorvastatin 40 mg Tablets (lot # EC8308) comparing it to Pfizer's Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 0982068).

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:

   NLT (b) (4) (Q) of Atorvastatin dissolved in 15 minutes

4. The waiver requests for in vivo BE study requirements for the firm's lower strength of the test product, 10 mg and 20 mg, are granted.

5. The Division of Bioequivalence deems the test product, Atorvastatin 40 mg Tablets (lot # EC8308), manufactured by Dr. Reddy's Laboratories, to be bioequivalent to the

reference product, Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg Base (lot # 0982068), manufactured by Pfizer.

The firm should be informed the above recommendations.

3.14 Comments for Other OGD Disciplines

Discipline	Comment
N/A	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	01621/09-10
Study Title	An open-label, randomized, single oral dose, two way crossover bioequivalence study to compare Atorvastatin Calcium 40 mg Tablets of Dr.Reddy's Laboratories Limited, India with Lipitor® 40 mg (Containing Atorvastatin Calcium) Tablets of Pfizer Ireland pharmaceuticals in 74 healthy, adult, human study participants under fasting conditions.
Clinical Site (Name & Address)	Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad - 500 051, India. Tel: +91-40-27264141
Principal Investigator	Dr. V. Venkateswarlu, MD
Dosing Dates	Period I: 28 May 2009 Period II: 11 June 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	20 June 2009 – 03 July 2009
Analytical Director	(b) (6) Bioanalytical Group Leader
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	37 days

Table 5. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Atorvastatin calcium 40 mg Tablets	Lipitor® 40 mg Tablets
Manufacturer	Dr. Reddy's Laboratories Limited, Bachepalli – 502 325, INDIA	Pfizer Ireland Pharmaceuticals
Batch/Lot No.	EC8308	0982068
Manufacture Date	09/2008	
Expiration Date		May 2011

Strength	40mg	40mg
Dosage Form	Tablet	Tablet
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	98.8 %	102.0 %
Content Uniformity (mean, %CV)	Mean: 99.1 %, %CV: 1.6	
Dose Administered	40mg	40mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	The planned sample size was 74. Out of 74 participants enrolled for the study, 69 of them completed clinical phase of the study.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	A washout period of 14 days was observed between the two periods.
Randomization Scheme	AB: 02, 04, 05, 07, 10, 11, 13, 16, 17, 20, 21, 22, 24, 25, 28, 29, 32, 34, 35, 38, 40, 41, 44, 46, 47, 49, 52, 53, 56, 58, 59, 62, 63, 66, 67, 70, 72, 73 BA: 01, 03, 06, 08, 09, 12, 14, 15, 18, 19, 21, 23, 26, 27, 30, 31, 33, 36, 37, 39, 42, 43, 45, 48, 50, 51, 54, 55, 57, 60, 61, 64, 65, 68, 69, 71, 74
Blood Sampling Times	The blood samples were collected as per the following schedule in each period: The first blood sample was collected within 1 hour prior to drug administration (0.0 hour) (2x 4ml) and the others (1x 4ml) at 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, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post dose.
Blood Volume Collected/Sample	In each period, a total of 26 blood samples (4 mL) each were collected. The total volume collected per study participant did not exceed 264 mL including 9 mL for screening, 7-9 mL for post-clinical assessment of lab parameters, and 21 for discarding saline mixed blood samples resulting from us of intravenous cannula.
Blood Sample Processing/Storage	Blood samples were collected by means on intravenous cannula until 10.0 hours post dose and the rest of the blood samples were collected by means of fresh, clean, sterile venipuncture usine pre-labeled 4 mL K2EDTA vacutainers. All plasma samples, meant for estimation of Atorvastatin, Ortho and Para hydroxy Atorvastatin levels, were stored at temperature ranging between –61.0°C and –81.4°C (from the date of first sample collection during period-I to the date of completion of analysis).
IRB Approval	Yes; 18 May 2009
Informed Consent	Yes; 18 May 2009

Length of Fasting	Subjects fasted 11 hours predose until four hours postdose.
Length of Confinement	Subjects were housed from at least 60 hours prior to drug administration until 48 hours after dosing.
Safety Monitoring	The safety assessments included monitoring of adverse events including adverse drug reactions, periodic physical examination, vital signs monitoring at regular predetermined intervals and as determined by Medical Investigator. Pre study 12-lead ECG, Chest X-ray, Urinalysis and Serology were conducted for screening of volunteers. Pre study Hematology and Serum Chemistry assessments were done to select participants with baseline values within reference ranges or clinically non-significant values if outside the reference range. These were repeated in post study to determine any clinically significant abnormality. Urine Drug Screening was done at the time of check-in of each study period to identify participants for any recent substance abuse. A clinical assessment, which includes general and systemic examination was conducted initially at the pre-study screening and finally at post study examination. These investigations were carried out for safety of participants and scientific integrity of the study.

Comments on Study Design:

The study design is **adequate**.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. 01624/09-10			
		Treatment Groups	
		Test Product N = 69	Reference Product N = 69
Age (years)	Mean ± SD	26.20 ± 5.596	26.20 ± 5.596
	Range	18 - 38	18 – 38
Age Groups	< 18	--	--
	18 – 40	69 (100%)	69 (100%)
	41 – 64	--	--
	65 – 75	--	--
	> 75	--	--
Sex	Male	69 (100%)	69 (100%)
	Female	--	--
Race	Asian	69 (100%)	69 (100%)
	Black	--	--
	Caucasian	--	--
	Hispanic	--	--
	Other	--	--
BMI	Mean + SD	21.95 ± 1.839	21.95 ± 1.839
	Range	19 – 25	19 – 25
Other Factors		--	--

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
39	Withdrawn from the study in period I after dosing due to AE (fever)	II	No
49	Participant had not presented himself for study participation on Period II admission day due to personal reasons, other than AE.	II	No
59	Detected positive in urine for recent abuse of drugs prior to period II admission.	II	No
62	Withdrawn from the study in period I after dosing due to adverse events (fever & headache).	I	No
73	Participant had not presented himself for study participation on Period II admission day due to personal reasons, other than AE	II	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. 01624/09-10	
	Test	Reference
General Disorders		
Fever N (%)	4 (5.56%)	1 (1.40%)
Cardiovascular N (%)	Nil	Nil
Nervous system disorders N (%)		
Headache N (%)	1(1.39%)	Nil
Haemopoetic system*		
Increased Total bilirubin Levels N (%)	8 (10.81%)	
Potassium increased N (%)	1 (1.35%)	

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
In Period I & II, listed participants were admitted late into the CPU due to administrative reasons for period I and late arrival of participants for period II. Though the admission was delayed, the predose meals restriction was complied.	All	All
In period I for participant 01, 0.833 hours and for participant 42, 1.25 hours post dose blood samples were collected late due to cannula block.		01, 42
In period II for participant 13, 16.0 hours postdose blood samples were collected late due to difficult vein and for participant 32, 0.50 hours post dose blood samples were collected late due to cannula block.		13, 32
In period II for participant 02 immediately after administration of study drug with 240 mL of drinking water extra 10 mL of water was provided as the participant wanted some more water to swallow the drug.		02
In period I listed participants, 0.0 hours pre dose blood samples centrifugation was delayed due to logistic reasons.	All	All
In Period I & II, listed participants vital signs were measured before scheduled time of 30 minutes due to logistic reasons.	All	All

Comments on Dropouts/Adverse Events/Protocol Deviations:

- No serious adverse events were reported. Each adverse event was resolved.

- Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points. Most sample collection time deviations were not significant (± 5%). In this case for statistical analysis, nominal times were used by the firm 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 11. Assay Validation – Within the Fasting Bioequivalence Study

Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.25	0.50	1.00	3.00	8.00	19.99	49.99	99.99
Inter day Precision (%CV)	2.53	5.70	4.32	3.19	2.97	1.89	3.27	4.70
Inter day Accuracy (%Actual)	99.60	99.00	102.70	101.07	101.69	98.60	99.11	98.20
Linearity	0.9952 to 0.9999							
Linearity Range (ng/mL)	0.250 to 99.994 ng/mL							
Sensitivity/LOQ (ng/mL)	0.250 ng/mL							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.750	5.002	40.016	80.032
Inter day Precision (%CV)	7.79	5.03	9.47	4.93
Inter day Accuracy (%Actual)	96.53	101.24	100.91	101.08

Orthohydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng, mcg/mL)	0.250	0.500	1.000	3.000	8.001	20.002	50.01	100.0
Inter day Precision (%CV)	2.87	6.26	4.39	2.35	2.93	2.06	2.61	2.94
Inter day Accuracy (%Actual)	100.40	97.40	103.1	100.1	101.16	98.92	99.47	99.38
Linearity	0.9955 to 0.9998							
Linearity Range (ng/mL)	0.250 to 100.012 ng/mL							
Sensitivity/LOQ (ng/mL)	0.250 ng/mL							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.750	5.003	40.024	80.048
Inter day Precision (%CV)	7.92	4.70	4.09	4.68
Inter day Accuracy (%Actual)	96.80	101.28	100.83	102.05

Parahydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (ng, mcg/mL)	0.05	0.10	0.25	0.50	1.00	2.00	5.00	10.00
Inter day Precision (%CV)	3.40	8.04	5.16	5.37	4.81	3.65	3.68	2.90
Inter day Accuracy (%Actual)	100.00	97.00	101.60	100.20	99.90	101.35	98.98	99.45
Linearity	0.9953 to 0.9997							
Linearity Range (ng/mL)	0.050 to 10.001 ng/mL							
Sensitivity/LOQ (ng/mL)	0.050 ng/mL							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.150	0.600	4.002	8.004
Inter day Precision (%CV)	10.91	6.88	9.51	4.38
Inter day Accuracy (%Actual)	110.00	104.33	103.15	103.32

Comments on Study Assay Validation:

The study assay is **adequate**.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes; Subjects 1-14
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

The chromatograms are **adequate**.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
23/13	2008-04-30	REPEAT ANALYSIS OF SAMPLES & REINTEGRATION OF CHROMATOGRAMS

Table 13. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

The study assay is **adequate**.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in **Error! Reference source not found.** and **Error! Reference source not found.**

Fasting Bioequivalence Study, Study No. 01621/09-10									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	134.92	37.40	45.46	279.27	140.92	39.69	50 97	350.21	0.96
AUC∞ (hr *ng/ml)	138.08	36.66	48.97	281.69	145.77	37.95	52 97	353.15	0.95
Cmax (ng/ml)	32.67	57.23	7.23	118.11	35.25	56.84	6.88	115.62	0.93
Tmax* (hr)	0.83	.	0.33	4.00	0.67	.	0.33	4.00	1.25
Kel (hr^{-1})	0.14	27.06	0.07	0.22	0.14	30.59	0.00	0.23	1.02
T1/2 (hr)*	5.45	29.11	3.18	9.86	7.52	217.04	2.98	140.02	0.72

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 01621/09-10				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	125.9430	130.2783	96.67	92.98 – 100.51
AUC∞ (hr *ng/ml)	130.1977	134.8910	96.52	92.93 – 100.25
Cmax (ng/ml)	28.7084	30.2439	94.92	85.33 – 105.60

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. 01621-09-10					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	125.94	130.62	0.96	92.74	100.24
AUC∞ (hr *ng/ml)	129.25	135.96	0.95	91.33	98.96
Cmax (ng/ml)	28.71	30.24	0.95	85.33	105.60

Orthohydroxy Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. 01621-09-10					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	232.95	231.54	1.01	97.28	104.05
AUC∞ (hr *ng/ml)	240.20	238.78	1.01	97.37	103.92
Cmax (ng/ml)	23.48	23.78	0.99	90.31	107.93

Parahydroxy Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. 01621-09-10					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	33.75	31.92	1.06	102.08	109.50
AUC∞ (hr *ng/ml)	48.44	45.14	1.07	98.90	116.43
Cmax (ng/ml)	1.60	1.44	1.11	104.44	118.94

Table 17. Additional Study Information for Atorvastatin, Fasting Study No. 01621/09-10

Root mean square error, AUC0-t	0.1370	
Root mean square error, AUC∞	0.1412	
Root mean square error, Cmax	0.3752	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	69	69
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	2
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	69	0.97	0.93	0.99
Reference	69	0.96	0.46*	0.99

* There is one subject (subject 16, period 2, reference product) that has a low ratio of AUCt/AUCi; the AUCt/AUC1 ratio of all other subjects range from 0.87-0.99.

Comments on 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: T23 (16 hours)

Ke last: T26 (48 hours)

The firm has also analyzed the data of sixty-nine subjects. The reviewer agrees with the firm's assessment.

Subject 37 (period I, reference product) and subject 38 (period II, reference product) both show a measurable drug concentrations at zero (0) hours for the parent drug. Since this drug concentration is less than 5% of the C_{MAX} for this subject, no further analysis is needed[10].

The 90% confidence intervals for log-transformed primary parameters of the active metabolites, orthohydroxy and parahydroxy atorvastatin, meet the acceptable BE limits of 80.00% - 125.00%. As a result, the orthohydroxy – and parahydroxy atorvastatin data is adequate and considered supporting documentation.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{MAX} of Atorvastatin, are within the acceptable BE limits of 80.00% - 125.00%. The study is **adequate**.

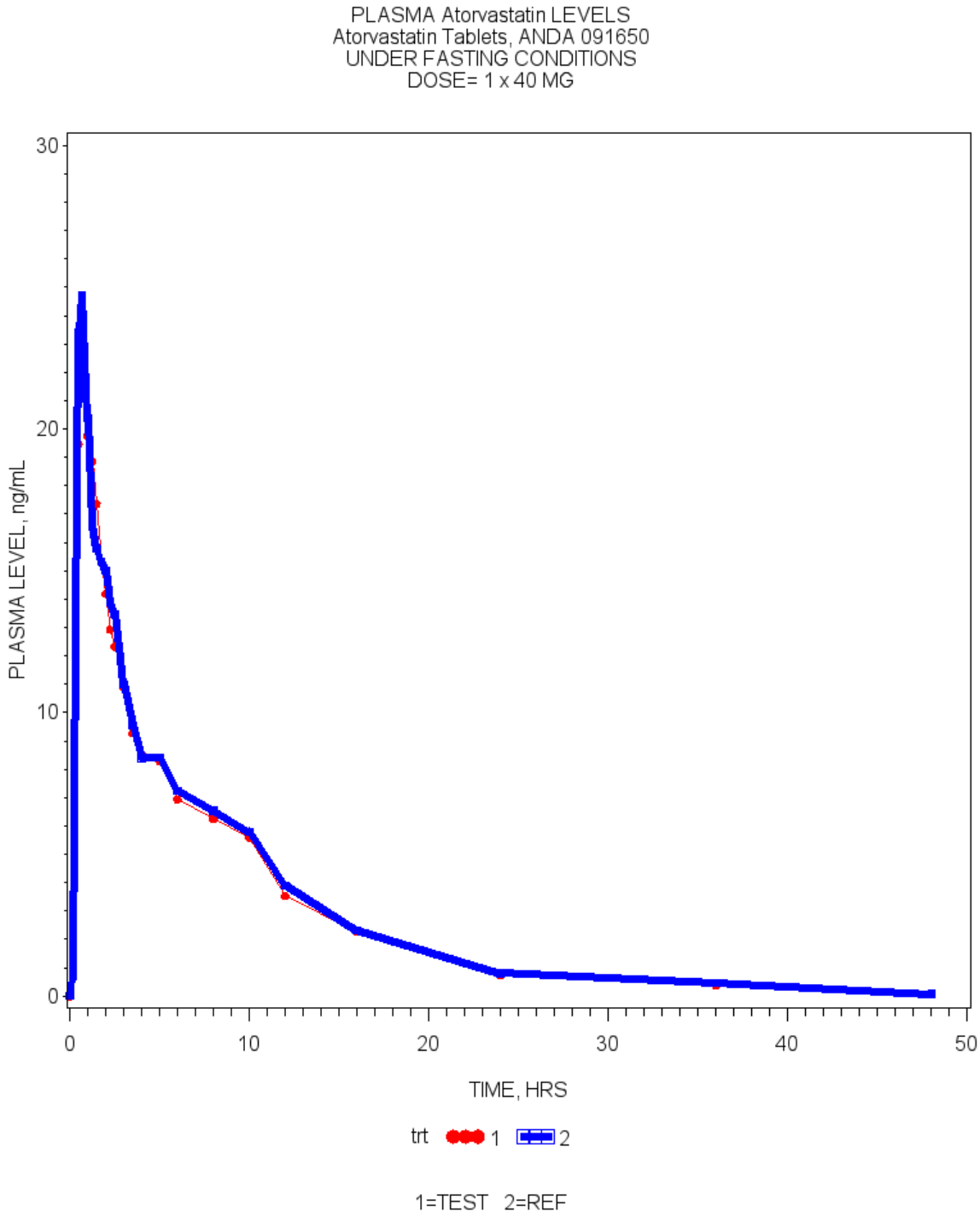
[10] Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations: March 2003.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n= 69)		Reference (n= 69)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.03	645.20	0.00
0.17	1.36	263.15	0.70	217.04	1.96
0.33	11.37	124.46	12.81	119.16	0.89
0.50	19.48	83.60	23.44	97.32	0.83
0.67	21.59	67.24	24.74	74.29	0.87
0.83	21.34	76.49	22.49	71.12	0.95
1.00	19.77	67.11	20.40	70.64	0.97
1.25	18.85	68.30	16.58	59.54	1.14
1.50	17.37	66.41	15.78	61.28	1.10
1.75	15.29	56.56	15.33	54.47	1.00
2.00	14.19	50.32	15.01	61.72	0.95
2.25	12.93	49.33	13.88	67.43	0.93
2.50	12.33	50.84	13.49	68.43	0.91
2.75	12.32	70.09	12.31	61.20	1.00
3.00	10.89	48.57	11.01	55.18	0.99
3.50	9.28	45.03	9.54	51.72	0.97
4.00	8.55	49.14	8.40	43.12	1.02
5.00	8.29	44.96	8.43	47.77	0.98
6.00	6.95	42.20	7.23	41.68	0.96
8.00	6.25	38.61	6.54	49.31	0.96
10.00	5.59	42.72	5.82	40.09	0.96
12.00	3.54	40.32	3.90	43.45	0.91
16.00	2.27	47.24	2.31	45.13	0.98
24.00	0.74	48.21	0.82	50.27	0.91
36.00	0.38	70.21	0.46	71.46	0.82
48.00	0.09	193.63	0.09	176.06	1.04

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Atorvastatin



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	09-VIN-057
Study Title	Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Atorvastatin calcium 40 mg Tablets of Dr. Reddy's Laboratories Limited, India and Lipitor® 40 mg Tablets manufactured by Pfizer Ireland Pharmaceuticals 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	Dharmesh Domadia, MD (Pharmacology)
Dosing Dates	21 March 2009 04 April 2009
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	01 May 2009 – 26 May 2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	67 days

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	T	R
Product Name	Atorvastatin calcium 40 mg Tablets	Lipitor® 40mg Tablets
Manufacturer	Dr. Reddy's Laboratories Limited, Bachepalli – 502 325, INDIA	Pfizer Ireland pharmaceuticals
Batch/Lot No.	EC8308	0982068
Manufacture Date	09/2008	
Expiration Date		May 2011
Strength	40mg	40mg
Dosage Form	Tablet	Tablet
Bio-Batch Size	(b) (4)	

Production Batch Size	(b) (4)	
Potency (Assay)	98.8 %	102.0 %
Content Uniformity (mean, %CV)	Mean: 99.1 %, %CV: 1.6	
Dose Administered	40mg	40mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Seventy-four (74) healthy, adult human subjects were enrolled in the study. Seventy-one (71) subjects completed all the periods of the study as per protocol.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	A washout period of 14 days was kept between each consecutive dosing period.
Randomization Scheme	AB: 02, 04, 05, 07, 09, 11, 14, 16, 17, 20 22, 24, 25, 27, 30, 32, 33, 35, 37, 39, 42, 44, 45, 47, 49, 51, 53, 56, 58, 60, 61, 63, 66, 68, 69, 71, 73 BA: 01, 03, 06, 08, 10, 12, 13, 15, 18, 19, 21, 23, 26, 28, 29, 31, 34, 36, 38, 40, 41, 43, 46, 48, 50, 52, 54, 55, 57, 59, 62, 64, 65, 67, 70, 72, 74
Blood Sampling Times	A total of 27 blood samples were collected during each period. Predose blood samples were collected within one hour prior to dosing (0.00 hour). Postdose samples were collected at 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	For each subject, a total of 54 blood samples were collected during the study and the total volume of blood drawn including up to 10.0 mL for screening, up to 10.0 mL for post study assessment and 23.0 mL of 'discarded' heparinized blood prior to each sampling through venous cannula, did not exceed 313.0 mL.
Blood Sample Processing/Storage	All the blood samples were collected in ice bath. Blood samples were collected in vacutainers containing K3EDTA as the anticoagulant. 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 4ºC (short term excursion permitted up to 8ºC). Transfer centrifuged plasma into two pre-labeled RIA vials containing 0.05 mL of 1M sodium phosphate buffer in an ice water bath and transferred to deep freezer at -70 ºC until analysis. In first RIA vial, approximately 1.0 mL of plasma was transferred and in second RIA vial, 1.0 mL of plasma (duplicate sample) was transferred, if the amount was less or more than one mL then buffer was adjusted accordingly.
IRB Approval	Yes; 13 March 2009
Informed Consent	Yes; 13 March 2009
Length of Fasting Before Meal	All subjects fasted (overnight) for at least 10 hours before their scheduled time for the start of the high-fast, high-calorie diet breakfast on Day 0 (dosing).
Length of Confinement	Subjects were housed in the clinical facility from Day -3 (72 hours predose) and were allowed to leave the facility after 24 hours postdose in each period.

Safety Monitoring	Vital signs (sitting blood pressure and radial pulse rate) were measured before dosing of investigational products (in the morning of the day of dosing) and at 1, 3, 6, and 12 hours after dosing in each period. Clinical examination (vital signs, physical examination and systemic examination) was done at the time of admission, before discharge and at the end of the study. Vitals check and clinical examination were performed at the time by physician when subject reported any adverse event. Subjects were questioned for well being at the time of clinical examination, during recording of sitting blood pressure, radial pulse rate and at ambulatory sample collection. Post-study safety assessment (hematology and biochemical parameters – SGOT, SGPT, Bilirubin, Creatinine and Urea) were done at the end of the study.

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	56.38	515.4
Carbohydrate	27.52	251.6
Protein	16.1	147
Total		914

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study	
Component	**Kcal**
Buttered bread – 1 slice	--
Whole milk – 1 glass	--
Soya Cutlet – 2	--
Cheese – half piece	--
Total	914

Comments on Study Design:

The DBE has noticed that the firm used a non-standard high-fat vegetarian breakfast in its fed study (Study No. 09-VIN-057). 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. Subsequently, the study design is **adequate**.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. 09-VIN-057			
		Treatment Groups	
		Test Product N = 71	Reference Product N = 71
Age (years)	Mean ± SD	29.75 ± 6.18	29.75 ± 6.18
	Range	20-42	20-42
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	69(97.18%)	69(97.18%)
	41 – 64	2 (2.82%)	2 (2.82%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	71(100%)	71(100%)
	Female	0 (0%)	0 (0%)
Race	Asian	71(100%)	71(100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean + SD	21.46 ± 1.84	21.46 ± 1.84
	Range	18.64 to 24.86	18.64 to 24.86
Other Factors		--	--

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
43	Withdrawn – adverse events (see details below)	I	No
28	Withdrawn – adverse events (see details below)	II	No
42	Withdrawn – found positive in urine screen for drugs of abuse	II	No

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. 09-VIN-057	
	Test	Reference
Digestive system		
Vomiting	-	1 (1.37%)
Viral Hepatitis	-	1 (1.37%)
Body as a Whole		
Fever (High grade associated with chills)	-	1 (1.37%)
TOTAL	-	3 (4.11%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
None	N/A	N/A

Comments on Adverse Events/Protocol Deviations:

- No serious adverse events were reported. Each adverse event was resolved.
- Subject 43 (period I) experienced emesis at 10:30 AM (approximately one hour after dosing). This event occurred within the time period before two times the median T_{max}. As a result, this subject was withdrawn from the study. The reviewer agrees with the firm's decision.
- Subject 28 (period II) experienced fever at 9:40 PM on 01 April 2009 (approximately 276 hours after dosing). The subject was subsequently withdrawn from the study.
- Primary protocol deviations that occurred during the study consisted of blood sample collection deviations at various time points. No sample collection time deviation was not significant (less than ± 5%). In this case for statistical analysis, nominal times were used by the firm and 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 26. Assay Validation – Within the Fed Bioequivalence Study

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)	5.81	4.43	4.75	3.87	3.77	3.70	4.08	4.49	3.87	4.86
Inter day Accuracy (%Actual)	98.30	103.00	101.67	100.83	99.00	99.17	99.17	98.00	99.20	102.00
Linearity	0.100 to 100 ng/mL									
Linearity Range (ng/mL)	0.100 ng/mL									
Sensitivity/LOQ (ng/mL)	0.9901 to 0.9998									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.300	3.60	10.0	90.0
Inter day Precision (%CV)	4.88	4.45	4.25	4.00
Inter day Accuracy (%Actual)	95.67	93.61	105.00	94.67

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)	5.17	4.14	3.29	2.72	2.51	2.60	2.69	2.61	2.67	2.68
Inter day Accuracy (%Actual)	97.30	104.00	103.13	101.67	97.67	98.67	98.33	97.60	98.80	102.00
Linearity	0.100 to 100 ng/mL									
Linearity Range (ng/mL)	0.100 ng/mL									
Sensitivity/LOQ (ng/mL)	0.9949 to 0.9989									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.300	3.60	10.0	90.0
Inter day Precision (%CV)	3.98	2.81	2.78	2.26
Inter day Accuracy (%Actual)	94.67	92.78	104.00	94.89

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)	6.60	5.26	3.83	2.93	2.65	3.00	2.66	2.82	2.70	2.77
Inter day Accuracy (%Actual)	97.60	102.00	105.42	107.67	96.67	97.67	97.83	96.80	98.00	101.00
Linearity	0.0500 to 50.0ng/mL									
Linearity Range (ng/mL)	0.0500ng/mL									
Sensitivity/LOQ (ng/mL)	0.9933 to 0.9978									

Parameter	Quality Control Samples			
Concentration (ng/mL)	0.150	0.500	1.80	45.0
Inter day Precision (%CV)	4.64	3.04	2.70	2.17
Inter day Accuracy (%Actual)	93.33	94.20	89.44	91.33

Comments on Study Assay Validation:

The study assay is **adequate**.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes; Subjects 58 -73
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

The chromatograms are **adequate**.

Table 27. 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 28. 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 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in **Error! Reference source not found.** and **Error! Reference source not found.**

Fed Bioequivalence Study, Study No. 09-VIN-057									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	115.47	40.61	48.66	325.22	124.20	43.26	43.35	311.65	0.93
AUC∞ (hr *ng/ml)	119.01	39.90	50.06	333.81	127.23	42.56	45.45	322.70	0.94
Cmax (ng/ml)	15.16	42.51	5.91	33.90	16.92	47.29	5.87	43.60	0.90
Tmax* (hr)	4.50	.	0.50	8.00	4.50	.	0.75	5.00	1.00
Kel (hr^{-1})	0.07	22.10	0.04	0.11	0.08	25.31	0.04	0.12	0.95
T1/2 (hr)	9.99	26.45	6.43	18.08	9.69	29.46	5.89	18.14	1.03

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 09-VIN-057				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	106.999	113.381	94.37	90.96% - 97.91%
AUC∞ (hr *ng/ml)	110.705	116.739	94.83	91.43% - 98.36%
Cmax (ng/ml)	13.894	15.171	91.58	85.69% - 97.88%

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 09-VIN-057					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	107.03	113.44	0.94	90.94	97.88
AUC∞ (hr *ng/ml)	110.65	116.60	0.95	91.52	98.41
Cmax (ng/ml)	13.89	15.17	0.92	85.69	97.88

Orthohydroxy Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 09-VIN-057					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	103.13	110.96	0.93	90.60	95.34
AUC∞ (hr *ng/ml)	107.48	114.81	0.94	91.20	96.09
Cmax (ng/ml)	7.68	8.48	0.91	86.47	94.91

Parahydroxy Atorvastatin 1 x 40 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 09-VIN-057					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	20.02	20.40	0.98	94.59	101.85
AUC∞ (hr *ng/ml)	31.18	30.44	1.02	86.74	120.98
Cmax (ng/ml)	0.70	0.73	0.95	90.98	98.53

Table 32. Additional Study Information for Atorvastatin:

Root mean square error, AUC0-t	0.1315	
Root mean square error, AUC∞	0.1297	
Root mean square error, Cmax	0.2375	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	71	71
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	71	0.97	0.88	0.99
Reference	71	0.97	0.89	0.99

Comments on 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: T23 (16 hours)

Ke last: T26 (48 hours)

The firm has also analyzed the data of seventy-one subjects.

The 90% confidence intervals for log-transformed primary parameters of the active metabolites, orthohydroxy and parahydroxy atorvastatin, meet the acceptable BE limits of 80.00% - 125.00%. As a result, the orthohydroxy – and parahydroxy atorvastatin data is adequate and considered supporting documentation.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

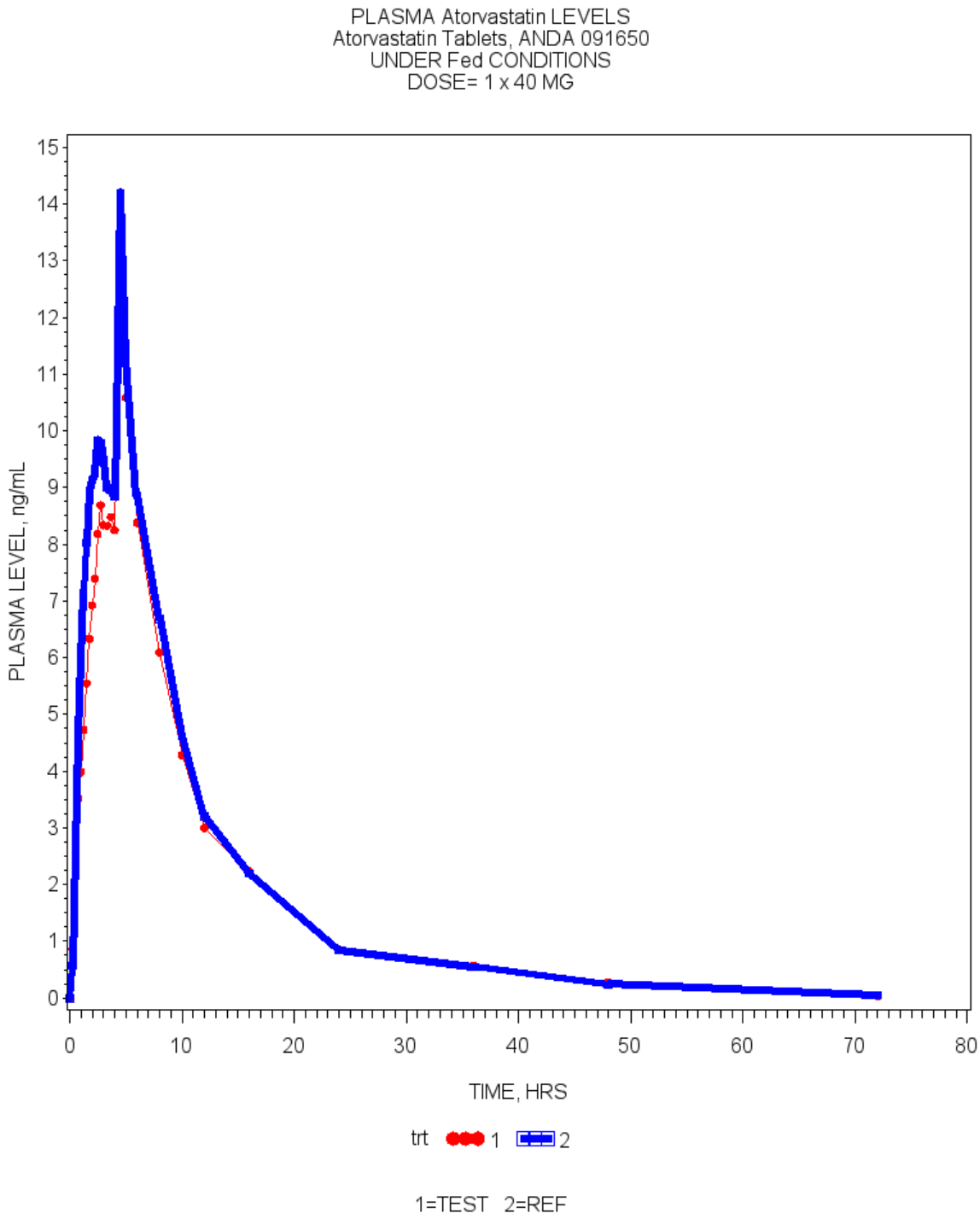
The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{MAX} of Atorvastatin, are within the acceptable BE limits of 80.00% - 125.00%. The fed study is **adequate**.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin					
Time (hr)	Test (n= 71)		Reference (n= 71)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	0.87	119.17	0.57	137.48	1.51
0.50	2.79	182.97	2.61	192.95	1.07
0.75	3.53	165.43	4.62	155.29	0.76
1.00	4.00	131.36	5.98	129.01	0.67
1.25	4.73	105.62	7.15	99.45	0.66
1.50	5.55	85.50	8.03	73.91	0.69
1.75	6.34	74.59	8.96	59.75	0.71
2.00	6.93	68.16	9.13	51.62	0.76
2.25	7.40	55.22	9.26	50.10	0.80
2.50	8.19	55.31	9.84	55.76	0.83
2.75	8.69	52.19	9.79	60.58	0.89
3.00	8.34	47.68	9.48	57.51	0.88
3.33	8.33	46.36	9.01	54.92	0.92
3.67	8.49	49.58	8.96	52.27	0.95
4.00	8.25	48.40	8.84	53.16	0.93
4.50	13.09	44.54	14.21	43.83	0.92
5.00	10.59	40.27	11.26	47.60	0.94
6.00	8.38	35.81	8.86	44.78	0.95
8.00	6.10	42.74	6.69	46.43	0.91
10.00	4.29	44.80	4.61	51.46	0.93
12.00	3.00	48.02	3.21	50.56	0.94
16.00	2.23	53.17	2.19	48.65	1.02
24.00	0.86	65.66	0.84	53.71	1.02
36.00	0.58	65.44	0.56	63.32	1.04
48.00	0.28	128.28	0.24	114.37	1.16
72.00	0.04	257.21	0.06	253.43	0.70

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Atorvastatin



4.2 Formulation Data

S.No	Ingredients	Pharmaceutical Function	Weight/tablet			% w/w composition
			10 mg strength (mg/Tablet)	20 mg strength (mg/Tablet)	40 mg strength (mg/Tablet)	
1	Atorvastatin Calcium	Active ingredient				
	Total weight		**154.505**	**309.01**	**618.00**	**100.00**

4.2.1 Test Product Formulation Data – IIG Comparison Based on MDD

Ingredient	Maximum Amount Based on MDD (mg)[11]			Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit or Justified with MDD (mg)	Test formulation Acceptable?
	10 mg	20 mg	40 mg		
					(b) (4)

[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.

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	1. There is no overage of active pharmaceutical ingredient (API). 2. Each inactive ingredient of the test product also falls within acceptable limits listed in the FDA's Inactive Ingredient Guidance (IIG) limits based on MDD (80 mg/day). 3. The excipients, methanol, water, isopropyl alcohol, and methylene chloride (b) (4) . 4. The formulations for the lower strengths, 10 mg and 20 mg, Atorvastatin Tablets USP are proportionally similar to the bio strength 40 mg Atorvastatin Tablets USP. Therefore, the formulations are acceptable.

4.2.2 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	Not Assigned	
			(b) (4)
ANDA-091226	MATRIX LABORATORIES LTD	Hongling Zhang	(b) (4)
ANDA-078773	TEVA PHARMACEUTICALS USA	Suman Dandamudi	
ANDA-077575	SANDOZ INC	Li Gong	
ANDA-091624	KUDCO IRELAND LTD	Johnetta Walters	
ANDA-090548	APOTEX INC	Li Gong	
ANDA-076477	RANBAXY LABORATORIES LIMITED	Surendra Shrivastava	
NDA 020702 (Lipitor)	Pfizer		

4.3 Dissolution Data

Dissolution Review Path	DARRTS: ANDA 091650. REV-BIOEQ-02(Dissolution Review). 12/18/2009.

Table 34. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	Dissolution media (Phosphate buffer pH 6.8) (degassed)
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications[12]	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	

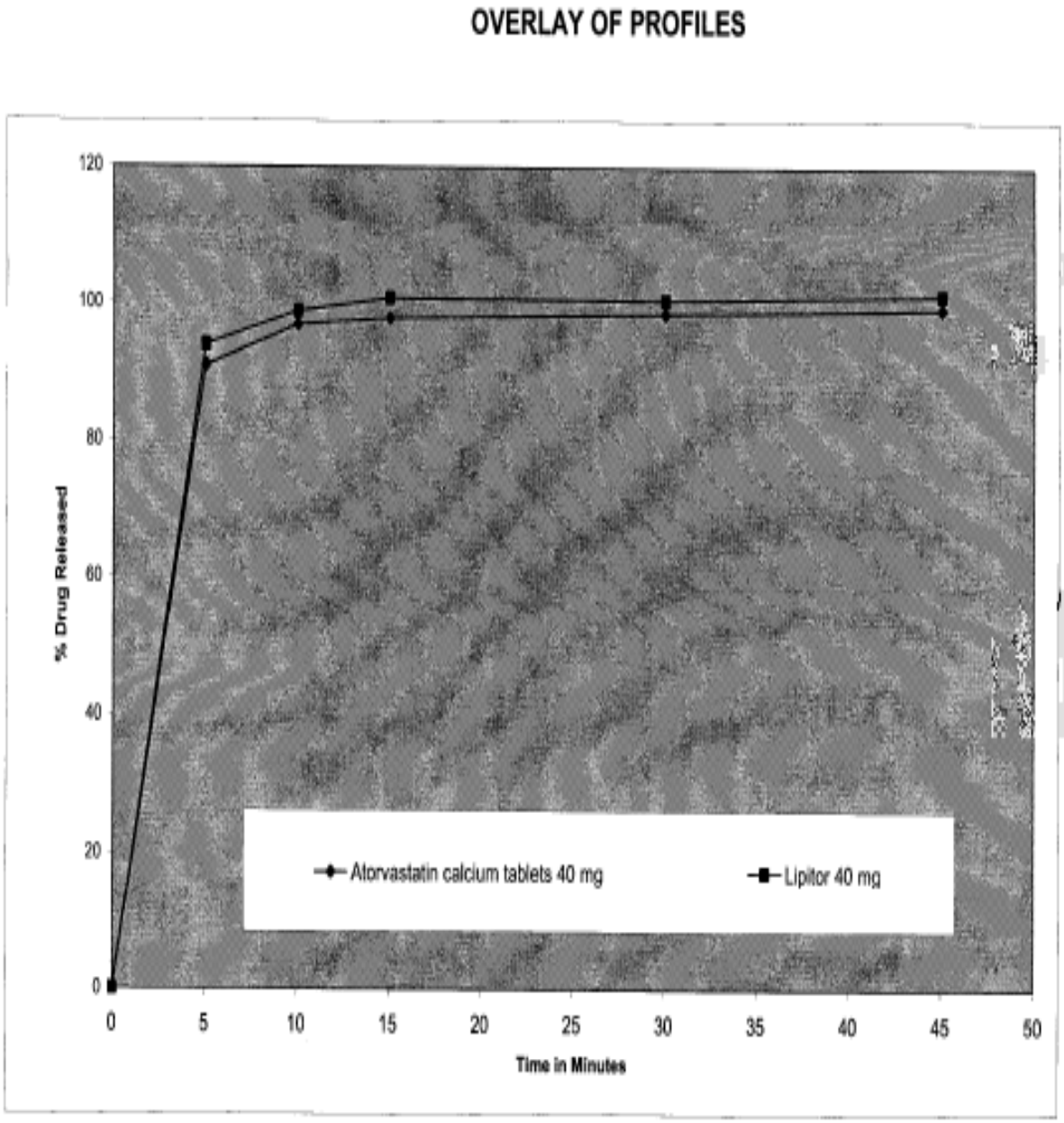
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						5 min	**10 min**	**15 min**	**30 min**	**45min**	
BN02455	03/10/08	Atorvastatin calcium Tablets10 mg, Batch No.: EC8306 Mfg. date: 09/2008	10 mg Tablets	12	Mean	90	96	97	97	97	Module 5.3.1.2
					Range	(b) (4)					
					%CV	7.6	2.8	2.5	2.1	2.0	
BN02528	17/10/08	Lipitor 10mg Batch No.: 14116V Exp .date :08/2009	10 mg Tablets	12	Mean	97	98	98	98	98	
					Range	(b) (4)					
					%CV	1.4	0.7	0.7	0.5	0.5	
BN02460	06/10/08	Atorvastatin calcium Tablets 20 mg, Batch No.: EC8307 Mfg. date: 09/2008	20 mg Tablets	12	Mean	99	101	102	102	103	
					Range	(b) (4)					
					%CV	2.6	1.5	2.0	2.6	3.2	

[12] NOTE: In an amendment dated 09 February 2010, the firm has accepted the FDA – recommended dissolution specification of "NLT (b) (4) (Q) in 15 minutes".

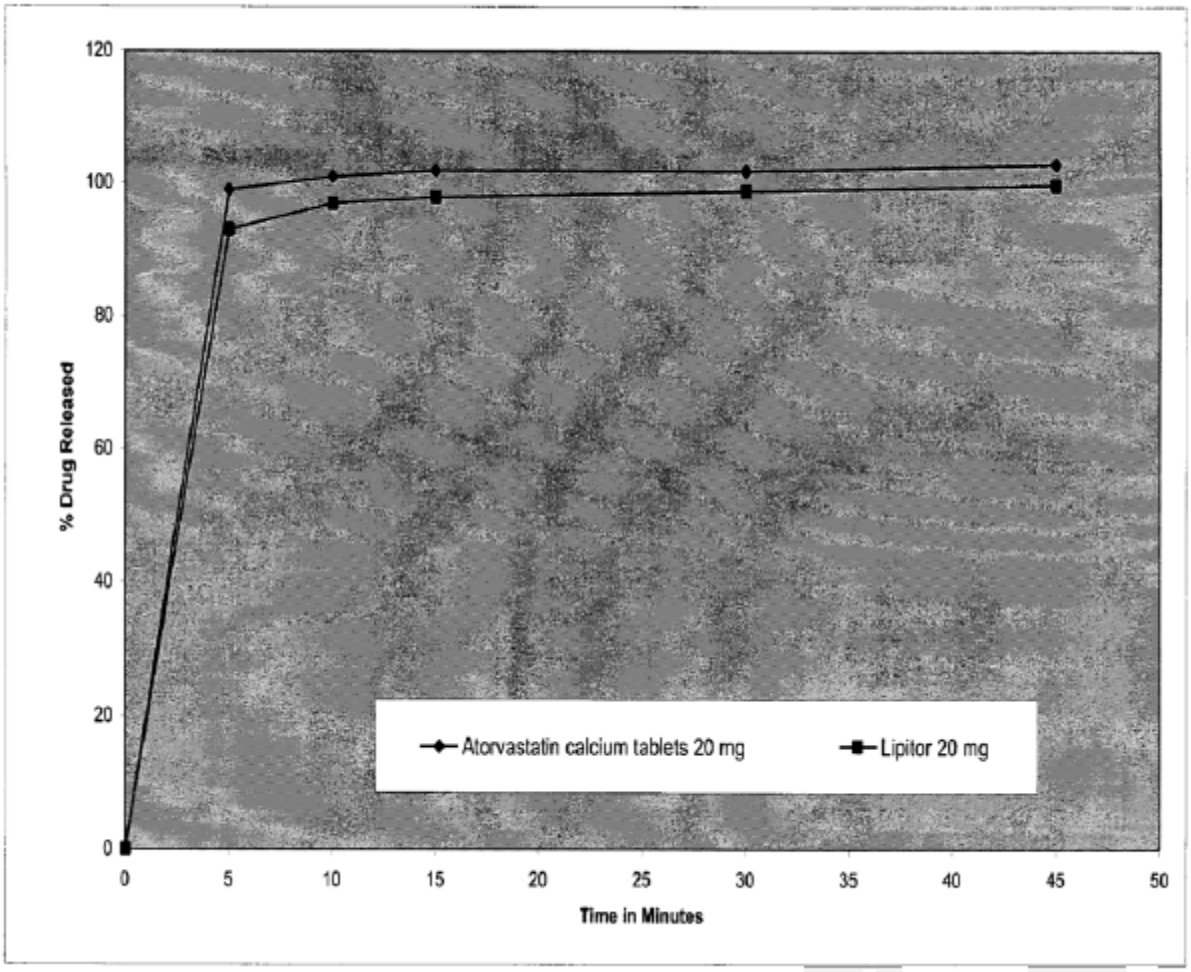
Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	Dissolution media (Phosphate buffer pH 6.8) (degassed)
	Volume:	900 mL
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) (Q) of the labeled amount of Atorvastatin is dissolved 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**	
BN02541	24/10/08	Lipitor 20mg Batch No.: 0431086 Exp. date: 07/2009	20 mg Tablets	12	Mean	93	97	98	99	100	Module 5.3.1.2
					Range	(b) (4)					
					%CV	3.1	2.5	2.0	2.0	1.8	
BN02463	06/10/08	Atorvastatin calcium Tablets 40 mg, Batch No.: EC8308 Mfg. date: 09/2008	40 mg Tablets	12	Mean	91	97	98	99	100	
					Range	(b) (4)					
					%CV	2.9	1.6	1.8	1.8	2.0	
BN02532	17/10/08	Lipitor 40mg Batch No.: 0391096 Exp. date: 08/2009	40 mg Tablets	12	Mean	94	99	101	101	102	
					Range	(b) (4)					
					%CV	2.7	0.9	0.8	0.8	0.7	

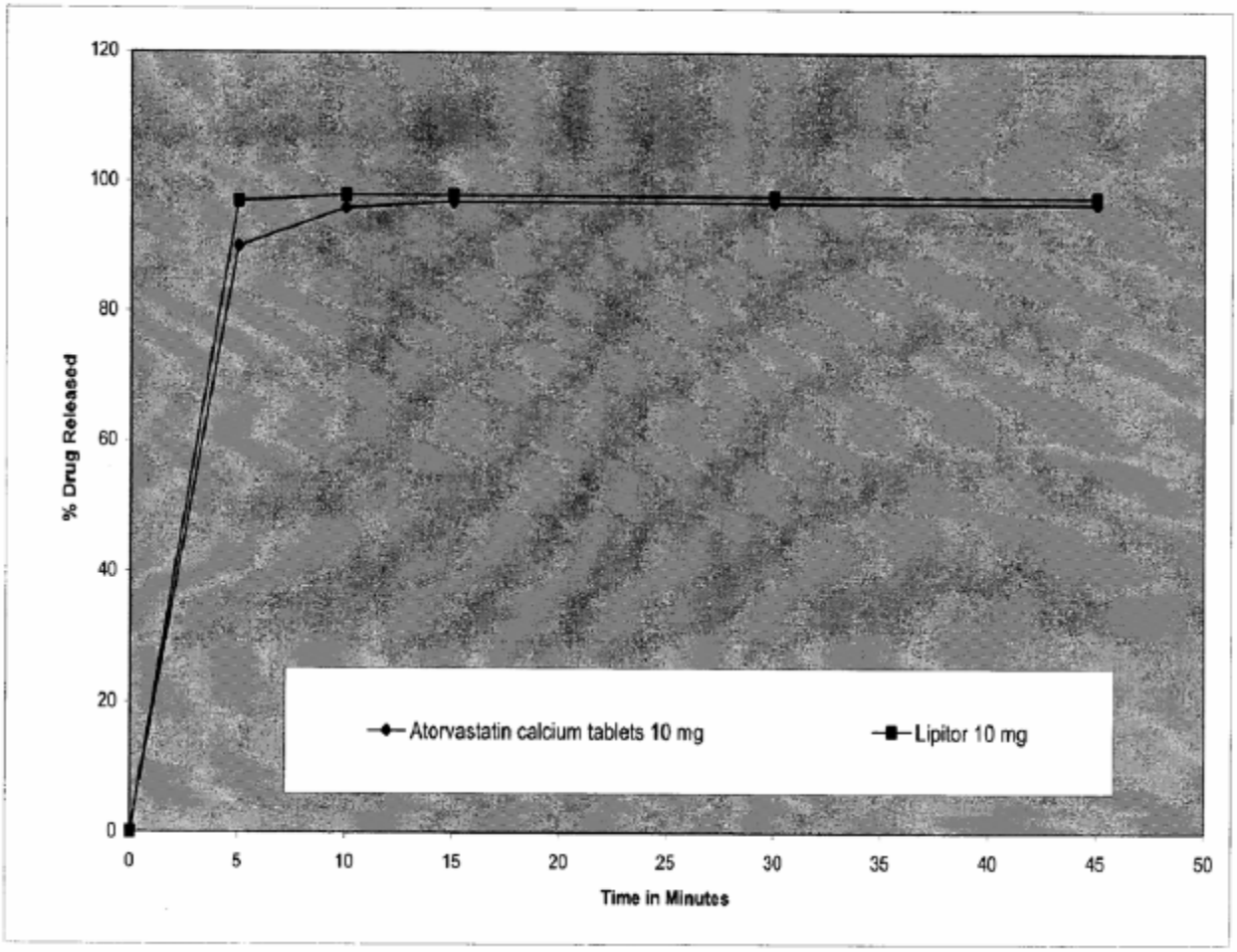
Figure 3. Dissolution Profiles



OVERLAY OF PROFILES



OVERLAY OF 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

(b) (4)

4.8 Additional Attachments

N/A

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	091650
APPLICANT:	Dr. Reddys Laboratories
DRUG PRODUCT:	Atorvastatin Calcium Tablets, 10 mg, 20 mg, and 40 mg

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

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

Medium:	0.05 M Phosphate Buffer, pH 6.8
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	Type II (Paddle)
Rotation (rpm):	75 rpm

The test product should meet the following specification:

NLT (b) (4) (Q) of the labeled amount of Atorvastatin is dissolved in 15 minutes

The DBE has noticed that you have used a non-standard high-fat vegetarian breakfast in your fed study (Study No. 09-VIN-057). 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, please note for future submissions, that the DBE does not encourage the use of vegetarian breakfasts for fed bioequivalence studies.

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

4.9 Outcome Page

ANDA: 091650

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
13856	7/9/2009	Bioequivalence Study	Fasting Study	1	1
13856	7/9/2009	Bioequivalence Study	Fed Study	1	1
13856	7/9/2009	Other	Dissolution Waiver	1	1
13856	7/9/2009	Other	Dissolution Waiver	1	1
13856	7/9/2009	Other	DSI Inspection Report (b) (4) (b) (4)	1	1
13856	7/9/2009	Other	DSI Inspection Report ((b) (4) (b) (4)	1	1
13856	2/9/2010	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	6

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
07/15/2011

BING V LI
07/18/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/20/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	091650		
Drug Product Name	Atorvastatin Calcium Tablets		
Strength(s)	10 mg, 20 mg, and 40 mg		
Applicant Name	Dr. Reddy's Laboratories Limited		
Address	Bachepalli, Post Bage No. 15, Kukatpally P.O., Hyderabad – 500 072, India Factory Address: Bachepalli 502 325, India		
Applicant's Point of Contact	Kumara Sekar 200 Somerset Corporate Blvd, 7th Floor Bridgewater, NJ 08807		
Contact's Telephone Number	(908) 203 – 4937		
Contact's Fax Number	(908) 203 – 4937		
Original Submission Date(s)	09 July 2009		
Submission Date(s) of Amendment(s) Under Review	09 February 2010		
Reviewer	Johnetta F. Walters, Ph.D.		
Study Number (s)	01621/09-10	09-VIN-057	
Study Type (s)	Fasting	Fed	
Strength (s)	40 mg	40 mg	
Clinical Site	Clinical Research Division	(b) (4)	
Clinical Site Address	Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA Tel: 91-40-27264141 Extn: 107		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI INSPECTION RESULT	**INADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2	**Fasting**	**40 mg**	**INADEQUATE**

1, 2	**Fed**	**40 mg**	**INADEQUATE**
1, 2	**Dissolution**	**40 mg**	**ADEQUATE**
1, 2	**Dissolution**	**20 mg**	**ADEQUATE**
1, 2	**Dissolution**	**10 mg**	**ADEQUATE**
2	**Amendment**	**10 mg, 20 mg, and 40 mg**	**INADEQUATE**

In an amendment dated 09 February 2010, the firm has submitted long-term storage stability (LTSS) data to cover a storage period of 48 days at -70°C. The firm previously provided LTSS data for 58 days at -20°C in its original submission. The samples were stored for the fasting study from May 28, 2009 to July 03, 2009 (37 days) and for the fed study from March 21, 2009 to May 26, 2009 (67 days), therefore, the firm will again be asked to provide LTSS data to cover a storage period of **at least 67 days**.

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/s/

NAM J CHUN
05/23/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	091650	
Drug Product Name	Atorvastatin Calcium Tablets	
Strength (s)	10 mg, 20 mg and 40 mg	
Applicant Name	Dr. Reddy's Laboratories Limited	
Address	200 Somerset Corporate Blvd, 7th Floor Bridgewater, NJ 08807	
Applicant's Point of Contact	Kumara Sekar, Ph.D. Sr. Director, Global Regulatory Affairs	
Contact's Phone Number	908-203-4900	
Contact's Fax Number	908-203-4937	
Submission Date(s)	July 15, 2009	
First Generic	No	
Reviewer	Deanah L. Mitchell, Ph.D.	
Study Number (s)	Fasting	Fed
Study Type (s)	09-VIN-057	09-VIN-057
Strength(s)	40 mg	40 mg
Clinical Site	Veeda Clinical Research Pvt. Ltd.	
Clinical Site Address	Shivalik Plaza- A, Near I.I.M., Ambawadi Ahmedabad- 380015, India	
Analytical Site	(b) (4)	
Analytical Address		
OVERALL REVIEW RESULT	**INADEQUATE**	
DSI INSPECTION RESULT	**ADEQUATE**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
#1	DISSOLUTION	10 MG	INADEQUATE
#1	DISSOLUTION	20 MG	INADEQUATE
#1	DISSOLUTION	40 MG	INADEQUATE

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product, but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). The firm's proposed specification of NLT (b) (4) (Q) in 30 minutes is not acceptable. Based on the dissolution data submitted, the DBE recommends the specification of NLT (b) (4) (Q) in 15 minutes. The firm should acknowledge the FDA-recommended method and specification.

Also, the firm should submit Long Term Storage Stability data to cover a storage period of at least 67 days.

No Division of Scientific Investigations (DSI) inspections for the clinical site[1] or analytical site[2] are pending or necessary.

The DBE will review the fasted and fed BE studies, along with the waiver requests at a later date.

[1] A routine inspection was completed for the Clinical site on (b) (4) for NDA (b) (4). The outcome was Voluntary Action Indicated (VAI). Based on the inspection, it was determined that the data was acceptable for review. (DARRTS, Search: NDA (b) (4) Kassim, Sean Y/(b) (4)/REV-NONCLINICAL-03(General Review)).

[2] A routine inspection was completed for the Analytical Site on (b) (4) for NDA (b) (4) The outcome was Voluntary Action Indicated (VAI). Based on the inspection, it was determined that the data was acceptable for review. (DARRTS, Search: NDA (b) (4) Skelly, Michael F (b) (4) REV-NONCLINICAL-03(General Review)).

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing*			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)*			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☐	☒	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	Dissolution media (Phosphate buffer pH 6.8) (degassed)
	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**	
BN02455	03/10/08	Atorvastatin calcium Tablets10 mg, Batch No.: EC8306 Mfg. date: 09/2008	10 mg Tablets	12	Mean	90	96	97	97	97	Module 5.3.1.2
					Range	(b) (4)					
					%CV	7.6	2.8	2.5	2.1	2.0	
BN02460	06/10/08	Atorvastatin calcium Tablets 20 mg, Batch No.: EC8307 Mfg. date: 09/2008	20 mg Tablets	12	Mean	99	101	102	102	103	
					Range	(b) (4)					
					%CV	2.6	1.5	2.0	2.6	3.2	
BN02463	06/10/08	Atorvastatin calcium Tablets 40 mg, Batch No.: EC8308 Mfg. date: 09/2008	40 mg Tablets	12	Mean	91	97	98	99	100	
					Range	(b) (4)					
					%CV	2.9	1.6	1.8	1.8	2.0	

Dissolution Conditions	**Apparatus:**	USP apparatus II (paddle)
	Speed of Rotation:	75 rpm
	Medium:	Dissolution media (Phosphate buffer pH 6.8) (degassed)
	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**	
BN02528	17/10/08	Lipitor 10mg Batch No.: 14116V Exp .date :08/2009	10 mg Tablets	12	Mean	97	98	98	98	98	Module 5.3.1.2
					Range	(b) (4)					
					%CV	1.4	0.7	0.7	0.5	0.5	
BN02541	24/10/08	Lipitor 20mg Batch No.: 0431086 Exp. date: 07/2009	20 mg Tablets	12	Mean	93	97	98	99	100	
					Range	(b) (4)					
					%CV	3.1	2.5	2.0	2.0	1.8	
BN02532	17/10/08	Lipitor 40mg Batch No.: 0391096 Exp. date: 08/2009	40 mg Tablets	12	Mean	94	99	101	101	102	
					Range	(b) (4)					
					%CV	2.7	0.9	0.8	0.8	0.7	

II. COMMENTS:

1. Currently, there is no USP method for Atorvastatin Calcium Tablets, but there is an FDA-recommended dissolution method. The FDA-recommended dissolution method is available on the public dissolution database on the Office of Generic Drugs website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The firm's dissolution testing data with the FDA-recommended method is acceptable.

2. The firm proposed a specification of NLT (b) (4)(Q) in 30 minutes is not acceptable. Based on the dissolution data submitted, the DBE recommends the specification of NLT (b) (4)(Q) in 15 minutes.

3. The firm's test product meets the FDA-recommended specification at the S1 level.

4. The firm provided Long Term Storage Stability data for 58 days at -20°C. The samples were stored for the fasting study from May 28, 2009 to July 03, 2009 (37 days) and for the fed study from March 21, 2009 to May 26, 2009 (67 days), therefore, the firm will be asked to provide Long Term Storage Stability data to cover a storage period of at least 67 days.

III. DEFICIENCY COMMENTS:

1. The firm's proposed specification is not acceptable. The firm should acknowledge and accept the FDA-recommended dissolution method and specification for its test product, Atorvastatin Calcium Tablets.

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed of Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Specification	**NLT (b) (4)(Q) in 15 minutes**

2. The firm should provide Long Term Storage Stability data to cover a storage period of at least 67 days.

IV. RECOMMENDATIONS

1. The in vitro dissolution testing conducted by Dr. Reddy's Laboratories, Inc. on its test product, Atorvastatin Calcium Tablets, 10 mg (Lot # EC8306), 20 mg (Lot # EC8307) and 40 mg (Lot # EC8308) comparing it to Pfizer Pharmaceutical's Lipitor® (Atorvastatin Calcium) Tablets, 10 mg (Lot # 14116V), 20 mg (Lot # 0431086) and 40 mg (Lot # 0391096) is incomplete due to the deficiency comment # 1.

2. The firm should conduct dissolution testing using the following FDA-recommended dissolution method:

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed of Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Specification	**NLT** (b) (4) **(Q) in 15 minutes**

3. The firm should provide Long Term Storage Stability data to cover a storage period of at least 67 days.

   The firm should be informed of the above deficiency comments and recommendations.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 091650

APPLICANT: Dr. Reddy's Laboratories Limited

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

The Division of Bioequivalence (DBE) has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the fasting and fed studies along with the waiver requests will be conducted later. The following deficiencies have been identified:

1. The dissolution testing data for your test product, Atorvastatin Calcium Tablets, are acceptable. However, the proposed specification of NLT (b) (4) (Q) in 30 minutes for your test product is not acceptable. Based on the dissolution testing data, the DBE recommends a more appropriate specification below. Please provide acknowledgement for your acceptance of the following FDA-recommended dissolution method and specification for your test product:

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed of Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Specification	**NLT** (b) (4) **Q) in 15 minutes**

2. Please provide Long Term Storage Stability data for Atorvastatin Calcium in frozen biological matrix to cover the maximum storage period of the study samples (i.e., from the day of the first sample collection to the day of the last sample analysis, which was at least **67 days** for your 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

V. OUTCOME

ANDA: 091650

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
9919	7/15/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

DEANAH L MITCHELL
12/17/2009

APRIL C BRADDY
12/17/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/18/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 91650

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 #:091650
Firm Name:Dr Reddy's Laboratories Limited
ANDA Name:Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base)
RLD Name:Lipitor by Pfizer

Electronic AP Routing Summary Located:
Z:\Chemistry Division III\Team 34\Electronic AP Summary\91650.ap.doc

AP/TA Letter Located:
Z:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\91650.apltr.DOC

Project Manager Evaluation: **Date: 5/23/12 Initials:** RG

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 7/16/09	Date of Application 7/15/09	Date Acceptable for Filing 10/19/09
Patent Certification (type) P-IV	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** 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) _____ Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 7/20/11 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: 5/23/12 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 5/25/12

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 5/24/2012**

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 7/16/2009, BOS=Lipitor NDA 20702, PIII to '893, '995 and '667, PIV to '104, '156 and '971. ANDA ack for filing for the 10 mg, 20 mg and 40 mg strengths with a PIV certification on 7/16/2009(LO dated 10/19/2009). Patent Amendment rec'd on 4/27/2012-RR from Warner-Lamber in Morris Plains NJ signed and dated 10/27/2009, RR from Pfizer in NY, NY signed and dated 10/27/2009, CA 09 CV 0943 filed in the D of DE on 12/8/2009 for infringement of the '156 patent, this CA was dismissed without prejudice on 8/26/2011-this dismissal immediately ended any 30 month stay of approval.
The only remaining barrie to the approval of this ANDA is Ranbaxy's(ANDA 76477) eligibility for 180 day exclusivity. This exclusivity is set to expire on 5/28/2012 which is a Federal holiday. Therefore, this ANDA will be eligible for Full Approval on Tuesday the 29th of May.

2. ***Labeling Endorsement***

Reviewer, BT:
Date5/23/12
InitialsBT/RG for

Labeling Team Leader, RW:
Date5/23/12
InitialsRW/RG for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Wu, Ruby (Chi-Ann)
Sent: Wednesday, May 23, 2012 2:08 PM
To: Turner, Betty; Gaines, Robert
Subject: RE: ANDA 91650

I concur

Bob,

As Betty requested, please delete references to the 80 mg strength since it is filed under another ANDA.

Thanks!

Ruby

From: Turner, Betty
Sent: Wednesday, May 23, 2012 12:21 PM
To: Gaines, Robert; Wu, Ruby (Chi-Ann)
Subject: RE: ANDA 91650

Hi Bob,

Dr. Reddy's 80 mg strength is approved under ANDA 202357.

I have checked the OB, USP, REMS, Medwatch, Drugs@fda, and DARRTS and there are no new updates since the last labeling review was completed.

Thanks,

Betty

From: Gaines, Robert
Sent: Wednesday, May 23, 2012 9:56 AM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: ANDA 91650

Hi Betty and Ruby.

The subject Atorvastatin ANDA by DRL is ready for approval. Please provide labeling endorsement.

Thanks

Bob

<< File: 91650 label rev.pdf >> << File: 91650.apltr.DOC >>

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 25May2012**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:AP Letter okay.

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, The applicant provided PIII certs to '893, '995 and '667 patents which have all since expired. The applicant also provided PIV certs to '104, '156 and '971 patents, but was sued for infringement of the '156 patent only. This CA was dismissed without prejudice on 8/26/2011. There are no exclusivity issues. Ranbaxy's (ANDA 76477) has 180 day exclusivity which expired on 5/28/2012. Chemistry acceptable 6/29/2012 and 7/12/2012. Bio acceptable 7/20/2011 (fsating and fed studies 40 mg). Labeling acceptable 5/18/2012 per AP Summary, TL sign-off 5/23/2012. EER acceptable 4/25/2012. This ANDA is eligible for Full Approval.

AND/OR

7. Robert L. West
Deputy Director, OGD
Date _____
Initials _____

Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes☐ No☐
Petition: Yes☐ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments:

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

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/s/

ROBERT T GAINES
07/17/2012

Vera, Matthew

From: Vera, Matthew
Sent: Friday, June 22, 2012 2:49 PM
To: Davis Bruno, Karen L; Antonipillai, Indra
Cc: Nagavelli, Laxma; Gill, Devinder; Sayeed, Vilayat A
Subject: ANDA 91650 – Revision of (b) (4) Impurity' (b) (4)

Karen and Indra,

In response to the Agency's communications dated June 4 and 8, 2012 regarding (b) (4) (b) (4) of atorvastatin calcium, Dr. Reddy's Laboratories submitted an amendment dated 14-June-2012. The CMC review team has summarized below the key information of the submission and full details are available in the EDR submission for ANDA 91650.

(b) (4)

(b) (4)

I appreciate all of your efforts and expertise on this complicated application, often under very tight timelines. If the Applicant had been more thorough at the outset, we could probably have avoided a lot of extra work all around.

Thanks again!

Regards,
Matt

Matthew D. Vera, Ph.D.
CMC Review Scientist

CDER/OPS/Office of Generic Drugs
U.S. Food and Drug Administration
7500 Standish Place HFD-630
Rockville, MD 20855

Tel. 240/276-8493
matthew.vera@fda.hhs.gov

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: Nagavelli, Laxma
Sent: Thursday, May 31, 2012 1:17 PM
To: Gaines, Robert
Cc: Sayeed, Vilayat A; Gill, Devinder; Vera, Matthew; Antonipillai, Indra; Davis Bruno, Karen L
Subject: RE: 91650 follow up

Bob,
Below is the final version that has okayed by Pharm-Tox and CMC teams:

DMEP has reviewed the 4 week rat study, comparative data with Lipitor and the AMES study report and has the following concerns:

- Safety concerns exist with the proposed limits for impurities (b) (4)

(b) (4)

In addition, the CMC team would recommend you to (b) (4) impurities to (b) (4) and adjust the total impurity limit accordingly.

Thanks,
Laxma

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/s/

MATTHEW D VERA
07/11/2012

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)

(b) (4) Please provide revised drug product release specification and an updated certificate of analysis.

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/s/

MATTHEW D VERA
06/26/2012

LAXMA R NAGAVELLI
06/26/2012

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:

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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.

(b) (4)

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/s/

MATTHEW D VERA
06/04/2012

LAXMA R NAGAVELLI
06/04/2012

Record of Teleconference Discussion

Date: May 29, 2012, 1:15 P.M.
Applicant: Dr. Reddy's Laboratories
Subject: ANDA 91650, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg

Attendees:

From Dr. Reddy's Laboratories:
Nicholas Cappuccino Vice President Scientific Affairs
Krishna Venkatesh, Senior Director, IPDO
A. Karunakar, Senior Director, Regulatory Affairs
Kimberly Ernst, Director, Regulatory Affairs
Shaik Imam Mohiddin, Senior Manager, Regulatory Affairs
Jaya Lakshmi, Senior Manager, Regulatory Affair

From OGD/DCIII:
Vilayat Sayeed
Devinder Gill
Laxma Nagavelli
Matthew Vera

From OGD/DLPS/RSB:
Robert Gaines

From OND/ODEII/DMEP:
Karen Davis Bruno
Indra Antonipillai

Background:

This teleconference with Dr. Reddy's Laboratories was initiated by OGD to discuss the Inadequate status of the firm's impurity qualification studies per consult review #2012-0668.

Summary of Discussion:

The following comments and recommendations were relayed to Dr. Reddy's Laboratories:

DMEP has reviewed the 4 week rat study, comparative data with Lipitor and the AMES study report and has the following concerns:

- Safety concerns exist with the proposed limits for impurities (b) (4)
- (b) (4)

(b) (4)

In addition, the CMC team would recommend you (b) (4)

(b) (4)

and adjust the total impurity limit accordingly.

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/s/

MATTHEW D VERA
06/08/2012

LAXMA R NAGAVELLI
06/08/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2012-0668**	
TO *(Division/Office)* Division of Metabolic and Endocrinology Products			**FROM:** Matthew Vera, OGD/DCIII	
DATE: 5/21/2012	**IND NO.**	**~TYPE~ NO.** 91-650	**TYPE OF DOCUMENT** ~TYPE_OF_DOCUMENT~	**DATE OF DOCUMENT** 2/8/2012
NAME OF DRUG Atorvastatin calcium		**PRIORITY CONSIDERATION** 15 days	**CLASSIFICATION OF DRUG** Antihyperlipidemic	**DESIRED COMPLETION DATE** 05/25/2012

NAME OF FIRM Dr. Reddy's Laboratories Inc.

REASON FOR REQUEST

I. GENERAL

- Γ NEW PROTOCOL
- Γ PROGRESS REPORT
- Γ NEW CORRESPONDENCE
- Γ DRUG ADVERTISING
- Γ ADVERSE REACTION REPORT
- Γ MANUFACTURING CHANGE/ADDITION
- Γ MEETING PLANNED BY _____
- Γ PRE NDA MEETING
- Γ END OF PHASE II MEETING
- Γ RESUBMISSION
- Γ SAFETY/EFFICACY
- Γ PAPER NDA
- Γ CONTROL SUPPLEMENT
- Γ RESPONSE TO DEFICIENCY LETTER
- Γ FINAL PRINTED LABELING
- Γ LABELING REVISION
- Γ ORIGINAL NEW CORRESPONDENCE
- Γ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

- □ DISSOLUTION
- □ PROTOCOL-- BIOPHARMACEUTICS
- □ IN--VIVO WAIVER REQUEST
- □ DEFICIENCY LETTER RESPONSE
- □ BIOAVAILABILITY STUDIES
- □ PHASE IV STUDIES

IV.DRUG EXPERIENCE

- □ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- □ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- □ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- □ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- □ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- □ SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS

OGD is requesting a pharm/tox review of information submitted by the Applicant to qualify a revised specified limit of (b) (4) (b) (4) impurity. (b) (4) The sponsor previously submitted 4-week rat toxicity data and an Ames test for genotoxicity, which had been reviewed in consults 2010-0429, 2011-0542 and 2012-0625 (Indra Antonipillai.) Through several amendments, the Applicant has provided (b) (4) impurity limits and additional information OGD has attached a summary of the pertinent information for the convenience of the consult reviewer.Please review and comment if the (b) (4) impurity can be considered as qualified at the revised level of (b) (4) The drug product Maximum Daily Dose is 80 mg.For additiona information or clarification, please contact Matthew Vera, 24 or matthew.vera@fda.hhs.govPlease provide an electronic copy of the review to the requestor by email (matthew.vera@fda.hhs.gov) and cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA

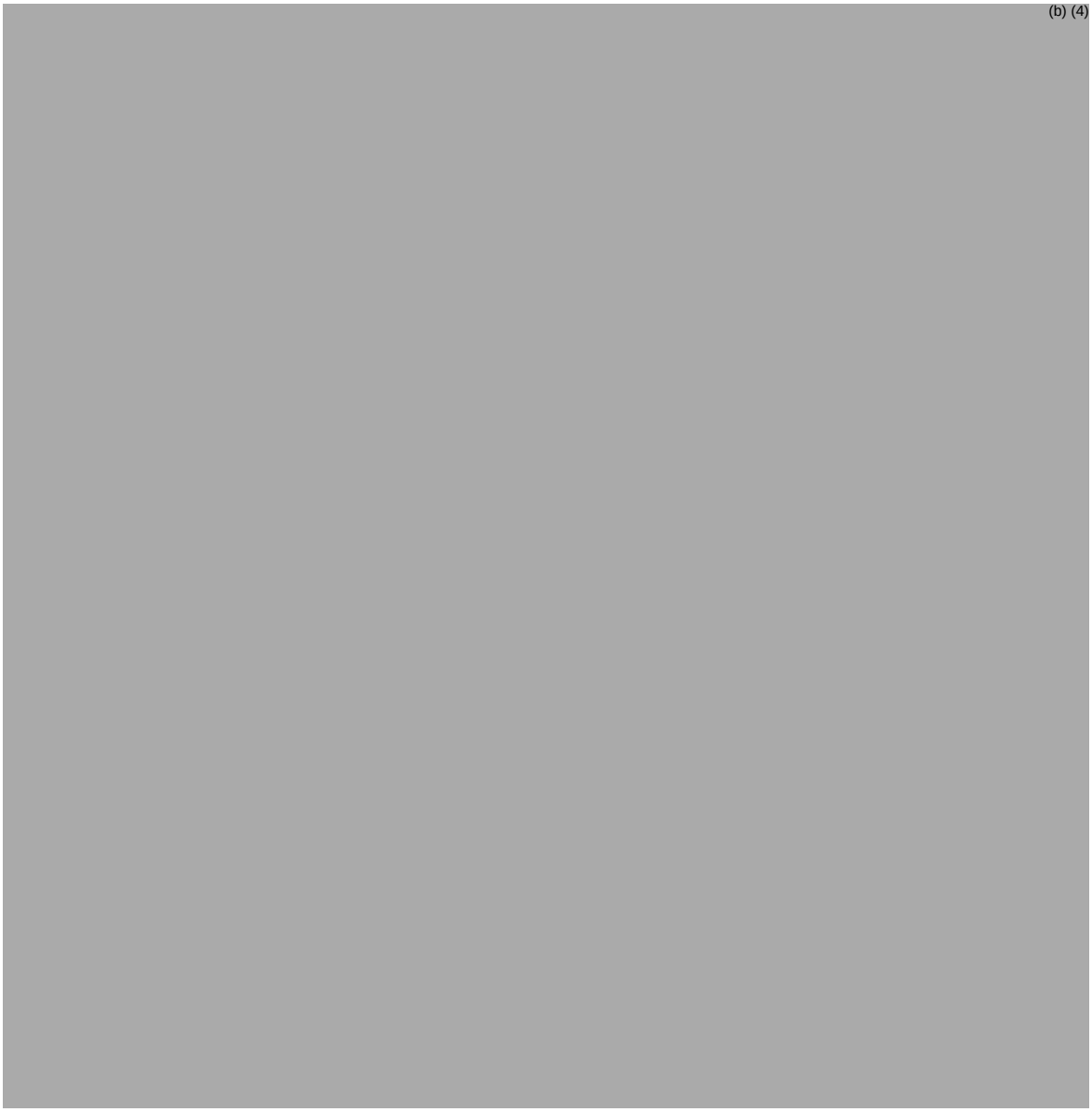
ANDA 91650 Consult Request

<u>Background information for consideration for Pharm-Tox review team</u>:

Note: All the impurities listed in this application for DP release and stability are satisfactory meeting either RLD limits or limits qualified for other Atorvastatin applications, (b) (4)

(b) (4)

Following this page, 5 Pages Withheld in Full as (b)(4)



For additional details, please see previous consults 2010-0429, 2011-0542, and 2012-0625.

CMC Question: Is the proposed limit (b) (4) qualified based on firm's response through amendments listed in items 1, 2, 3, and 4?

If additional clarification or information is needed, please contact Matthew Vera at 240-276-8493 or matthew.vera@fda.hhs.gov.

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/s/

MATTHEW D VERA
05/21/2012

LAXMA R NAGAVELLI
05/21/2012

TRANG Q TRAN
05/21/2012

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. Reference is also made to your amendments dated November 16, 2011 and February 8, 2012.

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 deficiencies presented below represent telephone deficiencies.

(b) (4)

[redacted]

c) Please provide revised drug product release and stability specifications.

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/s/

MATTHEW D VERA
05/19/2012

LAXMA R NAGAVELLI
05/19/2012

Please send an email to the labeling reviewer (betty.turner@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 091650

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, 10 mg, 20 mg and 40 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: 091650 Date of Submission: March 5, 2012

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

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

---

LABELING DEFICIENCIES:

1. **CONTAINER:**

   Revise the "*Each tablet contains…" statement to read [redacted] (b) (4)

2. **CARTON**:

   i. Revise [redacted] (b) (4)

   ii. See comment 1.

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 [redacted] (b) (4)" 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.
   [redacted] (b) (4)

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

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/s/

BETTY B TURNER
05/15/2012
For Wm Peter Rickman

Record of Telephone Conversation

(b) (4)

The firm would like to coordinate a conference call with the development technical personnel at sites in India, during the week of 03/19/2012.

Food and Drug Administration
Division of Chemistry III
7500 Standish Place
MPN II Rockville, MD 20855
Tel: 240-276-8430

Date:
03-15-2012

ANDA Number:
091650

Product Name:
Atorvastatin calcium tablets, 10 mg, 20 mg and 40 mg

Firm Name:
Dr. Reddy Labs

Firm Representative:
Jaya Ayyagari

Phone Number:
908-2034977
Fax Number:

FDA Representative:
Khalid M. Khan
Laxma Nagavelli

Signatures:
KMK

CC: ANDA
V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\Telephone Deficiencies\091650-Verbal-03152012.doc

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/s/

KHALID M KHAN
04/02/2012
091650-Verbal Communication

LAXMA R NAGAVELLI
04/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2012-0625	
TO *(Division/Office)* DMEP – HFD-510 Thru: Leah Ripper			FROM: Khalid M. Khan	
DATE: 3/13/2012	IND NO.	ANDA NO. 091650	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 11/16/2011,
NAME OF DRUG Atorvastatin Calcium		PRIORITY CONSIDERATION 30 days	CLASSIFICATION OF DRUG Antihyperlipidemic	DESIRED COMPLETION DATE 4/12/2012

NAME OF FIRM Dr. Reddy

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL	Γ PRE NDA MEETING	ΞΞ RESPONSE TO DEFICIENCY LETTER
Γ PROGRESS REPORT	Γ END OF PHASE II MEETING	Γ FINAL PRINTED LABELING
Γ NEW CORRESPONDENCE	Γ RESUBMISSION	Γ LABELING REVISION
Γ DRUG ADVERTISING	Γ SAFETY/EFFICACY	Γ ORIGINAL NEW CORRESPONDENCE
Γ ADVERSE REACTION REPORT	Γ PAPER NDA	Γ FORMULATIVE REVIEW
Γ MANUFACTURING CHANGE/ADDITION	Γ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
Γ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

OGD is requesting a Pharm/Tox Review (b) (4), as a follow up to the previous consult No. 2011-0542. The firm has responded to the deficiency letter dated 10/06/2011, which was written in light of the Pharm-Tox Consult Report by Dr. Indra Antonipillai, DARRTS dated 07/27/2011. By initiating this consult, review of the response, specifically to the deficiency No. 11 is requested. Please review the data provided by the firm and recommend if the specifications for individual and total impurities in the drug product are acceptable.

Previous Phar-Tox Consult Nos. are 2011-0542 and 2010-0429 by Dr. Antonipillai.

Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.Sears@fda.hhs.gov)on the review when it is being checked into DFS. Thank you..

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Pharm-Tox consults-ANDA 091650

HFD-630/K. M. Khan/CR/
HFD-630/L. Nagavelli/TL
HFD-617/L.A.Sears/PM

As recommended in Pharm-Tox consult No. 201-0542, DARRTS date 07/27/2011, the firm was requested to clarify (b) (4) impurities in question given to the rats in the toxicological studies.

The deficiency (letter dated 10/06/2011) and the firm's response (letter dated 11/16/2011) are as follows:

(b) (4)

The pertinent sections of Module 3.2.P.5.6 are provided on the following pages.

Following this page, 4 Pages Withheld in Full as (b)(4)

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/s/

LEIGH A SEARS
03/13/2012

TRANG Q TRAN
03/13/2012

QUALITY DEFICIENCY - MINOR

ANDA 091650

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: 908-203-4977

ATTN: Jaya Ayyagari 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 July 15, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg, and 40 mg.

Reference is also made to your amendment dated May 13, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091650 APPLICANT: Dr. Reddy's Laboratories Ltd.

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

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

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(b) (4)

B. Please acknowledge and respond to the following comments:

1. Please provide all available long-term stability data with updated stability specifications.

(b) (4)

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

LEIGH A SEARS
10/06/2011

LAXMA R NAGAVELLI
10/06/2011
Signed for Vilayat A Sayeed, PhD

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0542	
TO *(Division/Office)* DMEP - HFD-510 Thru: Leah Ripper			FROM: Leigh Ann Sears	
DATE: 7/11/2011	IND NO.	ANDA NO. 091650	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 5/13/2011,
NAME OF DRUG Atorvastatin Calcium		PRIORITY CONSIDERATION 30 days	CLASSIFICATION OF DRUG Lipid Lowering Agent	DESIRED COMPLETION DATE 8/10/2011

NAME OF FIRM Dr. Reddy's Labs Ltd.

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL
Γ PROGRESS REPORT
Γ NEW CORRESPONDENCE
Γ DRUG ADVERTISING
Γ ADVERSE REACTION REPORT
Γ MANUFACTURING CHANGE/ADDITION
Γ MEETING PLANNED BY _____
Γ PRE NDA MEETING
Γ END OF PHASE II MEETING
Γ RESUBMISSION
Γ SAFETY/EFFICACY
Γ PAPER NDA
Γ CONTROL SUPPLEMENT
Γ RESPONSE TO DEFICIENCY LETTER
Γ FINAL PRINTED LABELING
Γ LABELING REVISION
Γ ORIGINAL NEW CORRESPONDENCE
Γ FORMULATIVE REVIEW
X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION
PROTOCOL-- BIOPHARMACEUTICS
IN--VIVO WAIVER REQUEST
DEFICIENCY LETTER RESPONSE
BIOAVAILABILITY STUDIES
PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
_SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review. [redacted] (b) (4) Please evaluate the toxicological studies performed by the firm including the additional information requested in response to the previous Phar-Tox Consult No. 2010-0429 by Dr. Antonipillai.

Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) and Leigh Ann Sears, HFD-617 (Leigh.Sears@fda.hhs.gov)on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Pharm-Tox consults-ANDA 091650
HFD-630/K. M. Khan/CR/
HFD-630/L. Nagavelli/TL
HFD-617/L.A.Sears/PM

As recommended in Pharm-Tox consult No. 2010-0429, dated 07/09/2010 (DARRTS date 09/07/2010), the sponsor was requested to clarify what concentrations and composition of impurities they were tested (b) (4) (b) (4) before an assessment of qualification of these impurity levels and safety of the proposed generic atorvastatin could be determined.

(b) (4)

Continued Page 2

Complete toxicological study is available with the original submission in Module 3.2.P.5.6, dated 07/09/2009. Please provide your assessment whether the submitted information renders the subject impurities qualified at the suggested specification limits for individual as well as total impurities.

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/s/

LEIGH A SEARS
07/11/2011

TRANG Q TRAN
07/11/2011

QUALITY DEFICIENCY - MINOR

ANDA 091650

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) 203-4937

ATTN: Kumara Sekar FAX: (908) 203-4980

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 15, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendment dated August 27, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091650 APPLICANT: Dr. Reddy's Laboratories, Ltd.

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

A. The deficiencies presented below represent MINOR deficiencies.

1. The Drug Master File 21125 is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies. Please also make any applicable changes to the drug substance specifications based on consultation with DMF holder and provide the revised specifications and certificate of analysis.

2. (b) (4)

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B. Please acknowledge and respond to the following comments:

1. Please provide all available long-term stability data with updated stability specifications.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

LEIGH A SEARS
04/26/2011

LAXMA R NAGAVELLI
04/28/2011
Signed for Vilayat A Sayeed, PhD

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2010-0429**	
TO *(Division/Office)* DCRP - HFD 110 Thru: Devi Kozeli, ODE I - HFD 101			FROM: Leigh Ann Bradford	
DATE: 6/1/2010	IND NO.	ANDA NO. 091650	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 7/9/2009,
NAME OF DRUG ATORVASTATIN CALCIUM		PRIORITY CONSIDERATION 90 days	CLASSIFICATION OF DRUG Lipid lowering agent	DESIRED COMPLETION DATE 8/30/2010

NAME OF FIRM DR REDDYS LABS LTD

REASON FOR REQUEST

I. GENERAL

✆ NEW PROTOCOL	✆ PRE NDA MEETING	✆ RESPONSE TO DEFICPENCY LETTER
✆ PROGRESS REPORT	✆ END OF PHASE II MEETING	✆ FINAL PRINTED LABELING
✆ NEW CORRESPONDENCE	✆ RESUBMISSION	✆ LABELING REVISION
✆ DRUG ADVERTISING	✆ SAFETY/EFFICACY	✆ ORIGINAL NEW CORRESPONDENCE
✆ ADVERSE REACTION REPORT	✆ PAPER NDA	✆ FORMULATIVE REVIEW
✆ MANUFACTURING CHANGE/ADDITION	✆ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
✆ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW	✆ CHEMISTRY
✆ END QF PHASE II MEETING	✆ PHARMACOLOGY
✆ CONTROLLED STUDI ES	✆ BIOPHARMACEUTICS
✆ PROTOCOL REVIEW	✆ OTHER
✆ OTHER	

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review. (b) (4) Please evaluate the original ANDA in EDR Module 3.2.P.5.6 pgs. 4-5 and pgs. 49-334. Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) and Leigh Ann Bradford, HFD-617 (Leigh.Bradford@fda.hhs.gov) on the review when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

LEIGH A BRADFORD
06/01/2010

THERESA C LIU
06/02/2010

QUALITY DEFICIENCY - MINOR

ANDA 091650

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 Limited TEL: (908) 203-4937

ATTN: Kumara Sekar FAX: (908) 203-4980

FROM: Leigh Ann Bradford FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated Junly 9, 2010, 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 Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **6** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091650 APPLICANT: Dr. Reddy's Laboratories, Ltd.

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

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

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a.

(b) (4)

Following this page, 3 Pages Withheld in Full as (b)(4)

24. (b) (4) [redacted]

25. [redacted]

26. [redacted]

B. Please acknowledge and respond to the following comments:

1. (b) (4) [redacted]

2. Please provide all available long-term stability data.

3. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

ROBERT L ISER
06/02/2010
signed for V. Sayeed

Telephone Fax

ANDA 91650

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Dr. Reddy's Laboratories, Inc.
U.S. Agent for Dr. Reddy's Laboratories, Inc.

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, 10 mg, 20mg, and 40 mg.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: 091650 Date of Submission: July 15, 2009

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

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

---

Labeling Deficiencies:

1. CONTAINER (all strengths in bottles of 30s, 60s, 90s and 500s):

   Revise [redacted] (b) (4) " to "USUAL DOSAGE".

2. [redacted] (b) (4)

3. CARTON

   [redacted] (b) (4)

4. INSERT

   11 DESCRIPTION

   The third paragraph of this subsection is significantly different than the RLD's. Please provide an explanation as to why the physical properties of your drug product differ significantly from the RLD's.

5. PATIENT INFORMATION SHEET

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

Submit labels and labeling electronically.

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

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

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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

/s/

JOHN F GRACE
01/25/2010
for Wm Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 091650

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 Limited TEL: (908) 203-4900

ATTN: Kumara Sekar FAX: (908) 203-4937

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240) 276-8782

:

This facsimile is in reference to the bioequivalence data submitted on July 15, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Tablets, 10 mg, 20 mg and 40 mg.

The Division of Bioequivalence has completed its review of the submission 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 **Bioequivalence Dissolution Acknowledgement**
Bioequivalence Long Term Stability Storage Data

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 091650

APPLICANT: Dr. Reddy's Laboratories Limited

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

The Division of Bioequivalence (DBE) has completed its review of only the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasting and fed studies along with the waiver requests will be conducted later. The following deficiencies have been identified:

1. The dissolution testing data for your test product, Atorvastatin Calcium Tablets, are acceptable. However, the proposed specification of NLT (b)(4)% (Q) in 30 minutes for your test product is ***not acceptable***. Based on the dissolution testing data, the DBE recommends a more appropriate specification below. Please provide acknowledgement for your acceptance of the following FDA-recommended dissolution method and specification for your test product:

Medium	0.05 M Phosphate Buffer, pH 6.8
Apparatus	USP Type II (Paddle)
Speed of Rotation	75 rpm
Temperature	37° ± 0.5° C
Volume	900 mL
Specification	**NLT (b)(4)%(Q) in 15 minutes**

2. Also, please provide Long Term Storage Stability data for Atorvastatin Calcium in frozen biological matrix to cover the maximum storage period of the study samples (i.e. from the day of the first sample collection to the day of the last sample analysis, which was at least **67 days** for your 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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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

/s/

DALE P CONNER
01/21/2010

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 91-650 **FIRM NAME**: DR. REDDY'S LABORATORIES LIMITED

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ATORVASTATIN CALCIUM
DOSAGE FORM: TABLETS, 10 MG, 20 MG AND 40 MG

Review Team: (Bolded/Italicized Lines indicate Assignment or DARRTS designation)

Quality Team: DC3 Team 12	***Bio Team 8: Bing Li***
ANDA/Quality RPM: Jeanne Skanchy or Sarah Nguyen	Bio PM: Nam J. Chun (Esther) FYI: Lizzie Sanchez
Quality Team Leader: Iser, Robert	☐ ***Clinical Endpoint Team Assignment: (No)***
Labeling Reviewer: Thuyanh (Ann) Vu	☐ ***Micro Review (No)***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: JULY 15, 2009 **Received Date**: JULY 16, 2009

Comments: EC- 3 YES **On Cards:** YES
Therapeutic Code: 3021600 LIPID ALTERING AGENTS

Archival copy: ELECTRONIC (ECTD FORMAT) **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Ted Palat **Date 10/05/2009**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA: 908-203-4937 Kumara Sekar

(b) (4)

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JULY 15, 2009	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒

*	**Table of Contents (paper submission only)** 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) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES, form 3454 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 PIII – '893, '995, '667 PIV – '104, '156, '971

1. Patent number(s)

Patent and Exclusivity Search Results from query on Appl No 020702 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020702	004	4681893	Sep 24, 2009	Y	Y	U-161	
020702	004	4681893*PED	Mar 24, 2010			U-161	
020702	004	5273995	Dec 28, 2010	Y	Y	U-162	
020702	004	5273995*PED	Jun 28, 2011			U-162	
020702	004	5686104	Nov 11, 2014		Y	U-213	
020702	004	5686104*PED	May 11, 2015			U-213	
020702	004	5969156	Jul 8, 2016	Y			
020702	004	5969156*PED	Jan 8, 2017				
020702	004	6126971	Jan 19, 2013		Y		
020702	004	6126971*PED	Jul 19, 2013				
020702	004	RE40667	Dec 28, 2010	Y	Y	U-162	
020702	004	RE40667*PED	Jun 28, 2011				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020702	004	I-471	Sep 21, 2008
020702	004	I-523	Mar 2, 2010

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

I-471 INDICATED TO REDUCE THE RISK OF MYOCARDIAL INFARCTION AND STROKE IN PATIENTS WITH TYPE 2 DIABETES AND WITHOUT CLINICALLY EVIDENT CORONARY HEART DISEASE BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE

I-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

2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☒
   PIV ☒ (Statement of Notification) ☒
3. Expiration of Patent(s): 1/8/2017
   a. Pediatric exclusivity submitted? YES
   b. Expiration of Pediatric Exclusivity? 01/08/2017
4. Exclusivity Statement: YES market after expiration

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, DMF 21125 Type II DMF No. YES 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	☒

(b) (4)

[redacted]

1.12.11	**Basis for Submission OK** NDA# : 20-702 Ref Listed Drug: LIPITOR Firm: PFIZER ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 10 MG AND 20 MG	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) 1 copy, e-submission **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** YES **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) **Dr. Reddy's Laboratories Limited,** (b) (4) 2. Function or Responsibility YES 3. Type II DMF number for API YES 4. CFN or FEI numbers YES	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) not listed **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1 **Description and Composition of the Drug Product** ☒

1. Unit composition

S.No	Ingredients	Pharmaceutical Function	Weight/tablet			% w/w composition
A	Granulation stage (Stage-A Granulation)		10 mg strength (mg/Tablet)	20 mg strength (mg/Tablet)	40 mg strength (mg/Tablet)	
1	Atorvastatin Calcium (b) (4)	Active ingredient				(b) (4)
						(b) (4)
	Total weight		154.505	309.01	618.00	100.00

2. Inactive ingredients and amounts are appropriate per IIG YES

(b) (4)


(b) (4)

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) Dr. Reddy's Laboratories Limited (Generics) Located at Bachepalli – 502 325 INDIA 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers YES **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization YES 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation YES 2. Filter validation (if aseptic fill) YES	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers EC8306, EC8307, EC8308 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes Atorvastatin calcium tablets of 10 mg are white to off-white, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '121' on other side and are supplied in bottles of 30's, 60's, 90's, 500's (b) (4) Bottles of 30 NDC 55111-121-30 Bottles of 60 NDC 55111-121-60 Bottles of 90 NDC 55111-121-90 Bottles of 500 NDC 55111-121-05 (b) (4) Atorvastatin calcium tablets of 20 mg are white to off-white, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '122' on other side and are supplied in bottles of 30's, 60's, 90's, 500's (b) (4) Bottles of 30 NDC 55111-122-30 Bottles of 60 NDC 55111-122-60 Bottles of 90 NDC 55111-122-90 Bottles of 500 NDC 55111-122-05 (b) (4) Atorvastatin calcium tablets of 40 mg are white to off-white, capsule shaped, biconvex, film coated tablets debossed 'RDY' on one side and '123' on other side and are supplied in bottles of 30's, 60's, 90's, 500's (b) (4) Bottles of 30 NDC 55111-123-30 Bottles of 60 NDC 55111-123-60 Bottles of 90 NDC 55111-123-90 Bottles of 500 NDC 55111-123-05 (b) (4) 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package YES, see 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 (b) (4) **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** NO **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) YES b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) NA **2. Lot Numbers of Products used in BE Study(ies):** ANDA: EC8306, 8307 and 8308 RLD: 14116V, 0431086, 0391096 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

5.3.1.2 Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES ☒

Table 03: Statistical Summary of the Bioequivalence Data of Atorvastatin (Fed Study)

Atorvastatin calcium 40 mg Tablets Ln-transformed Geometric Least Squares Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 09-VIN-057)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}	106.999	113.381	94.37	90.96% - 97.91%
$AUC_{0-\infty}$	110.705	116.739	94.83	91.43% - 98.36%
C_{max}	13.894	15.171	91.58	85.69% - 97.88%

Table 03: Statistical Summary of the Bioequivalence Data of Atorvastatin (Fasting Study)

Study No.: 01621/09-10 Atorvastatin Calcium 40 mg Tablets **Least Squares Geometric Means, Ratio of the Means and 90% Confidence Intervals**				
Study report location: Table 14.2.3-1				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I**
AUC_{last} (ng*hr/mL)	125.9430	130.2783	96.67	92.98 – 100.51
AUC_{Inf} (ng*hr/mL)	130.1977	134.8910	96.52	92.93 – 100.25
C_{max} (ng/mL)	28.7084	30.2439	94.92	85.33 – 105.60

2. Summary Bioequivalence tables:
   - Table 10. Study Information YES
   - Table 12. Dropout Information YES
   - Table 13. Protocol Deviations YES

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   - Table 11. Product Information YES
   - Table 16. Composition of Meal Used in Fed Bioequivalence Study YES

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   - Table 9. Reanalysis of Study Samples YES
   - Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES
   - Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7

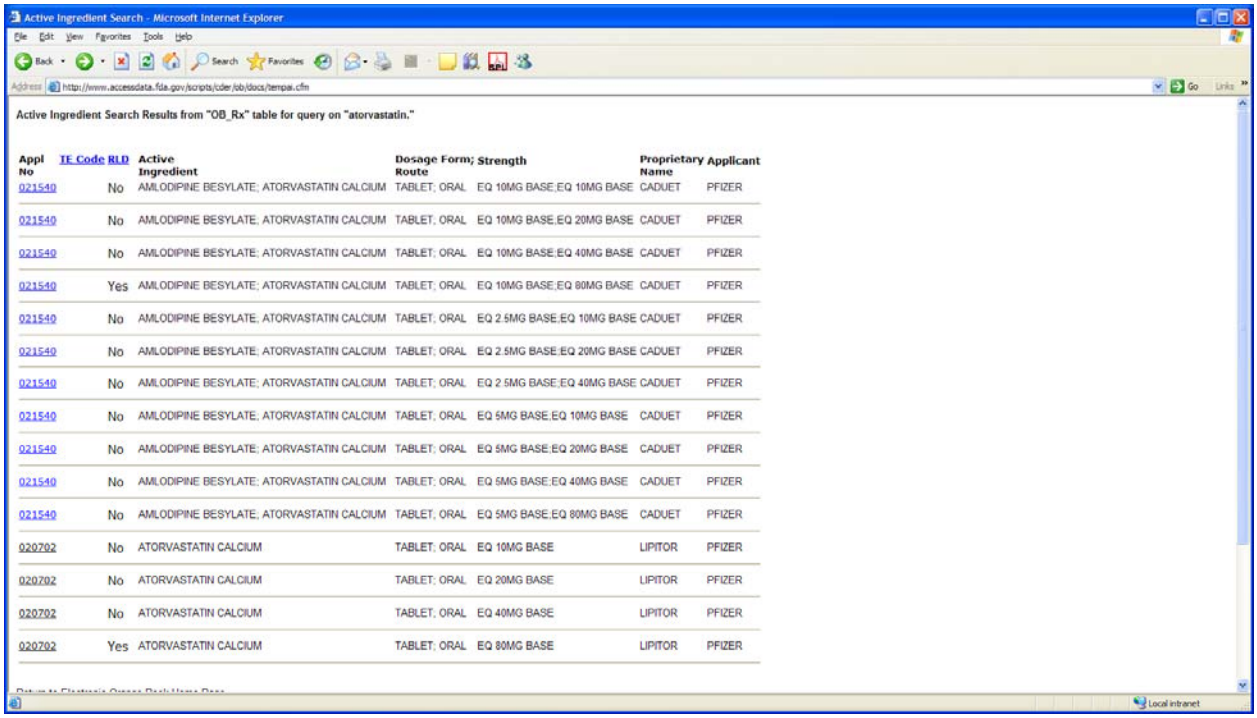
Case Report Forms and Individual Patient Listing YES

5.4	**Literature References**	☒
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 40 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) YES 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008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TE Code
RLD
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Dosage Form; Route
Strength
Proprietary Name
Applicant
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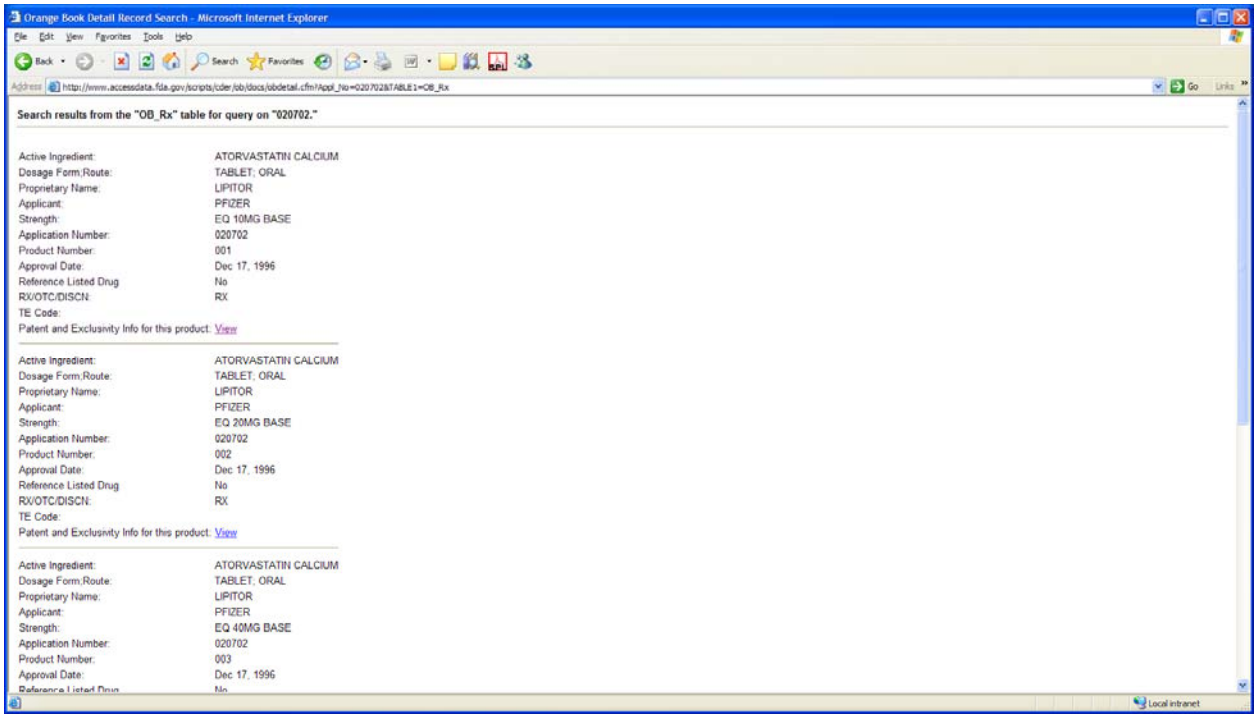
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Proprietary Name: LIPITOR
Applicant: PFIZER
Strength: EQ 10MG BASE
Application Number: 020702
Product Number: 001
Approval Date: Dec 17, 1996
Reference Listed Drug No
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TE Code:
Patent and Exclusivity Info for this product: View
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Proprietary Name: LIPITOR
Applicant: PFIZER
Strength: EQ 20MG BASE
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Product Number: 002
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Proprietary Name: LIPITOR
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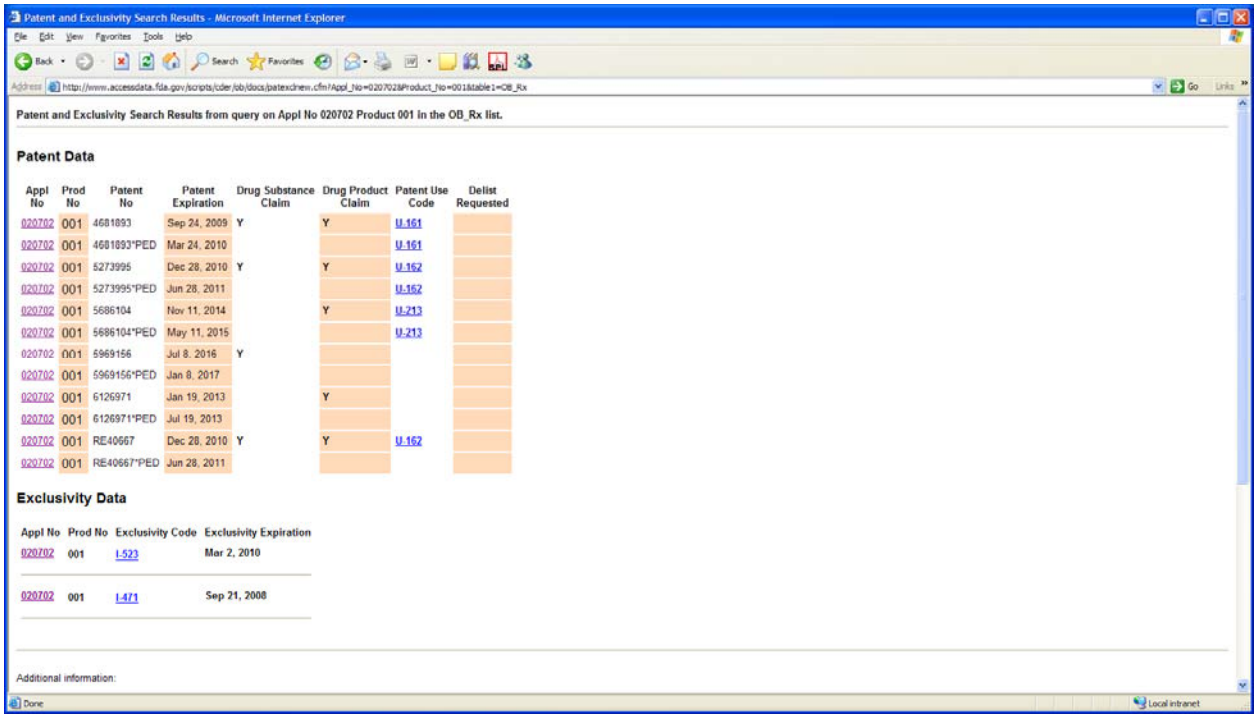
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020702 001 5969156 Jul 8, 2016 Y
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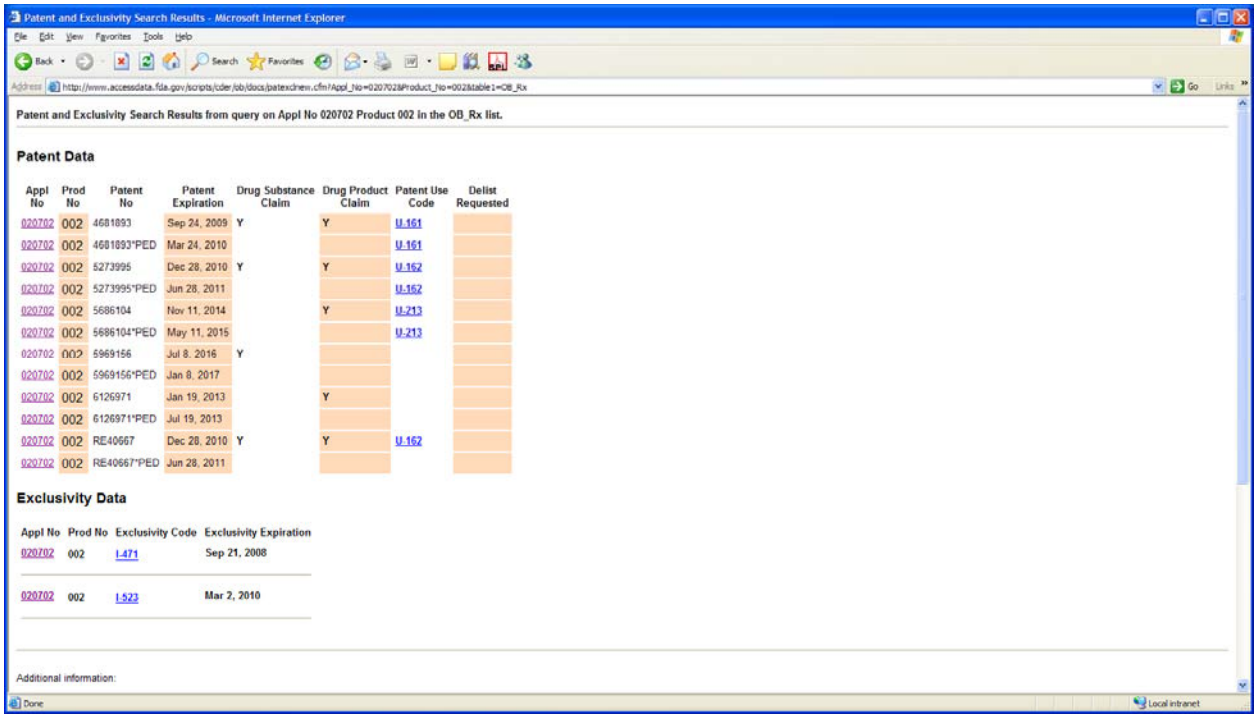
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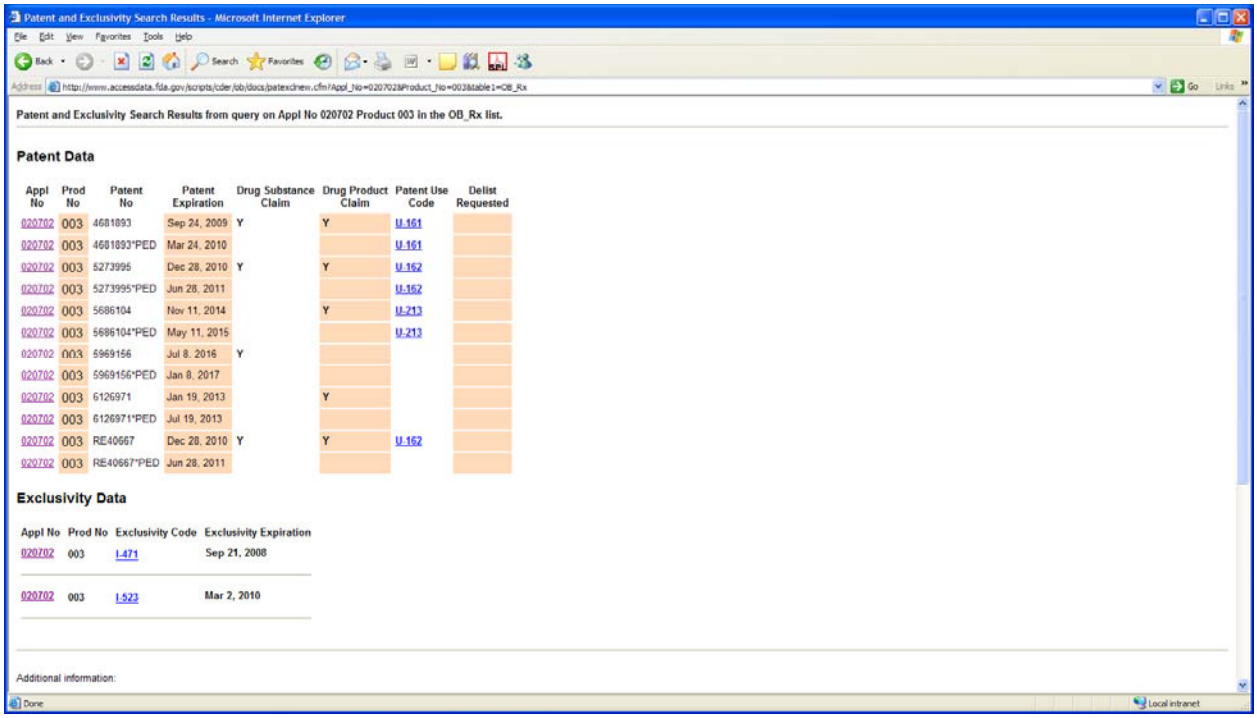
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Additional information:
Done
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/s/

TED C PALAT
10/13/2009

MARTIN H Shimer
10/19/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-650

Dr. Reddy's Laboratories, Inc.
US Agent for Dr. Reddy's Laboratories Limited
Attention: Kumara Sekar
200 Somerset Corporate Blvd.
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.

NAME OF DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg

DATE OF APPLICATION: July 15, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 16, 2009

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeanne Skanchy
Project Manager
240-276-8467

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91650	ORIG-1	DR REDDYS LABORATORIES LTD	ATORVASTATIN CALCIUM

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/s/

MARTIN H Shimer
10/19/2009
Signing for Wm Peter Rickman