CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 216848

Name: Atorvastatin Calcium; 10 mg, 20 mg, 40 mg, 80 mg

Sponsor: Lepu Pharmaceutical Technology Co., LTD.

Approval Date: November 3, 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANDA 216848

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216848

APPROVAL LETTER

Saxon International Associates
U.S. Agent for Lepu Pharmaceutical Technology Co., Ltd.
10 DeBary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Peter Saxon:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 4, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Lipitor Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, of Upjohn Manufacturing Ireland Unlimited.

Under section 506A of the FD&C 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 and 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 FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written

notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

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 https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.

ATORVASTATIN CALCIUM tablets, for oral use
Initial U.S. Approval:1996

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

Atorvastatin calcium tablets is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in adult 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 adult 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 adult 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 pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy (1.2).

Limitations of Use:

- Atorvastatin calcium tablets has not been studied in Fredrickson Types I and V dyslipidemias (1.3).

----------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 patients with HeFH: starting dose: 10 mg once daily; dose range: 10 to 20 mg/day for patients 10 years to 17 years of age (2.2).

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

- Tablets: 10, 20, 40, and 80 mg of atorvastatin (3).

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

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4).
- Hypersensitivity to any component of this medication (4).
- Pregnancy (4, 8.1, 8.3).
- Lactation (4, 8.2).

----------WARNINGS AND PRECAUTION----------

- Myopathy and Rhabdomyolysis: Risks increase when higher doses are used concomitantly with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, human immunodeficiency virus (HIV) or hepatitis C virus (HCV) 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. Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. Atorvastatin calcium tablets therapy should be discontinued if myopathy is diagnosed or suspected (2.6, 5.1, 8.5).
- Immune-Mediated Necrotizing Myopathy (IMNM): There have been rare reports of IMNM, an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents (5.2).
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.3).
- 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 tablets 80 mg group vs. placebo (5.6).

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

- Most common adverse reactions (incidence ≥2%) in patients treated with atorvastatin calcium tablets 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 Lepu Pharmaceutical Technology Co., Ltd. at 1-908-273-1303 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

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

- Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with atorvastatin calcium tablets (2.6, 5.1, 7.1, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, tipranavir plus ritonavir, glecaprevir plus pibrentasvir	Avoid atorvastatin
Clarithromycin, itraconazole, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir	Do not exceed 20 mg atorvastatin daily
Nelfinavir	Do not exceed 40 mg atorvastatin daily
Lopinavir plus ritonavir, simeprevir, fibric acid derivatives, erythromycin, azole antifungals, lipid-modifying doses of niacin, colchicine	Consider the risk/benefit of concomitant use with atorvastatin

- 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 tablets (7).
- Rifampin should be simultaneously co-administered with atorvastatin calcium tablets (7.2).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.3).
- Digoxin: Patients should be monitored appropriately (7.3).

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

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (8.6, 12.3).
- Females of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with atorvastatin calcium tablets (8.3).

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

Revised:06/2022

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 Adults

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 is indicated to:

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

In adult 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 is indicated to:

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

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

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

1.2 Hyperlipidemia

Atorvastatin calcium tablets is indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in adult 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 adult patients with elevated serum TG levels (*Fredrickson* Type IV);
- For the treatment of adult 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 (HoFH) 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 pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) 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 has 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 and Mixed Dyslipidemia

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. 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 Years to 17 Years of Age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the usual dose range is 10 to 20 mg orally once daily *[see Clinical Studies (14.6)]*. Doses should be individualized according to the recommended goal of therapy *[see Indications and Usage (1.2) and Clinical Pharmacology (12)]*. 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 HoFH 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 (5.1) and 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 (5.1) and Clinical Pharmacology (12.3)]*.

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

In patients taking cyclosporine or the HIV protease inhibitor tipranavir plus ritonavir or the hepatitis C virus (HCV) protease inhibitor glecaprevir plus pibrentasvir or letermovir when co-administered with cyclosporine, therapy with atorvastatin calcium tablets should be avoided. In patients with HIV taking lopinavir plus ritonavir, use the lowest dose necessary of atorvastatin calcium tablets. In patients taking clarithromycin, itraconazole, elbasvir plus grazoprevir, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir or letermovir therapy with atorvastatin calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is used. In patients taking the HIV protease inhibitor nelfinavir therapy with atorvastatin calcium tablets should be limited to 40 mg *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Atorvastatin calcium tablets, USP are white to off white, film-coated tablets containing 10, 20, 40, 80 mg of atorvastatin calcium.

Table 1: Atorvastatin Calcium Tablets, USP Strengths and Identifying Features

Tablets Strengths	Identifying Features
10 mg of atorvastatin	"I" on one side.
20 mg of atorvastatin	"I I" on one side.
40 mg of atorvastatin	"I I I" on one side.
80 mg of atorvastatin	"I I I I" on one side.

4 CONTRAINDICATIONS

- **Active Liver Disease, Which May Include Unexplained Persistent Elevations in Hepatic Transaminase Levels**
- **Hypersensitivity to Any Component of This Medication**
- **Pregnancy** *[see Use in Specific Populations (8.1, 8.3)]*.
- **Lactation** *[see Use in Specific Populations (8.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

Atorvastatin calcium tablets may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Rare fatalities have occurred as a result of rhabdomyolysis with statin use, including atorvastatin calcium tablets.

Risk Factors for Myopathy
Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher atorvastatin calcium tablets dosage *[see Drug Interactions (7.1)]*.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis
Atorvastatin calcium tablets exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with atorvastatin calcium tablets is not recommended. Atorvastatin calcium tablets dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications *[see Dosage and Administration (2.6)]*. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin coadministered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)]*.

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking atorvastatin calcium tablets *[see Drug Interactions (7.1)]*.

Discontinue atorvastatin calcium tablets if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Muscle symptoms and CK increases may resolve if atorvastatin calcium tablets is discontinued. Temporarily discontinue atorvastatin calcium tablets in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the atorvastatin calcium tablets dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

5.3 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 tablets in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. 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 tablets.

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

Atorvastatin calcium tablets 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 tablets *[see Contraindications (4)]*.

5.4 Endocrine Function

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

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin calcium tablets 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.

5.5 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.

5.6 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 tablets 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 tablets 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal 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: Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)]*
Liver enzyme abnormalities *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

In the atorvastatin calcium tablets placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium tablets vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium tablets and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium tablets 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 tablets 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 tablets (n=8755), from seventeen placebo-controlled trials.

Table 2: Clinical Adverse Reactions Occurring in ≥ 2% in Patients Treated with any Dose of Atorvastatin Calcium Tablets and at an Incidence Greater than Placebo Regardless of Causality (% of Patients).

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

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

Other adverse 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 tablets 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium tablets 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 tablets 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 tablets 10 mg daily (n=5006) or atorvastatin calcium tablets 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 tablets 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 tablets 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 (5.6)]*.

In a post-hoc analysis, atorvastatin calcium tablets 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 tablets 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 tablets vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium tablets 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 tablets 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 tablets 80 mg group (5.0%) than in the placebo group (4.0%).

Adverse Reactions from Clinical Studies of atorvastatin calcium tablets in Pediatric Patients
In a 26-week controlled study in boys and postmenarchal girls with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium tablets 10 to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels, was generally similar to that of placebo *[see Use in Special Populations (8.4) and Clinical Studies (14.6)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of atorvastatin calcium tablets. 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 tablets 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, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis and interstitial lung disease.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use *[see Warnings and Precautions (5.2)]*.

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).

7 DRUG INTERACTIONS

7.1 Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin Calcium Tablets

Atorvastatin calcium tablets is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). Atorvastatin calcium tablets plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 3 includes a list of drugs that may increase exposure to atorvastatin calcium tablets and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 3: Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin Calcium Tablets

Cyclosporine or Gemfibrozil	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin calcium tablets and cyclosporine, an inhibitor of CYP3A4 and OATP1B1 *[see Clinical Pharmacology (12.3)]*. Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with atorvastatin calcium tablets.
Intervention:	Concomitant use of cyclosporine or gemfibrozil with atorvastatin calcium tablets is not recommended.
Anti-Viral Medications	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin calcium tablets with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) *[see Clinical Pharmacology (12.3)]*. Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with atorvastatin calcium tablets.
Intervention:	• Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with atorvastatin calcium tablets is not recommended. • In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin. • In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed atorvastatin calcium tablets 20 mg. • In patients taking nelfinavir, do not exceed atorvastatin calcium tablets 40 mg *[see Dosage and Administration (2.6)]*. • Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with atorvastatin calcium tablets. • Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir, nelfinavir, and ledipasvir plus sofosbuvir.
Select Azole Antifungals or Macrolide Antibiotics	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin calcium tablets with select azole antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking clarithromycin or itraconazole, do not exceed atorvastatin calcium tablets 20 mg *[see Dosage and Administration (2.6)]*. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with atorvastatin calcium tablets. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (≥1 gram/day niacin) with atorvastatin calcium tablets.
Intervention:	Consider if the benefit of using lipid modifying dosages of niacin concomitantly with atorvastatin calcium tablets outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than Gemfibrozil)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with atorvastatin calcium tablets.

Intervention:	Consider if the benefit of using fibrates concomitantly with atorvastatin calcium tablets outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with atorvastatin calcium tablets.
Intervention:	Consider the risk/benefit of concomitant use of colchicine with atorvastatin calcium tablets. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit Juice	
Clinical Impact:	Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily, can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking atorvastatin calcium tablets.

7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets

Table 4 presents drug interactions that may decrease exposure to atorvastatin calcium tablets and instructions for preventing or managing them.

Table 4: Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets

Rifampin	
Clinical Impact:	Concomitant administration of atorvastatin calcium tablets with rifampin, an inducer of cytochrome P450 3A4 and inhibitor of OATP1B1, can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, delayed administration of atorvastatin calcium tablets after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
Intervention:	Administer atorvastatin calcium tablets and rifampin simultaneously.

7.3 Atorvastatin Calcium Tablets Effects on Other Drugs

Table 5 presents atorvastatin calcium tablets's effect on other drugs and instructions for preventing or managing them.

Table 5: Atorvastatin Calcium Tablets Effects on Other Drugs

Oral Contraceptives	
Clinical Impact:	Co-administration of atorvastatin calcium tablets and an oral contraceptive increased plasma concentrations of norethindrone and ethinyl estradiol *[see Clinical Pharmacology (12.3)]*.
Intervention:	Consider this when selecting an oral contraceptive for patients taking atorvastatin calcium tablets.
Digoxin	
Clinical Impact:	When multiple doses of atorvastatin calcium tablets and digoxin were co-administered, steady state plasma digoxin concentrations increased *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor patients taking digoxin appropriately.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Atorvastatin calcium tablets is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit of lipid lowering drugs during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, atorvastatin calcium tablets may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium tablets should be discontinued as soon as pregnancy is recognized *[see Contraindications (4)]*. Limited published data on the use of atorvastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies in rats and rabbits there was no evidence of embryo-fetal toxicity or congenital malformations at doses up to 30 and 20 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 80 mg, based on

body surface area (mg/m^2). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development was observed at doses ≥ 6 times the MRHD *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Human Data
Limited published data on atorvastatin calcium from observational studies, meta-analyses and case reports have not shown an increased risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a ≥3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Animal Data
Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. 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 at the MRHD based on surface area (mg/m^2). In rats, the maternally toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 and 100 mg/kg/day in rabbits, there was increased post-implantation loss, and at 100 mg/kg/day fetal body weights were decreased.

In a study in pregnant rats administered 20, 100, or 225 mg/kg/day from gestation day 7 through to lactation day 20 (weaning), there was decreased survival at birth, postnatal day 4, weaning, and post-weaning in pups of mothers dosed with 225 mg/kg/day, a dose at which maternal toxicity was observed. Pup body weight was decreased through postnatal day 21 at 100 mg/kg/day, and through postnatal day 91 at 225 mg/kg/day. Pup development was delayed (rotarod 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 exposure at the MRHD, based on AUC.

8.2 Lactation

Risk Summary
Atorvastatin calcium tablets use is contraindicated during breastfeeding *[see Contraindications (4)]*. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. It is not known whether atorvastatin is present in human milk, but it has been shown that another drug in this class passes into human milk and atorvastatin is present in rat milk. Because of the potential for serious adverse reactions in a breastfed infant, advise women that breastfeeding is not recommended during treatment with atorvastatin calcium tablets.

8.3 Females and Males of Reproductive Potential

Contraception
Atorvastatin calcium tablets may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with atorvastatin calcium tablets *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

Heterozygous Familial Hypercholesterolemia (HeFH)
The safety and effectiveness of atorvastatin calcium tablets have been established in pediatric patients, 10 years to 17 years of age, with HeFH as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels when, after an adequate trial of diet therapy, the following are present:

- LDL-C ≥ 190 mg/dL, or
- LDL-C ≥ 160 mg/dL and
  - a positive family history of FH, or premature CVD in a first, or second-degree relative, or
  - two or more other CVD risk factors are present.

Use of atorvastatin calcium tablets for this indication is supported by evidence from *[see Dosage and Administration (2.2),*

Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)]:

- A placebo-controlled clinical trial of 6 months duration in 187 boys and postmenarchal girls, 10 years to 17 years of age. Patients treated with 10 mg or 20 mg daily atorvastatin calcium tablets had an adverse reaction profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls.
- A three year open-label uncontrolled trial that included 163 pediatric patients 10 to 15 years of age with HeFH who were titrated to achieve a target LDL-C < 130 mg/dL. The safety and efficacy of atorvastatin calcium tablets in lowering LDL-C appeared generally consistent with that observed for adult patients, despite limitations of the uncontrolled study design

Advise postmenarchal girls of contraception recommendations, if appropriate for the patient *[see Use in Specific Populations (8.1), (8.3)]*.

The long-term efficacy of atorvastatin calcium tablets therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.

The safety and efficacy of atorvastatin calcium tablets have not been established in pediatric patients younger than 10 years of age with HeFH.

Homozygous Familial Hypercholesterolemia (HoFH)

Clinical efficacy of atorvastatin calcium tablets with dosages up to 80 mg/day for 1 year was evaluated in an uncontrolled study of patients with HoFH including 8 pediatric patients *[see Clinical Studies (14.5)]*.

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium tablets 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 tablets should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

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

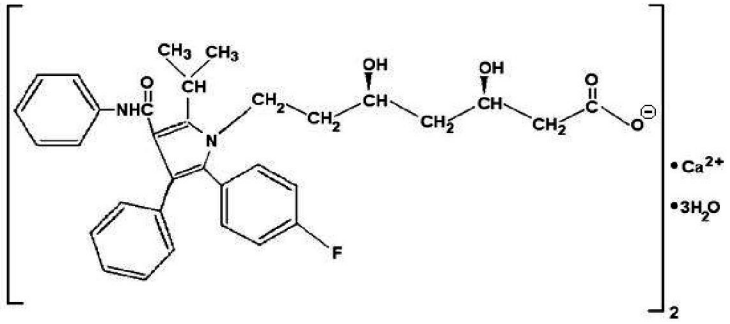
10 OVERDOSAGE

There is no specific treatment for atorvastatin calcium tablets 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 tablets clearance.

11 DESCRIPTION

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

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1- heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



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

Atorvastatin calcium tablets, USP for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040-CN (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF.

FDA approved dissolution test specifications differ from the USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium tablets is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3- methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In animal models, atorvastatin calcium tablets 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 tablets also reduces LDL production and the number of LDL particles.

12.2 Pharmacodynamics

Atorvastatin calcium tablets, 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 tablets is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium tablets dose. The absolute bioavailability of atorvastatin (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 tablets is given with or without food. Plasma atorvastatin calcium tablets 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 tablets is approximately 381 liters. Atorvastatin calcium tablets is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium tablets is likely to be secreted in human milk *[see Contraindications (4) and Use in Specific Populations (8.2)]*.

Metabolism: Atorvastatin calcium tablets 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 tablets. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin calcium tablets metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin calcium tablets 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 tablets 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 tablets 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 tablets is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium tablets are higher (approximately 40% for Cmax and 30% for AUC) in 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 (8.5)]*.

Pediatric: Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric HeFH patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

Gender: Plasma concentrations of atorvastatin calcium tablets 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 tablets between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin calcium tablets; thus, dose adjustment in patients with renal dysfunction is not necessary *[see Dosage and Administration (2.5) and Warnings and Precautions (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 tablets since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin calcium tablets 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)]*.

Drug Interaction Studies

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

TABLE 6: Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	**Ratio of AUC***	**Ratio of Cmax***
†Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD‡ for 28 days	8.69	10.66
†Tipranavir 500 mg BID§/ritonavir 200 mg BID§, 7 days	10 mg, SD¶	9.36	8.58
†Glecaprevir 400 mg QD‡/pibrentasvir 120 mg QD‡, 7 days	10 mg QD‡ for 7 days	8.28	22.00
†Telaprevir 750 mg q8h#, 10 days	20 mg, SD¶	7.88	10.60
†, ÞSaquinavir 400 mg BID§/ ritonavir 400 mg BID§, 15 days	40 mg QD‡ for 4 days	3.93	4.31
†Elbasvir 50 mg QD‡/grazoprevir 200 mg QD‡, 13 days	10 mg SD¶	1.94	4.34
†Simeprevir 150 mg QD‡, 10 days	40 mg SD¶	2.12	1.70
†Clarithromycin 500 mg BID§, 9 days	80 mg QD‡ for 8 days	4.54	5.38
†Darunavir 300 mg BID§/ritonavir 100 mg BID§, 9 days	10 mg QD‡ for 4 days	3.45	2.25
†Itraconazole 200 mg QD‡, 4 days	40 mg SD¶	3.32	1.20
†Letermovir 480 mg QD‡, 10 days	20 mg SD¶	3.29	2.17

†Fosamprenavir 700 mg BID§/ritonavir 100 mg BID§, 14 days	10 mg QD‡ for 4 days	2.53	2.84
†Fosamprenavir 1400 mg BID§, 14 days	10 mg QD‡ for 4 days	2.30	4.04
†Nelfinavir 1250 mg BID§, 14 days	10 mg QD‡ for 28 days	1.74	2.22
†Grapefruit Juice, 240 mL QD‡,ß	40 mg, SD¶	1.37	1.16
Diltiazem 240 mg QD‡, 28 days	40 mg, SD¶	1.51	1.00
Erythromycin 500 mg QIDà, 7 days	10 mg, SD¶	1.33	1.38
Amlodipine 10 mg, single dose	80 mg, SD¶	1.18	0.91
Cimetidine 300 mg QIDà, 2 weeks	10 mg QD‡ for 2 weeks	1.00	0.89
Colestipol 10 g BID§, 24 weeks	40 mg QD‡ for 8 weeks	NA	0.74è
Maalox TC® 30 mL QIDà, 17 days	10 mg QD‡ for 15 days	0.66	0.67
Efavirenz 600 mg QD‡, 14 days	10 mg for 3 days	0.59	1.01
†Rifampin 600 mg QD‡, 7 days (co-administered)ð	40 mg SD¶	1.12	2.90
†Rifampin 600 mg QD‡, 5 days (doses separated)ð	40 mg SD¶	0.20	0.60
†Gemfibrozil 600 mg BID§, 7 days	40 mg SD¶	1.35	1.00
†Fenofibrate 160 mg QD‡, 7 days	40 mg SD¶	1.03	1.02
Boceprevir 800 mg TIDø, 7 days	40 mg SD¶	2.32	2.66

* Represents ratio of treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).
† See Sections 5.1 and 7 for clinical significance.
‡ Once daily
§ Twice daily
¶ Single dose
# Every 8 hours
Þ 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.
ß Greater increases in AUC (ratio of AUC up to 2.5) and/or Cmax (ratio of Cmax up to 1.71) have been reported with excessive grapefruit consumption (≥ 750 mL – 1.2 liters per day).
à Four times daily
è Ratio based on a single sample taken 8–16 h post dose.
ð 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.
ø Three times daily

TABLE 7: Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	**Co-administered drug and dosing regimen**		
	Drug/Dose (mg)	**Ratio of AUC**	**Ratio of Cmax**
80 mg QD* for 15 days	Antipyrine, 600 mg SD†	1.03	0.89
80 mg QD* for 10 days	‡Digoxin 0.25 mg QD*, 20 days	1.15	1.20
40 mg QD* for 22 days	Oral contraceptive QD*, 2 months - norethindrone 1 mg - ethinyl estradiol 35µg	 1.28 1.19	 1.23 1.30
10 mg, SD†	Tipranavir 500 mg BID§/ritonavir 200 mg BID§, 7 days	1.08	0.96
10 mg QD* for 4 days	Fosamprenavir 1400 mg BID§, 14 days	0.73	0.82
10 mg QD* for 4 days	Fosamprenavir 700 mg BID§/ritonavir 100 mg BID§, 14 days	0.99	0.94

* Once daily
† Single dose
‡ See Section 7 for clinical significance.
§ Twice daily

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

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.

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male 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

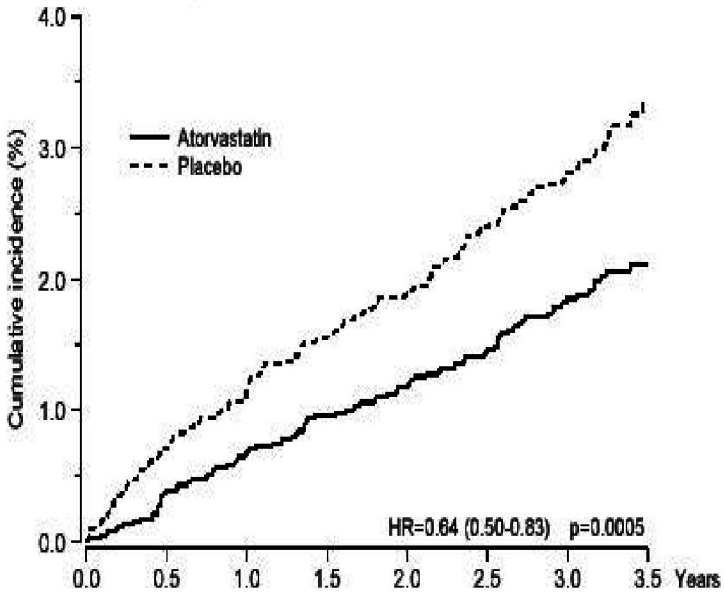
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin calcium tablets on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40–80 years of age (mean of 63 years), without a previous myocardial 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 tablets 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients 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 tablets on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin calcium tablets 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 tablets group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium tablets group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin calcium tablets vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium tablets 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 Tablets 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin calcium tablets also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for atorvastatin calcium tablets and 2.5% for placebo). 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 tablets 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 tablets 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 tablets 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

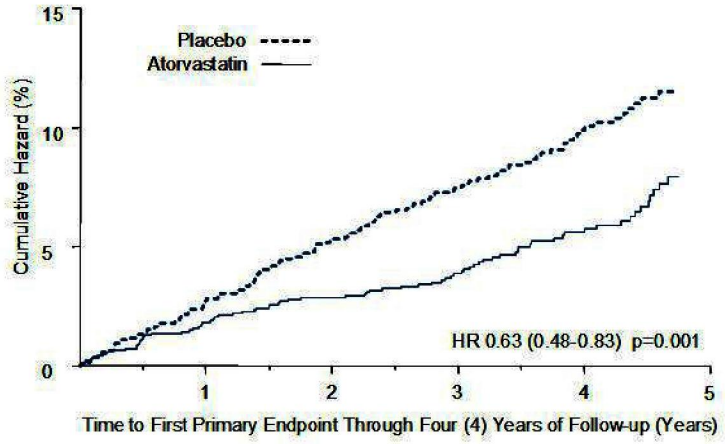
The effect of atorvastatin calcium tablets 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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

Atorvastatin calcium tablets significantly reduced the risk of stroke by 48% (21 events in the atorvastatin calcium tablets group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium tablets group vs. 64 events in the placebo 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 tablets group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

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



In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium tablets 80 mg/day vs. Atorvastatin calcium tablets 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 tablets 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium tablets and followed for a median duration of 4.9 years. The 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 tablets and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium tablets.

Treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day 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 9). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

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

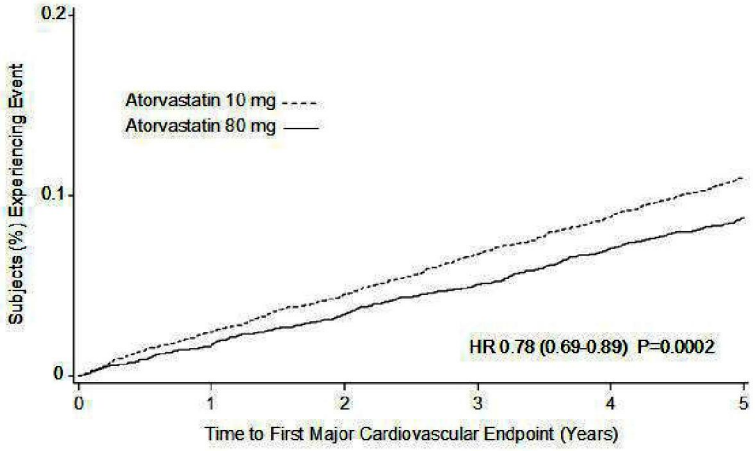


TABLE 8: Overview of Efficacy Results in TNT

Endpoint	**Atorvastatin 10 mg (N=5006)**		**Atorvastatin 80 mg (N=4995)**		**HR* (95%CI)**
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					

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

HR=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

[*] Atorvastatin 80 mg: atorvastatin 10 mg

[†] Secondary endpoints not included in primary endpoint

[‡] Component of other secondary endpoints

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin calcium tablets 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 8). Of the predefined secondary endpoints, treatment with atorvastatin calcium tablets 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 8). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium tablets 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age 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 tablets 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 tablets 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 tablets 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 tablets 80 mg group and the simvastatin 20–40 mg group.

14.2 Hyperlipidemia and Mixed Dyslipidemia

Atorvastatin calcium tablets reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb). Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin calcium tablets 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 tablets given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 9.)

TABLE 9: Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline) [*]

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

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

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median ($25^{th}$and 75^{th}percentile) percent changes from baseline in HDL-C for atorvastatin calcium tablets 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), 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 tablets was compared to other statins. After randomization, patients were treated for 16 weeks with either atorvastatin calcium tablets 10 mg per day or a fixed dose of the comparative agent (Table 10).

TABLE 10: Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

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

[*] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

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

‡ Significantly different from pravastatin, ANCOVA, p≤0.05
§ Significantly different from simvastatin, ANCOVA, p≤0.05

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

14.3 Hypertriglyceridemia

The response to atorvastatin calcium tablets in 64 patients with isolated hypertriglyceridemia (*Fredrickson* Type IV) treated across several clinical trials is shown in the table below (Table 11). For the atorvastatin calcium tablets-treated patients, median (min, max) baseline TG level was 565 (267–1502).

TABLE 11: Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

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

14.4 Dysbetalipoproteinemia

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 12).

TABLE 12: Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

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

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 years to 37 years with HoFH received maximum daily doses of 20 to 80 mg of atorvastatin calcium tablets. The mean LDL-C reduction in this study was 18%. Twenty-five patients 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 post-menarchal girls 10 years to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia, were randomized to atorvastatin calcium tablets (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium tablets 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 tablets group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium tablets (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium tablets-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin calcium tablets significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 13).

TABLE 13: Lipid-altering Effects of Atorvastatin Calcium Tablets in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

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

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0 242.0 mg/dL) in the atorvastatin calcium tablets group compared to 228.5 mg/dL (range: 152.0 385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

Atorvastatin was also studied in a three year open-label, uncontrolled trial that included 163 patients with HeFH who were 10 years to 15 years old (82 boys and 81 girls). All patients had a clinical diagnosis of HeFH confirmed by genetic analysis (if not already confirmed by family history). Approximately 98% were Caucasian, and less than 1% were Black or Asian. Mean LDL-C at baseline was 232 mg/dL. The starting atorvastatin dosage was 10 mg once daily and doses were adjusted to achieve a target of < 130 mg/dL LDL-C. The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous clinical studies in both adult and pediatric placebo-controlled trials.

The long-term efficacy of atorvastatin calcium tablets therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

10 mg tablets (10 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-016-01 bottles of 90, coded "I" on one side.
20 mg tablets (20 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-017-01 bottles of 90, coded "II" on one side.
40 mg tablets (40 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-018-01 bottles of 90, coded "III" on one side.
80 mg tablets (80 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-019-01 bottles of 90, coded "IIII" on one side.

Storage

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

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

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

17.1 Muscle Pain

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

17.2 Liver Enzymes

It is recommended that liver enzyme tests be performed before the initiation of atorvastatin calcium tablets and if signs or symptoms of liver injury occur. All patients treated with atorvastatin calcium tablets should be advised to report promptly

any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

17.3 Embryofetal Toxicity

Advise females of reproductive potential of the risk to a fetus, to use effective contraception during treatment and to inform their healthcare provider of a known or suspected pregnancy *[see Contraindications (4) and Use in Specific Populations (8.1, 8.3)]*.

17.4 Lactation

Advise women not to breastfeed during treatment with atorvastatin calcium tablets *[see Contraindications (4) and Use in Specific Populations (8.2)]*.

Manufactured by: Lepu Pharmaceutical Technology Co., Ltd.

No. 27 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province. P.R. China 318000

Patient Information

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

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

What is Atorvastatin Calcium Tablets?

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

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

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

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

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

Atorvastatin calcium tablets 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 Tablets?

Do not take atorvastatin calcium tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium tablets may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast feeding. Atorvastatin calcium tablets can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

Atorvastatin calcium tablets dosing has not been established in children under 10 years of age.

Before You Start Atorvastatin Calcium Tablets

Tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

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

- your immune system

- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS
- hepatitis C virus
- anti-virals

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

How Should I Take Atorvastatin Calcium Tablets?

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

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

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

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

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

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

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking atorvastatin calcium tablets. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

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

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

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

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

How do I store Atorvastatin Calcium Tablets

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

General Information About Atorvastatin Calcium Tablets

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

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals. Or you can contact Lepu Pharmaceutical Technology Co., Ltd. with 1-908-273-1303.

What are the Ingredients in Atorvastatin Calcium Tablets?

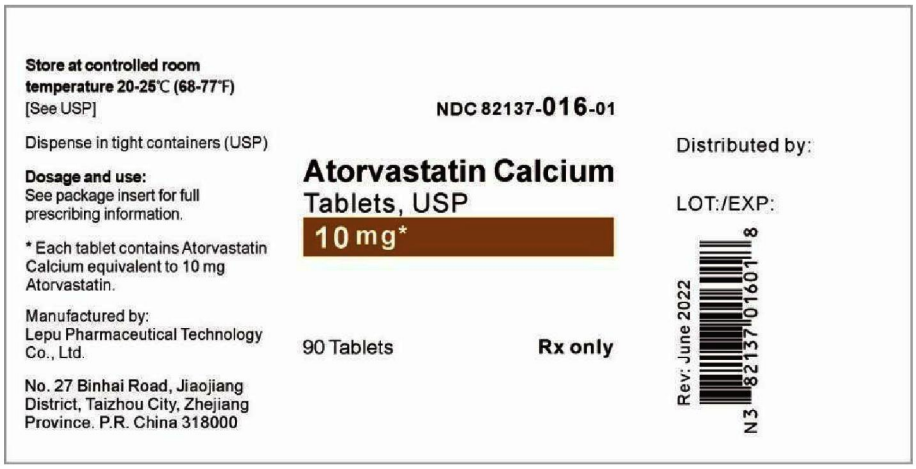
Active Ingredient: atorvastatin calcium

Inactive Ingredients:

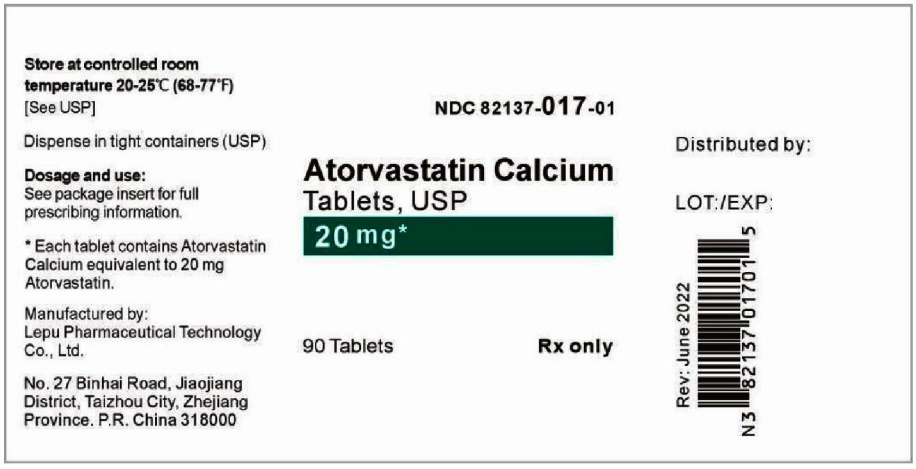
calcium carbonate, USP; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040-CN (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF.

1.14.1.1 Draft Carton and Container Labels

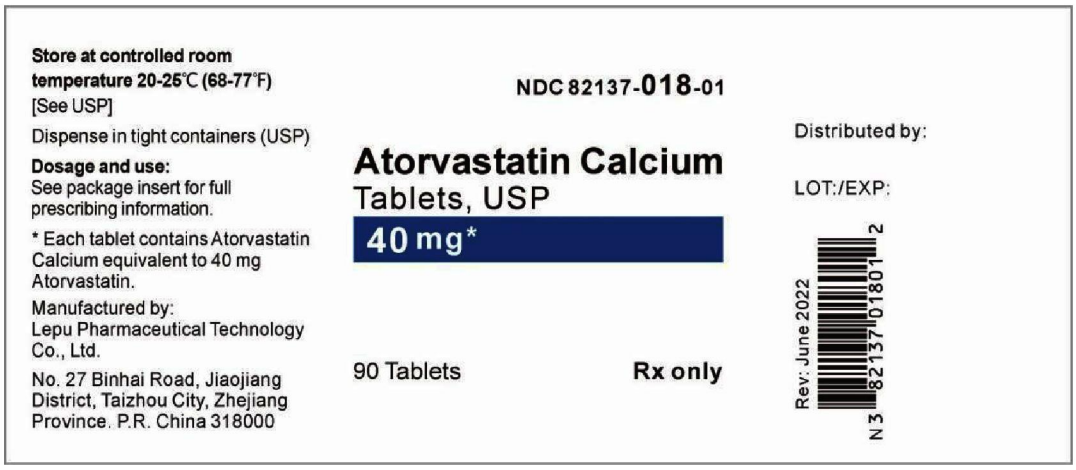
Content:
Container Label of Strength: 10 mg * 90 tablets (b) (4)
83mm×42mm



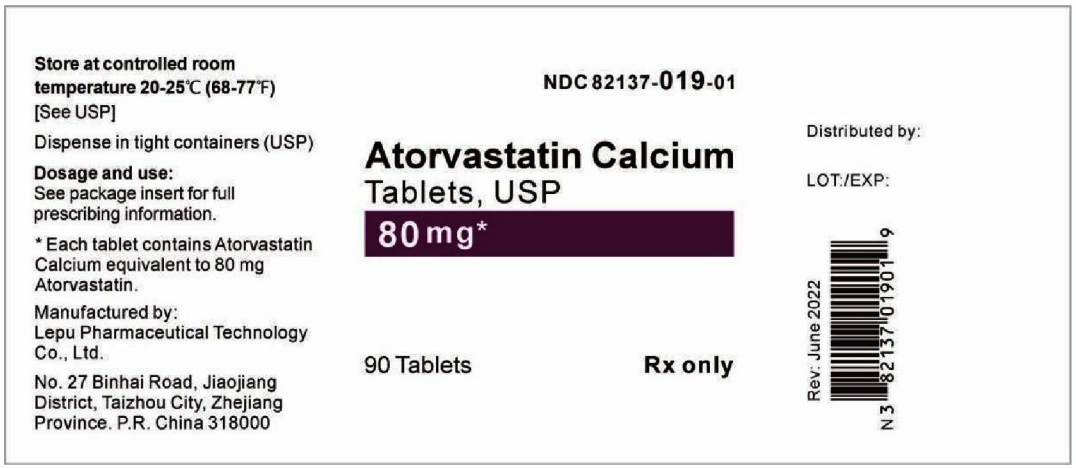
Container Label of Strength: 20 mg * 90 tablets (b) (4)
83mm×42mm



Container Label of Strength: 40 mg * 90 tablets (b) (4)
100mm×43mm



Container Label: Strength of 80 mg * 90 tablets (b) (4)
116mm×50mm



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216848

LABELING REVIEW(s)

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	10/17/2022
ANDA Number(s)	216848
Review Number	3
Applicant Name	Lepu Pharmaceutical Technology Co., Ltd.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg
Proposed Proprietary Name	N/A
Submission Received Date	September 30, 2022
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☐ Acceptable - No Comments
☒ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C3)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C3)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received September 30, 2022.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C3)

(b) (4)

[redacted]

2 INSTRUCTIONS FOR ASSESSMENT (C3)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

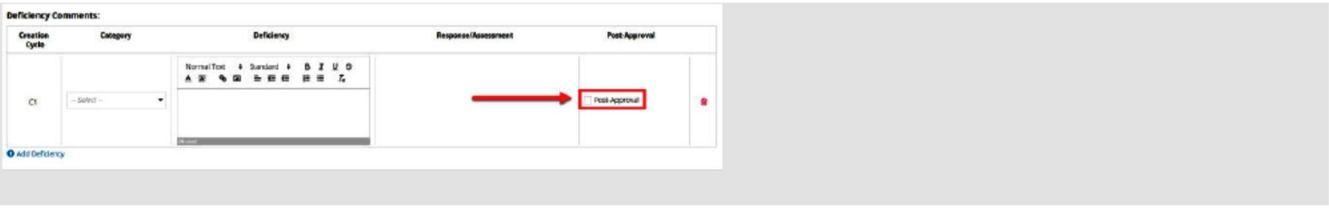
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C3)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	10 mg, 20 mg, 40 mg, and 80 mg bottles of 90s	06/13/2022	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised 06/2022	09/30/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Draft	None	09/30/2022	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C3)

4.1 REGULATORY INFORMATION (C3)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? (b) (4) [redacted]
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C3)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA020702 / S-077

Supplement Approval Date: 11/16/2020

Proprietary Name: Lipitor

Established Name: Atorvastatin Calcium Tablets

Description of Supplement:

This Prior Approval sNDA provides for revisions in the Prescribing Information (PI) with information regarding potential drug interactions between atorvastatin and HCV NS5A/NS5B inhibitors. In addition, the Warnings and Precautions for Myopathy and Rhabdomyolysis and Drug Interactions sections were updated to more clearly communicate the risk and mitigation information.

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
LIPITOR	ATORVASTATIN CALCIUM	EQ 10MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
LIPITOR	ATORVASTATIN CALCIUM	EQ 20MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
LIPITOR	ATORVASTATIN CALCIUM	EQ 40MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
LIPITOR	ATORVASTATIN CALCIUM	EQ 80MG BASE	TABLET;ORAL	Prescription	AB	Yes	Yes

Link: https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4701571_4290112_090140af805ad954_NDA020702_3105282

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

BPCA carve-out expired (see Regulatory Information section 4.1 above)

S-079 is pending (5/24/2021) and will impact labeling; no recent activity on this supplement so this approval does not appear to be imminent; goal date per DARRTS is 11/24/2021
This supplemental application proposes the following updates to the prescribing information for Lipitor:
- Revisions to Section 8 – Use in Special Populations
- Revisions to Section 17 – Patient Counseling Information

S-080 is a CMC supplement with no impact to labeling

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:
Proposed ANDA model labeling from RLD NDA 020702 S-077 (approved 11/16/2020); also note that there have been some additional changes to the RLD's current in-use labeling that are annual reportable in nature and the ANDA has incorporated those changes as well.

The following recommendations were issued after the C1 review:

(b) (4)

2. PRESCRIBING INFORMATION

a. GENERAL

i. (b) (4)

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

iii. Ensure there is adequate space between text, symbols and numerals throughout the Prescribing Information. (b) (4)

b. HIGHLIGHTS OF PRESCRIBING INFORMATION

i. (b) (4)

ii. Revise the Limitation statement and Title (as shown below) to be in accordance with the Guidance for Industry – Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements:

These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.

ATORVASTATIN CALCIUM tablets, for oral use
Initial U.S. Approval: 1996

iii. ADVERSE REACTIONS: Revise the contact phone number (b) (4) to a U.S. phone number.

iv. (b) (4)

v.

vi.

c. (b) (4)

d. DRUG INTERACTIONS, section 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets, Table 4, last sentence in Clinical Impact section: Revise (b) (4) to "atorvastatin".

e. DESCRIPTION: Indicate as the last paragraph of the DESCRIPTION section (b) (4) , "FDA approved dissolution test specifications differ from USP" at the end of the DESCRIPTION section. We refer you to the USP monograph for your drug product.

f. CLINICAL PHARMACOLOGY, section 12.3 Pharmacokinetics, subsection Specific Populations, Drug Interactions, Table 6: Conduct editorial revisions within the table to revise symbols to superscript. For example, revise "Tipranavir 500 mg BID§" to "Tipranavir 500 mg BID^§".

g. CLINICAL STUDIES
   i. section 14.1 Prevention of Cardiovascular Disease, Figure 3: Revise (b) (4) to "Atorvastatin 80 mg" and "Atorvastatin 10 mg" in accordance with the RLD.
   ii. section 14.1 Prevention of Cardiovascular Disease, Table 8, column 1, last row: Add a space between "othertraumatic" (i.e. other traumatic).
   iii. section 14.1 Prevention of Cardiovascular Disease, Table 8, footnotes section: Add the statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" to a new line below "CABG: coronary artery bypass graft" in accordance with the RLD.

h. (b) (4)

i. HOW SUPPLIED/ STORAGE AND HANDLING: Add the product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).

j. Manufacturer/Distributor/Packager: Add manufacturer information (e.g., name and location of business) per 21 CFR 201.1 and 21 CFR 201.100(e) after the PATIENT COUNSELING INFORMATION section.

3. PATIENT INFORMATION LEAFLET

a. Section entitled "What is Cholesterol?", 4th sentence: Revise (b) (4) to "…or if heart disease starts early in your family." in accordance with the RLD.

b. Section entitled "How Should I Take Atorvastatin Calcium Tablets?",
   i. Add a bullet to the first paragraph in accordance with the RLD.
   ii. (b) (4) Don't break Atorvastatin Calcium Tablets tablets before taking."
   iii. Create a line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." in accordance with the RLD.

c. section entitled "How do I store Atorvastatin Calcium Tablets?", 3rd bullet: Bold the statement "**Keep Atorvastatin Calcium Tablets and all medicines out of the reach of children**." in accordance with the RLD.

d. section entitled "General Information About Atorvastatin Calcium Tablets": Revise the contact phone number (b) (4) to a U.S. phone number.

e. section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?", Inactive Ingredients section: Revise (b) (4) lactose monohydrate in the list of inactive ingredients to be consistent with the information provided in your Quality submission.

The Applicant submitted revised (b) (4), Prescribing Information and Patient Information as requested.

Update 10/17/2022:

The following deficiencies were identified during the C2 review and will be requested for the Applicant to make as post-approval revisions:

(b) (4)

Furthermore, on 09/29/2022, the Biopharmaceutics discipline issued the following IR in regards to the dissolution for the drug product:

A. Biopharmaceutics

(b) (4)

, include the following statement in the description section on Labeling: "FDA approved dissolution test specifications differ from the USP."

On 09/30/2022, the Applicant provided their response and submitted revised Prescribing Information to address the Biopharmaceutics deficiency:

(b) (4)

Furthermore we have updated the relevant content of the ANDA, the prescription information refers to draft-labeling-text and the comparison summary between RLD and our product refers to 1.14.3.1 Annotated Comparison with Listed Drug and draft-labeling-text-noted.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C3)

The Orange Book was searched on 10/17/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA020702) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The USP was searched on 05/12/2022

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	Yes	[redacted]	Atorvastatin Calcium Tablets	ADDITIONAL REQUIREMENTS [redacted] (b) (4)
Not Yet Official	No	[redacted]	N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

From C1 Review:

[redacted] (b) (4)

Update 08/09/2022: [redacted] (b) (4)

Dissolution Method
[Deficiency/IR] (b) (4)

The Applicant provided a response to the deficiency on 08/02/2022. The Biopharmaceutics review of the Applicants response is pending. We defer to Biopharmaceutics on the final acceptability of the dissolution method.

The Applicant addressed all of our recommendations. The revisions are acceptable.

Update 10/17/2022:
Biopharmaceutics sent an IR to the Applicant on 09/23/2022 recommending a different dissolution method which differs from USP monograph. In their 09/27/2022 response, the Applicant accepted the FDA recommendations. Biopharmaceutics also requested that the Applicant initiate a revision to the Atorvastatin Calcium Tablets USP monograph under the USP Pending Monograph process and revise their labeling to include "FDA approved dissolution test specifications differ from the USP." The Applicant has agreed and revised the labeling and the biopharmaceutics review has found the application approvable.

Biopharmaceutics Executive Summary

This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed in-vitro dissolution method as a quality control test (QC) and the acceptance criterion for the proposed drug product. (b) (4)

Based on the totality of the information, the final dissolution method with lower paddle speed [using USP Apparatus 2 (paddle) at 60 RPM, 900 mL of 0.05 M phosphate buffer, pH 6.8] with an acceptance criterion of Q=80% in 30 minutes] was recommended for the proposed product in an IR on 9/23/2022.

The Applicant accepted FDA's recommendations in the response submitted on 09/27/2022. (b) (4)

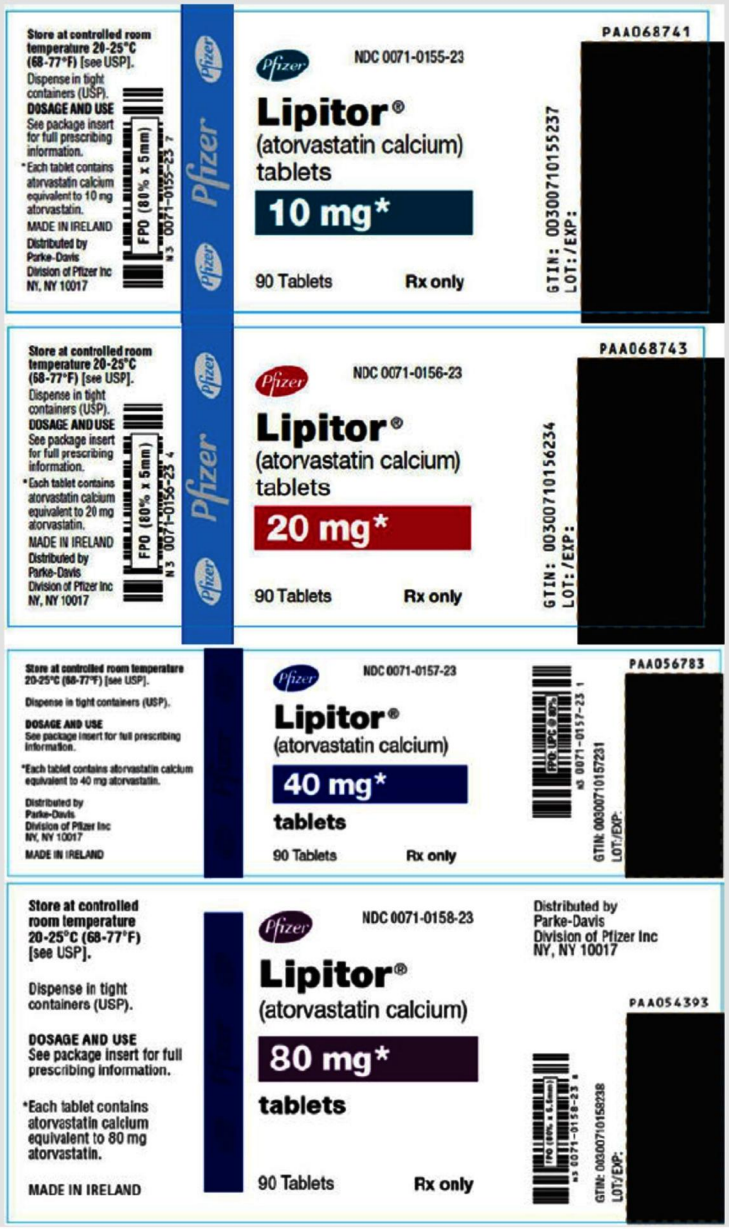
The recommended dissolution method for the drug product, differs from the method described in the USP monograph for *Atorvastatin Calcium Tablets*. *Therefore, the Applicant was notified on 9/28/2022 to petition USP for the revision of official monograph.*

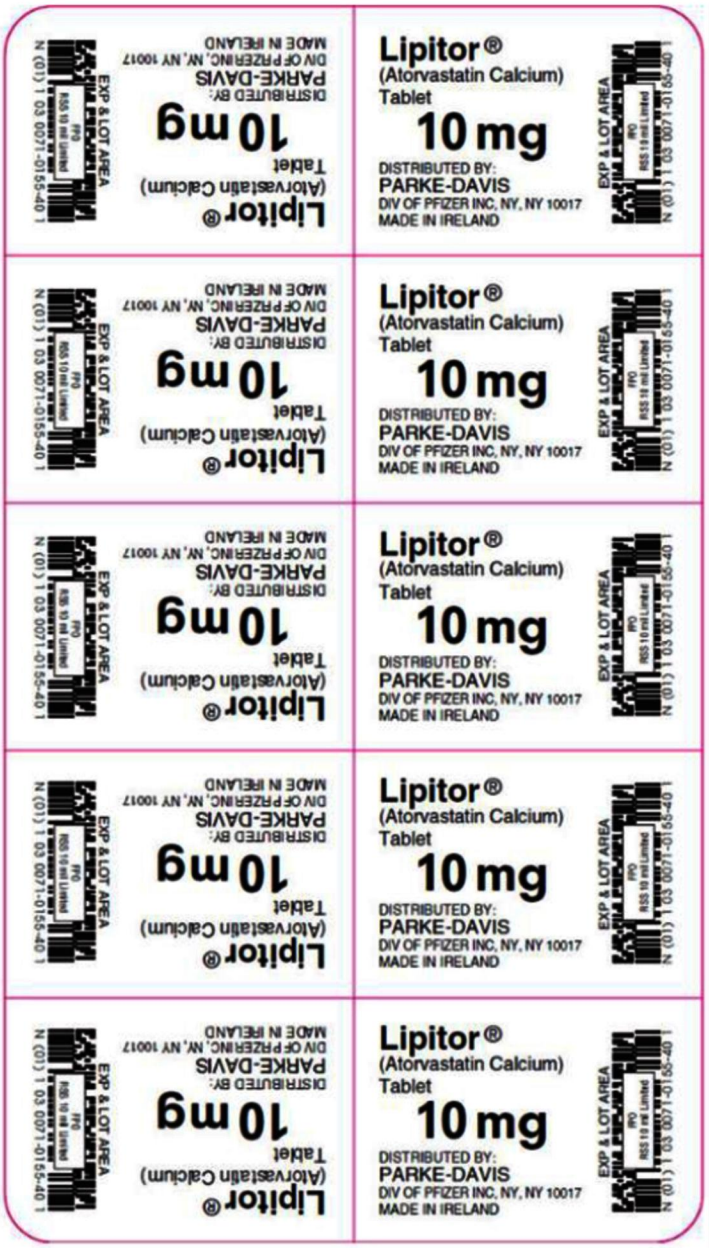
Recommendation: From a Biopharmaceutics perspective, **ANDA 216848** for the proposed Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 mg and 80 mg is recommended for **APPROVAL**.

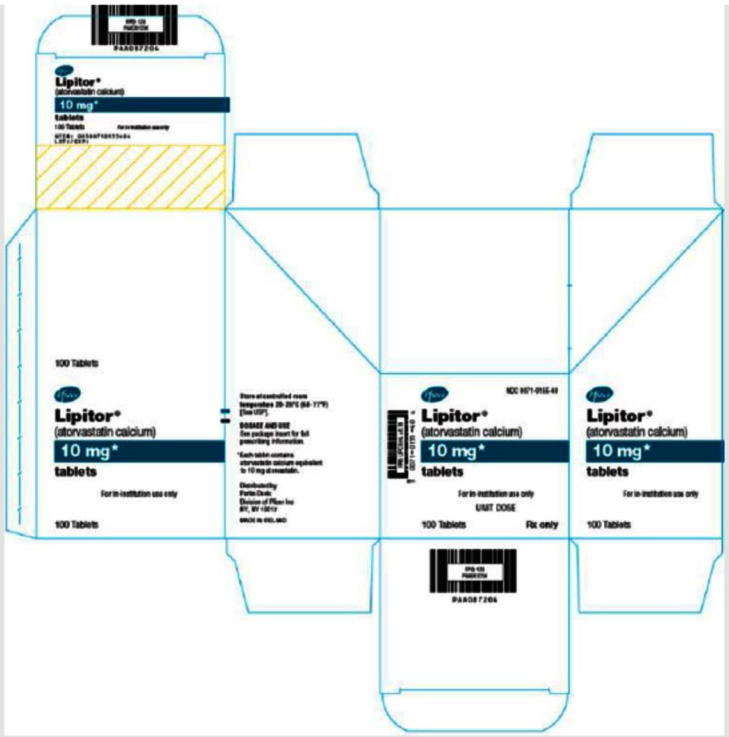
Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C3)

Model container/carton/blister labels (Source: annual report-27, dated 12/20/2021, SPL link from Summary of labeling changes document; included only 90-count container labels for each strength and one representative foil blister and carton labeling **)**


Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.
MADE IN IRELAND
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
NDC 0071-0155-23
Lipitor®
(atorvastatin calcium)
tablets
10 mg*
90 Tablets
Rx only
PAA068741
GTIN: 00300710155237
LOT:/EXP:
Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.
MADE IN IRELAND
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
NDC 0071-0156-23
Lipitor®
(atorvastatin calcium)
tablets
20 mg*
90 Tablets
Rx only
PAA068743
GTIN: 00300710156234
LOT:/EXP:
Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
MADE IN IRELAND
NDC 0071-0157-23
Lipitor®
(atorvastatin calcium)
40 mg*
tablets
90 Tablets
Rx only
PAA056783
GTIN: 00300710157231
LOT/EXP:
Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.
MADE IN IRELAND
NDC 0071-0158-23
Lipitor®
(atorvastatin calcium)
80 mg*
tablets
90 Tablets
Rx only
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
PAA054393
GTIN: 00300710158238
LOT/EXP:


Lipitor®
(Atorvastatin Calcium)
Tablet
10 mg
DISTRIBUTED BY:
PARKE-DAVIS
DIV OF PFIZER INC, NY, NY 10017
MADE IN IRELAND
EXP & LOT AREA



5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

Review finalized in Panorama on 06/13/2022:

Labeling	
Description Section	
Is the information accurate?	No

Comment
(b) (4) [redacted]

Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Yes

For Solid Oral Drug Product:		
ANDA Strength	Length(mm)	Imprint Code
Atorvastatin Calcium 10mg	8.5	"I"
Atorvastatin Calcium 20mg	12.2	"II"
Atorvastatin Calcium 40mg	15.4	"III"
Atorvastatin Calcium 80mg	19.1	"IIII"
Is the imprint code consistent with the labeling?	Yes	
Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	Yes	

AD	Reviewer Evaluation
No	(b) (4) [redacted]

The above deficiency was sent to the Applicant on 07/08/2022. The Applicant responded to the deficiency in their response and revised labeling submitted on 08/05/2022:

Response:

The chemical name of API in description of labeling (section 11) has been updated as [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) (b) (4) [redacted]

The response and revision is acceptable from a labeling perspective.

Update 10/17/2022: The DP review was updated on 10/14/2022 and the application is found to be adequate from DP review perspective. However, no changes were made to the labeling section of the review.

5.1.2 DESCRIPTION (C3)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	LIPITOR Tablets for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP;

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.
Previous ANDA Labeling	Atorvastatin calcium tablets, USP for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040-CN (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF. Reviewer assessment: 08/09/2022: In response to our C1 review recommendation, the Applicant revised [redacted] (b) (4) "lactose monohydrate" to be consistent with the quality submission. This revision is acceptable.
Current ANDA Labeling	Atorvastatin calcium tablets, USP for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040-CN (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF. FDA approved dissolution test specifications differ from the USP. Reviewer Assessment: 10/17/2022: In response to the biopharmaceutics review IR, the Applicant updated the Description section of the PI to include the statement "FDA approved dissolution test specifications differ from the USP." This revision is acceptable.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 10 mg tablets (10 mg of atorvastatin): coded “PD 155” on one side and “10” on the other. NDC 0071-0155-23 bottles of 90 NDC 0071-0155-34 bottles of 5000 NDC 0071-0155-40 10 x 10 unit dose blisters NDC 0071-0155-10 bottles of 1000 20 mg tablets (20 mg of atorvastatin): coded “PD 156” on one side and “20” on the other. NDC 0071-0156-23 bottles of 90 NDC 0071-0156-40 10 x 10 unit dose blisters NDC 0071-0156-94 bottles of 5000 NDC 0071-0156-10 bottles of 1000

Table 8: Comparison of Model Labeling to ANDA Labeling	
	40 mg tablets (40 mg of atorvastatin): coded "PD 157" on one side and "40" on the other. NDC 0071-0157-23 bottles of 90 NDC 0071-0157-73 bottles of 500 NDC 0071-0157-88 bottles of 2500 NDC 0071-0157-40 10 x 10 unit dose blisters 80 mg tablets (80 mg of atorvastatin): coded "PD 158" on one side and "80" on the other. NDC 0071-0158-23 bottles of 90 NDC 0071-0158-73 bottles of 500 NDC 0071-0158-88 bottles of 2500 NDC 0071-0158-92 8 x 8 unit dose blisters Storage Store at controlled room temperature 20 -25°C (68 -77°F) [see USP].
Previous ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** 10 mg tablets (10 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-016-01 bottles of 90, coded "l" on one side. 20 mg tablets (20 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-017-01 bottles of 90, coded "l l" on one side. 40 mg tablets (40 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-018-01 bottles of 90, coded "l l l" on one side. 80 mg tablets (80 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-019-01 bottles of 90, coded "l l l l" on one side. Storage Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP]. Reviewer Assessment: 08/09/2022: In response to our recommendations, Applicant added product descriptions for each strength. The revisions are acceptable.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** 10 mg tablets (10 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-016-01 bottles of 90, coded "l" on one side. 20 mg tablets (20 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-017-01 bottles of 90, coded "l l" on one side. 40 mg tablets (40 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-018-01 bottles of 90, coded "l l l" on one side. 80 mg tablets (80 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-019-01 bottles of 90, coded "l l l l" on one side. Storage Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP]. Reviewer Assessment: 10/17/2022: No changes from previous labeling

5.1.4 **MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C3)**

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Lepu Pharmaceutical Technology Co., Ltd. No. 27 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province. P.R. China 318000 Update 08/09/2022: In response to our recommendation, Applicant added the manufacturer information to the labeling. The revision is acceptable.
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Lepu Pharmaceutical Technology Co., Ltd. No. 27 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province. P.R. China 318000 Update 10/17/2022: No change from previous labeling

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:

Deficiency	No Deficiency	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(j)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Title case is used in expressing the established/proprietary name.

(b) (4)

[redacted]

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Update 08/10/2022: The Applicant addressed all of our recommendations. The revised Prescribing Information is acceptable.

Update 10/17/2022: The Applicant addressed the biopharmaceutics IR and revised the Description section of the PI to include "FDA approved dissolution test
specifications differ from the USP." The Biopharmaceutics reviewer has found this to be acceptable.

Deficiency Comments:

5.4 OTHER PATIENT LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Update 08/10/2022: The Applicant addressed all of our recommendations. The revised Patient Information is acceptable.

Update 08/23/2022: [redacted] (b) (4)

Update 10/17/2022: Post-approval comments to be sent to the Applicant during review of their first supplement.

Deficiency Comments:

Deficiency # 1 [redacted] (b) (4)

Created in C3

Patient Information Leaflet
Response / Assessment:

Deficiency # 2 [redacted] (b) (4)

Created in C3

Patient Information Leaflet
Response / Assessment:

Deficiency # 3 [redacted] (b) (4)

Created in C2

Patient Information Leaflet
Response / Assessment: [redacted] (b) (4)

Deficiency # 4 [redacted] (b) (4)

Created in C2

Patient Information Leaflet
Response / Assessment: [redacted] (b) (4)

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex

☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

- On 5/20/2022 [redacted] (b) (4) [redacted]. Issue has been resolved.

[redacted] (b) (4)

Update 08/10/2022: The Applicant revised the chemical name in their 08/02/2022 response to the Drug Product Reviewer recommendation:

[redacted] (b) (4)

Response:

The chemical name of API in description of labeling (section 11) has been updated as [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) [redacted] (b) (4) [redacted] (b) (4) [redacted]

- On 5/26/2022 sent a follow-up to the Drug Product reviewer's Issue to notify them of an identified discrepancy between [redacted] (b) (4)

[redacted] (b) (4)

Update 08/10/2022: The Applicant revised the inactive ingredient [redacted] (b) (4) to "lactose monohydrate" in the Description section of the PI. This is acceptable.

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 10/18/2022 03:34:43PM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 10/18/2022 03:35:45PM
GUID: 5256bdc00002af3bc3fa942a9512a891

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	08/09/2022
ANDA Number(s)	216848
Review Number	2
Applicant Name	Lepu Pharmaceutical Technology Co., Ltd.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg
Proposed Proprietary Name	N/A
Submission Received Date	June 13, 2022, August 05, 2022
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☐ Acceptable - No Comments
☒ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C2)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C2)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C2)

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received June 13, 2022, August 05, 2022.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C2)

These comments will be addressed post approval (in the first labeling supplement review).

(b) (4)

[redacted]

2 INSTRUCTIONS FOR ASSESSMENT (C2)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

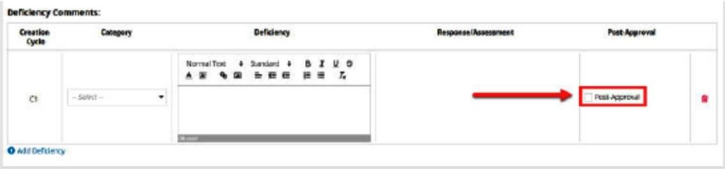
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C2)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	10 mg, 20 mg, 40 mg, and 80 mg bottles of 90s	06/13/2022	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 06/2022	08/05/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Draft	None	08/05/2022	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C2)

4.1 REGULATORY INFORMATION (C2)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? (b) (4) [redacted]
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C2)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA020702 / S-077

Supplement Approval Date: 11/16/2020

Proprietary Name: Lipitor

Established Name: Atorvastatin Calcium Tablets

Description of Supplement:

This Prior Approval sNDA provides for revisions in the Prescribing Information (PI) with information regarding potential drug interactions between atorvastatin and HCV NS5A/NS5B inhibitors. In addition, the Warnings and Precautions for Myopathy and Rhabdomyolysis and Drug Interactions sections were updated to more clearly communicate the risk and mitigation information.

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4701571_4290112_090140af805ad954_NDA020702_3105282

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

BPCA carve-out expired (see Regulatory Information section 4.1 above)

S-079 is pending (5/24/2021) and will impact labeling; no recent activity on this supplement so this approval does not appear to be imminent; goal date per DARRTS is 11/24/2021
This supplemental application proposes the following updates to the prescribing information for Lipitor:
- Revisions to Section 8 – Use in Special Populations
- Revisions to Section 17 – Patient Counseling Information

S-080 is a CMC supplement with no impact to labeling

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:
Proposed ANDA model labeling from RLD NDA 020702 S-077 (approved 11/16/2020); also note that there have been some additional changes to the RLD's current in-use labeling that are annual reportable in nature and the ANDA has incorporated those changes as well.

The following recommendations were issued after the C1 review:

(b) (4)

2. PRESCRIBING INFORMATION

a. GENERAL

i. (b) (4)

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

iii. Ensure there is adequate space between text, symbols and numerals throughout the Prescribing Information. (b) (4)
(b) (4)

b. HIGHLIGHTS OF PRESCRIBING INFORMATION

i. (b) (4)

ii. Revise the Limitation statement and Title (as shown below) to be in accordance with the Guidance for Industry – Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements:

These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.

ATORVASTATIN CALCIUM tablets, for oral use
Initial U.S. Approval: 1996

iii. ADVERSE REACTIONS: Revise the contact phone number (b) (4) to a U.S. phone number.

iv. (b) (4) [redacted]

v. [redacted]

vi. [redacted]

c. (b) (4) [redacted]

d. DRUG INTERACTIONS, section 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets, Table 4, last sentence in Clinical Impact section: Revise (b) (4) [redacted] to "atorvastatin".

e. DESCRIPTION: Indicate as the last paragraph of the DESCRIPTION section (b) (4) [redacted], "FDA approved dissolution test specifications differ from USP" at the end of the DESCRIPTION section. We refer you to the USP monograph for your drug product.

f. CLINICAL PHARMACOLOGY, section 12.3 Pharmacokinetics, subsection Specific Populations, Drug Interactions, Table 6: Conduct editorial revisions within the table to revise symbols to superscript. For example, revise "Tipranavir 500 mg BID§" to "Tipranavir 500 mg BID^§".

g. CLINICAL STUDIES
   i. section 14.1 Prevention of Cardiovascular Disease, Figure 3: Revise (b) (4) [redacted] to "Atorvastatin 80 mg" and "Atorvastatin 10 mg" in accordance with the RLD.
   ii. section 14.1 Prevention of Cardiovascular Disease, Table 8, column 1, last row: Add a space between "othertraumatic" (i.e. other traumatic).
   iii. section 14.1 Prevention of Cardiovascular Disease, Table 8, footnotes section: Add the statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" to a new line below "CABG: coronary artery bypass graft" in accordance with the RLD.

h. (b) (4) [redacted]

i. HOW SUPPLIED/ STORAGE AND HANDLING: Add the product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).

j. Manufacturer/Distributor/Packager: Add manufacturer information (e.g., name and location of business) per 21 CFR 201.1 and 21 CFR 201.100(e) after the PATIENT COUNSELING INFORMATION section.

3. PATIENT INFORMATION LEAFLET
   a. Section entitled "What is Cholesterol?", 4th sentence: Revise (b) (4) to "…or if heart disease starts early in your family." in accordance with the RLD.

   b. Section entitled "How Should I Take Atorvastatin Calcium Tablets?",
      i. Add a bullet to the first paragraph in accordance with the RLD.
      ii. (b) (4) Don't break Atorvastatin Calcium Tablets tablets before taking."
      iii. Create a line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." in accordance with the RLD.

   c. section entitled "How do I store Atorvastatin Calcium Tablets?", 3rd bullet: Bold the statement "**Keep Atorvastatin Calcium Tablets and all medicines out of the reach of children**." in accordance with the RLD.

   d. section entitled "General Information About Atorvastatin Calcium Tablets": Revise the contact phone number (b) (4) to a U.S. phone number.

   e. section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?", Inactive Ingredients section: Revise (b) (4) lactose monohydrate in the list of inactive ingredients to be consistent with the information provided in your Quality submission.

The Applicant submitted revised (b) (4) Prescribing Information and Patient Information as requested.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C2)

The Orange Book was searched on 08/09/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA020702) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C2)

The USP was searched on 05/12/2022

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	Yes	[redacted]	Atorvastatin Calcium Tablets	(b) (4) [redacted]
Not Yet Official	No	[redacted]	N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: From C1 Review:		

The DESCRIPTION section of the labeling is silent with respect to which dissolution test the drug product meets which implies that it meets Test 1. As the Biopharmaceutics Review is still pending, we will issue the following Standard Comment at this time.

Update 08/09/2022: The Applicant confirmed that USP Test 1 was utilized and therefore, no updates were made to the Description section of the Prescribing Information. However, the Biopharmaceutics review was completed on 07/07/2022 and found the dissolution testing to be inadequate. The following deficiency was issued to the Applicant regarding the dissolution method:

Dissolution Method
[Deficiency/IR]
(b) (4) [redacted]

The Applicant provided a response to the deficiency on 08/02/2022. The Biopharmaceutics review of the Applicants response is pending. We defer to Biopharmaceutics on the final acceptability of the dissolution method.

The Applicant addressed all of our recommendations. The revisions are acceptable.

Deficiency Comments:

Deficiency # 1

Created in C1

Prescribing Information

Response / Assessment:

(b) (4) [redacted]

Assessment: Acceptable from a labeling perspective. However, biopharmaceutics has issued a deficiency regarding the adequacy of the dissolution testing. Therefore, we defer to biopharmaceutics reviewer for final acceptability of the dissolution test.

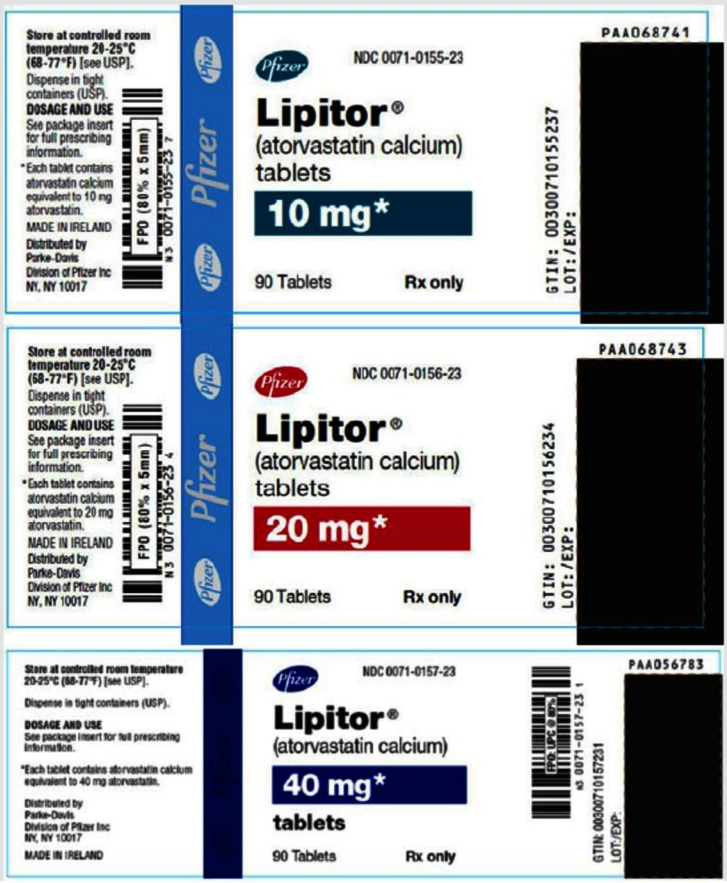
Deficiency # 2

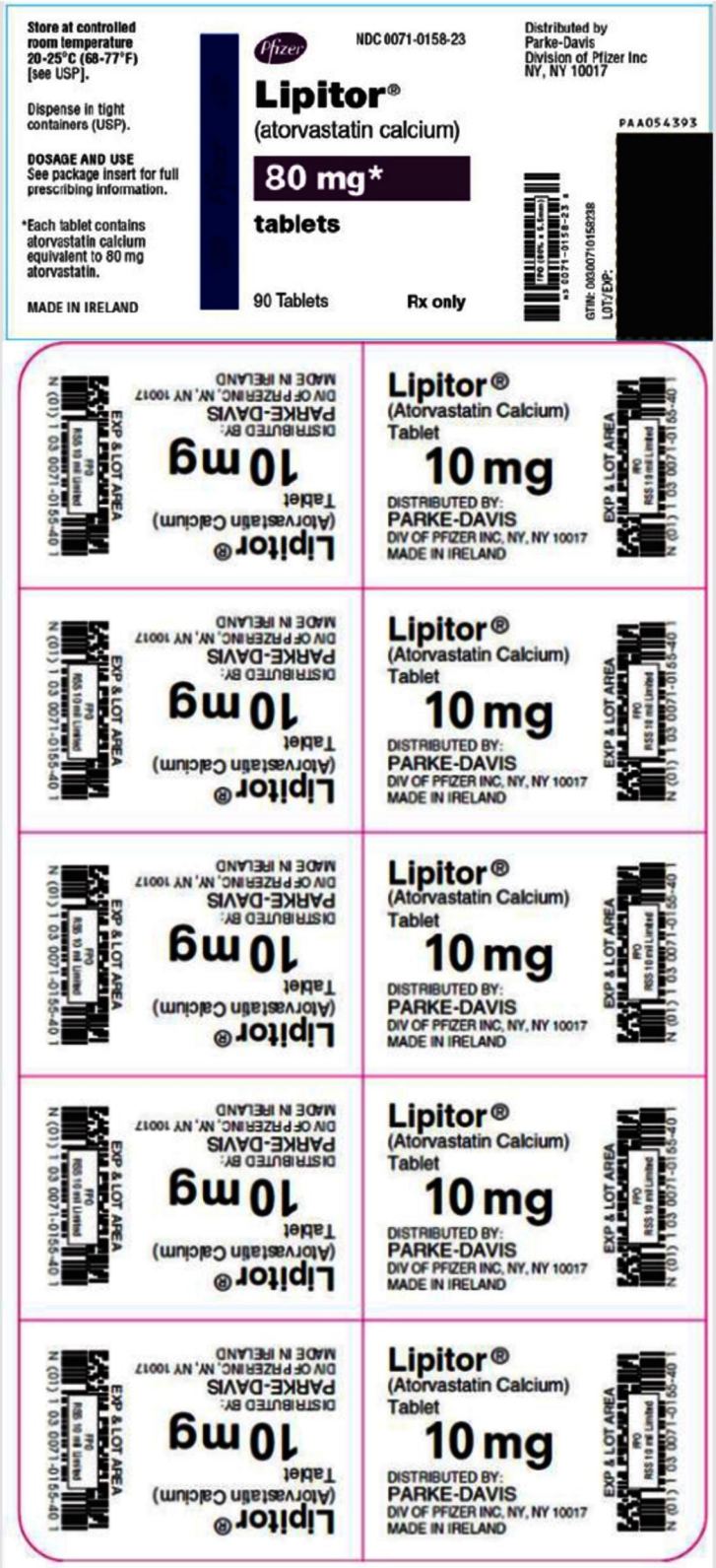
(b) (4) [redacted]

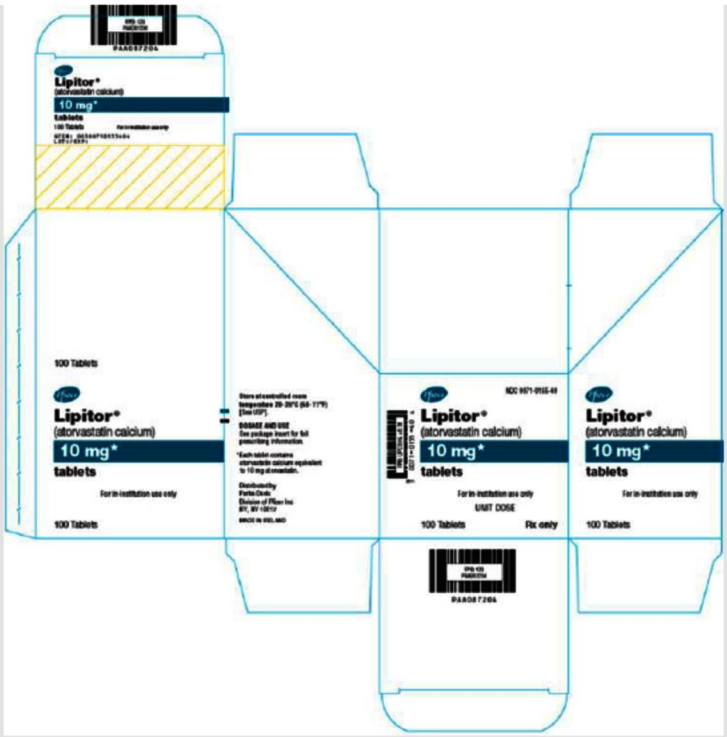
Created in C1 Container Label Response / Assessment:	(b) (4) [redacted] **Assessment:** Acceptable.
Deficiency # 3 Created in C1 Prescribing Information Response / Assessment:	(b) (4) [redacted] **Assessment:** Acceptable.

4.5 MODEL CONTAINER LABELS (C2)

Model container/carton/blister labels (Source: annual report-27, dated 12/20/2021, SPL link from Summary of labeling changes document; included only 90-count container labels for each strength and one representative foil blister and carton labeling)




Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
•Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.
MADE IN IRELAND
NDC 0071-0158-23
Lipitor®
(atorvastatin calcium)
80 mg*
tablets
90 Tablets
Rx only
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
PAA054393
Lipitor®
(Atorvastatin Calcium)
Tablet
10 mg
DISTRIBUTED BY:
PARKE-DAVIS
DIV OF PFIZER INC, NY, NY 10017
MADE IN IRELAND
EXP & LOT AREA



5 ASSESSMENT OF ANDA LABELING AND LABELS (C2)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C2)

5.1.1 DRUG PRODUCT REVIEW (C2)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

Review finalized in Panorama on 06/13/2022:

Labeling	
Description Section	
Is the information accurate?	No

Comment
(b) (4) [redacted]

Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Yes

For Solid Oral Drug Product:		
ANDA Strength	Length(mm)	Imprint Code
Atorvastatin Calcium 10mg	8.5	"I"
Atorvastatin Calcium 20mg	12.2	"II"
Atorvastatin Calcium 40mg	15.4	"III"
Atorvastatin Calcium 80mg	19.1	"IIII"
Is the imprint code consistent with the labeling?	Yes	
Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	Yes	

AD	Reviewer Evaluation
No	(b) (4) [redacted]

The above deficiency was sent to the Applicant on 07/08/2022. The Applicant responded to the deficiency in their response and revised labeling submitted on 08/05/2022:

Response:

The chemical name of API in description of labeling (section 11) has been updated as [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) (b) (4) [redacted]

The response and revision is acceptable from a labeling perspective.

5.1.2 DESCRIPTION (C2)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	LIPITOR Tablets for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	dioxide); polysorbate 80, NF; simethicone emulsion.
Previous ANDA Labeling	(b) (4) [redacted]

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	(b) (4) [redacted]
Current ANDA Labeling	Atorvastatin calcium tablets, USP for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040-CN (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF. Reviewer assessment: 08/09/2022: In response to our C1 review recommendation, the Applicant revised (b) (4) [redacted] to "lactose monohydrate" to be consistent with the quality submission. This revision is acceptable.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C2)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 10 mg tablets (10 mg of atorvastatin): coded "PD 155" on one side and "10" on the other. NDC 0071-0155-23 bottles of 90 NDC 0071-0155-34 bottles of 5000 NDC 0071-0155-40 10 x 10 unit dose blisters NDC 0071-0155-10 bottles of 1000 20 mg tablets (20 mg of atorvastatin): coded "PD 156" on one side and "20" on the other. NDC 0071-0156-23 bottles of 90 NDC 0071-0156-40 10 x 10 unit dose blisters NDC 0071-0156-94 bottles of 5000 NDC 0071-0156-10 bottles of 1000 40 mg tablets (40 mg of atorvastatin): coded "PD 157" on one side and "40" on the other. NDC 0071-0157-23 bottles of 90 NDC 0071-0157-73 bottles of 500 NDC 0071-0157-88 bottles of 2500 NDC 0071-0157-40 10 x 10 unit dose blisters 80 mg tablets (80 mg of atorvastatin): coded "PD 158" on one side and "80" on the other. NDC 0071-0158-23 bottles of 90

Table 8: Comparison of Model Labeling to ANDA Labeling	
	NDC 0071-0158-73 bottles of 500 NDC 0071-0158-88 bottles of 2500 NDC 0071-0158-92 8 x 8 unit dose blisters Storage Store at controlled room temperature 20 -25°C (68 -77°F) [see USP].
Previous ANDA Labeling	(b) (4) [redacted]
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** 10 mg tablets (10 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-016-01 bottles of 90, coded "l" on one side. 20 mg tablets (20 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-017-01 bottles of 90, coded "l l" on one side. 40 mg tablets (40 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-018-01 bottles of 90, coded "l l l" on one side. 80 mg tablets (80 mg of atorvastatin): White or off-white film-coated tablets, NDC 82137-019-01 bottles of 90, coded "l l l l" on one side. Storage Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP]. Reviewer Assessment: 08/09/2022: In response to our recommendations, Applicant (b) (4) [redacted] The revisions are acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C2)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b) (4) [redacted]
Current ANDA Labeling	
Name and Address on ANDA Prescribing	Manufactured by: Lepu Pharmaceutical Technology Co., Ltd.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Information	No. 27 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province. P.R. China 318000 Update 08/09/2022: In response to our recommendation, Applicant added the manufacturer information to the labeling. The revision is acceptable.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	ESTABLISHED/PROPRIETARY NAME and STRENGTH:	
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
	THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:	
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please

Deficiency	No Deficiency	
		enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Title case is used in expressing the established/proprietary name.

(b) (4)

(b) (4)

How Supplied: The differences in package size and configuration are allowable differences.

(b) (4)

The proposed container label is inadequate and I have included several recommendations below.

Update 08/09/2022: The Applicant addressed all of our recommendations. The revised container labels are acceptable.

Deficiency Comments:

Deficiency # 1 Created in C1 Container Label	Increase the prominence of the middle digits of the NDC numbers by increasing their size in comparison to the remaining digits or putting them in bold type to help minimize the risk for medication error (e.g., XXXX-**XXXX**-XX). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf
Response / Assessment:	**Applicant Response:** The font size of middle digits of the NDC numbers were increased, and the middle digits were putted in bold type as well. Please refer to 1-14-1-1-draft-container-labeling. **Assessment:** Acceptable.
Deficiency # 2 Created in C1	Product strength: Use a method to better distinguish the 40 mg and 80 mg strengths of the drug product (e.g., boxing, contrasting colors, and/or some other means) as currently presented the proposed colors appear

Container Label	similar. Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf
Response / Assessment:	**Applicant Response:** A different boxing color (bright purple) of 80 mg strengths of the drug product was chosen to distinguish from the boxing color (dark blue) of 40 mg strengths of the drug product. Please refer to 1-14-1-1-draft-container-labeling. **Assessment:** The revised purple color for the 80 mg strength is better contrasted from the blue color used for the 40 mg strength. This revision is acceptable.
Deficiency # 3 Created in C1 Container Label	Include a statement of the place of business per 21 CFR 201.1(i).
Response / Assessment:	**Applicant Response:** The statement of the place of business which include the street address, city, country, and ZIP code was added. Please refer to 1-14-1-1-draft-container-labeling. **Assessment:** Acceptable.
Deficiency # 4 Created in C1 Container Label	Bar code: Revise the bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf
Response / Assessment:	**Applicant Response:** The bar code was revised to a vertical orientation to ensure accurate scanning to minimize medication error. Please refer to 1-14-1-1-draft-container-labeling. **Assessment:** Acceptable.

5.3 PRESCRIBING INFORMATION (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].

Deficiency	No Deficiency	
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
		HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
		HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Update 08/10/2022: The Applicant addressed all of our recommendations. The revised Prescribing Information is acceptable.

Deficiency Comments:

Deficiency # 1 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4). **Applicant Response:** [redacted] (b) (4) **Assessment:** Acceptable.
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	DRUG INTERACTIONS, section 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets, Table 4, last sentence in Clinical Impact section: Revise [redacted] (b) (4) to "atorvastatin". **Applicant Response:** The word [redacted] (b) (4) was revised to "atorvastatin". Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.

Deficiency # 3 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4) [redacted] [redacted] [redacted]". **Applicant Response:** [redacted] (b) (4) [redacted] [redacted] **Assessment:** Acceptable.
Deficiency # 4 Created in C1 Prescribing Information Response / Assessment:	CLINICAL STUDIES, section 14.1 Prevention of Cardiovascular Disease, Figure 3: Revise [redacted] (b) (4)" to "Atorvastatin 80 mg" and "Atorvastatin 10 mg" in accordance with the RLD. **Applicant Response:** The Figure 3 was revised in accordance with the RLD. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 5 Created in C1 Prescribing Information Response / Assessment:	CLINICAL STUDIES, section 14.1 Prevention of Cardiovascular Disease, Table 8, column 1, last row: Add a space between "othertraumatic" (i.e. other traumatic). **Applicant Response:** The "othertraumatic" was revised to "other traumatic". Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 6 Created in C1 Prescribing Information Response / Assessment:	CLINICAL STUDIES, section 14.1 Prevention of Cardiovascular Disease, Table 8, footnotes section: Add the statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" to a new line below "CABG: coronary artery bypass graft" in accordance with the RLD. **Applicant Response:** The statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" was added in a new line below "CABG: coronary artery bypass graft" in accordance with the RLD. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 7 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4) [redacted] **Applicant Response:** [redacted] (b) (4) [redacted] **Assessment:** Acceptable.

Deficiency # 8 Created in C1 Prescribing Information Response / Assessment:	HIGHLIGHTS, ADVERSE REACTIONS: Revise the contact phone number [redacted] (b) (4) to a U.S. phone number. **Applicant Response:** The U.S. phone number 1-908-273-1303 was added in ADVERSE REACTION. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 9 Created in C1 Prescribing Information Response / Assessment:	HIGHLIGHTS: Revision date: Include a revision date at the end of the HIGHLIGHTS section per 21 CFR 201.57(a)(15). **Applicant Response:** A revision date was added at the end of the HIGHLIGHTS section. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 10 Created in C1 Prescribing Information Response / Assessment:	HOW SUPPLIED/ STORAGE AND HANDLING: Add the product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17). **Applicant Response:** The color and coating description for atorvastatin calcium tablets were added in HOW SUPPLIED/ STORAGE AND HANDLING section. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 11 Created in C1 Prescribing Information Response / Assessment:	Manufacturer/Distributor/Packager: Add manufacturer information (e.g., name and location of business) per 21 CFR 201.1 and 21 CFR 201.100(e) after the PATIENT COUNSELING INFORMATION section. **Applicant Response:** The manufacturer name and address were added after the PATIENT COUNSELING INFORMATION section. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 12 Created in C1 Prescribing Information Response / Assessment:	GENERAL: Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the Prescribing Information. **Applicant Response:** All the USAN names in the Prescribing Information were all revised in lower case. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 13 Created in C1	GENERAL: Ensure there is adequate space between text, symbols and numerals throughout the Prescribing Information. For example, in subsection 1.2, revise "≥190 mg/dL" to "≥ 190 mg/dL" and in the

Prescribing Information	subsection 2.2 heading, revise “to17 Years” to “to 17 Years”.
Response / Assessment:	**Applicant Response:** Adequate space has been added between text, symbols and numerals throughout the Prescription Information. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 14 Created in C1 Prescribing Information	[redacted] (b) (4)
Response / Assessment:	**Applicant Response:** [redacted] (b) (4) **Assessment:** Acceptable.
Deficiency # 15 Created in C1 Prescribing Information	HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the Limitation statement and Title (as shown below) to be in accordance with the Guidance for Industry – Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements: **These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.** **ATORVASTATIN CALCIUM tablets, for oral use** **Initial U.S. Approval: 1996**
Response / Assessment:	**Applicant Response:** The Limitation statement and Title were revised. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 16 Created in C1 Prescribing Information	[redacted] (b) (4)
Response / Assessment:	**Applicant Response:** [redacted] (b) (4) **Assessment:** Acceptable.
Deficiency # 17 Created in C1 Prescribing Information	HIGHLIGHTS OF PRESCRIBING INFORMATION, DRUG INTERACTIONS table, 2nd column, 4th row: Add a space between the numerical dose and unit of measure (i.e. change "40mg" to "40 mg").
Response / Assessment:	**Applicant Response:** The space between the numerical dose and unit of measure in 2nd column, 4th row of DRUG INTERACTIONS table was

	added. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.

5.4 OTHER PATIENT LABELING (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Update 08/10/2022: The Applicant addressed all of our recommendations. The revised Patient Information is acceptable.

Update 08/23/2022: [redacted] (b) (4)

Deficiency Comments:

Deficiency # 1 Created in C1 Patient Information Leaflet Response / Assessment:	Patient Information, section entitled What is Cholesterol?, 4th sentence: Revise [redacted] (b) (4) to "…or if heart disease starts early in your family." in accordance with the RLD. **Applicant Response:** The 4th sentence in "What is Cholesterol" section was revised in accordance with the RLD. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 2 Created in C1 Patient Information Leaflet	1. "How Should I Take Atorvastatin Calcium Tablets?", 2. Add a bullet to the first paragraph in accordance with the RLD. 3. [redacted] (b) (4) 4. Create a line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." in accordance with the RLD.
Response / Assessment:	**Applicant Response:** A bullet was added to the first paragraph. Please refer to draft-labeling-text-in-pdf. [redacted] (b) (4). Please refer to draft-labeling-text-in-pdf. A line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." was created in accordance with the RLD. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 3	Patient Information, section entitled "How do I store Atorvastatin Calcium Tablets?", 3rd bullet: Bold the statement "**Keep Atorvastatin Calcium**

Created in C1 Patient Information Leaflet Response / Assessment:	**Tablets and all medicines out of the reach of children**." in accordance with the RLD. **Applicant Response:** The sentence "Keep Atorvastatin Calcium Tablets and all medicines out of the reach of children." was bolded. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 4 Created in C1 Patient Information Leaflet Response / Assessment:	(b) (4) **Assessment:** Acceptable.
Deficiency # 5 Created in C1 Patient Information Leaflet Response / Assessment:	Patient Information, section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?", Inactive Ingredients section: Revise (b) (4) to lactose monohydrate in the list of inactive ingredients to be consistent with the information provided in your Quality submission. **Applicant Response:** (b) (4) was revised to lactose monohydrate in both section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?" and 11 DESCRIPTION. Please refer to draft-labeling-text-in-pdf. **Assessment:** Acceptable.
Deficiency # 6 Created in C2 Patient Information Leaflet Response / Assessment:	(b) (4)
Deficiency # 7 Created in C2 Patient Information Leaflet Response / Assessment:	(b) (4)

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C2)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)

☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

(b) (4)

[redacted]

Drug product review of response is pending.

(b) (4)

Update 08/10/2022: The Applicant revised the inactive ingredient from (b) (4) to "lactose monohydrate" in the Description section of the PI. This is acceptable.

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 8/23/2022 03:15:49PM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 8/23/2022 03:24:26PM
GUID: 5256bdc00002af3bc3fa942a9512a891

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	05/12/2022
ANDA Number(s)	216848
Review Number	1
Applicant Name	Lepu Pharmaceutical Technology Co., Ltd.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg
Proposed Proprietary Name	N/A
Submission Received Date	January 04, 2022, February 18, 2022
Primary Labeling Reviewer	Cameron Clark
Secondary Labeling Reviewer	Ellen Hwang

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submission received January 04, 2022:

1. CONTAINER LABEL
   a. Add the "USP" descriptor to the end of the established name on all container labels (i.e. Atorvastatin Calcium Tablets, USP).

   b. Increase the prominence of the middle digits of the NDC numbers by increasing their size in comparison to the remaining digits or putting them in bold type to help minimize the risk for medication error (e.g., XXXX-**XXXX**-XX). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

   c. Product strength: Use a method to better distinguish the 40 mg and 80 mg strengths of the drug product (e.g., boxing, contrasting colors, and/or some other means) as currently presented the proposed colors appear similar. Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

   d. Include a statement of the place of business per 21 CFR 201.1(i).

   e. Bar code: Revise the bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

2. PRESCRIBING INFORMATION
   a. GENERAL
      i. (b) (4)).
      ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the Prescribing Information.
      iii. Ensure there is adequate space between text, symbols and numerals throughout the Prescribing Information. For example, in subsection 1.2, revise "≥190 mg/dL" to "≥ 190 mg/dL" and in the subsection 2.2 heading, revise “to17 Years” to “to 17 Years”.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION
      i. (b) (4)

ii. Revise the Limitation statement and Title (as shown below) to be in accordance with the Guidance for Industry – Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements:

These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.

ATORVASTATIN CALCIUM tablets, for oral use
Initial U.S. Approval: 1996

iii. ADVERSE REACTIONS: Revise the contact phone number (e.g. 86-0576-88812311) to a U.S. phone number.

iv. [redacted] (b) (4)

v. DRUG INTERACTIONS table, 2nd column, 4th row: Add a space between the numerical dose and unit of measure (i.e. change "40mg" to "40 mg").

vi. Revision date: Include a revision date at the end of the HIGHLIGHTS section per 21 CFR 201.57(a)(15).

c. [redacted] (b) (4)

d. DRUG INTERACTIONS, section 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets, Table 4, last sentence in Clinical Impact section: Revise "[redacted] (b) (4) to "atorvastatin".

e. DESCRIPTION: [redacted] (b) (4), "FDA approved dissolution test specifications differ from USP" at the end of the DESCRIPTION section. We refer you to the USP monograph for your drug product.

f. [redacted] (b) (4)

g. CLINICAL STUDIES

i. section 14.1 Prevention of Cardiovascular Disease, Figure 3: Revise [redacted] (b) (4) " to "Atorvastatin 80 mg" and "Atorvastatin 10 mg" in accordance with the RLD.

ii. section 14.1 Prevention of Cardiovascular Disease, Table 8, column 1, last row: Add a space between "othertraumatic" (i.e. other traumatic).

iii. section 14.1 Prevention of Cardiovascular Disease, Table 8, footnotes section: Add the statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" to a new line below "CABG: coronary artery bypass graft" in accordance with the RLD.

h. [redacted] (b) (4)

i. HOW SUPPLIED/ STORAGE AND HANDLING: Add the product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).

j. Manufacturer/Distributor/Packager: Add manufacturer information (e.g., name and location of business) per 21 CFR 201.1 and 21 CFR 201.100(e) after the PATIENT COUNSELING INFORMATION section.

3. PATIENT INFORMATION LEAFLET

a. Section entitled "What is Cholesterol?", 4th sentence: Revise [redacted] (b) (4) [redacted]" to "…or if heart disease starts early in your family." in accordance with the RLD.

b. Section entitled "How Should I Take Atorvastatin Calcium Tablets?",
   i. Add a bullet to the first paragraph in accordance with the RLD.
   ii. [redacted] (b) (4) [redacted]."
   iii. Create a line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." in accordance with the RLD.

c. section entitled "How do I store Atorvastatin Calcium Tablets?", 3rd bullet: Bold the statement "**Keep Atorvastatin Calcium Tablets and all medicines out of the reach of children**." in accordance with the RLD.

d. [redacted] (b) (4) [redacted].

e. section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?", Inactive Ingredients section: Revise [redacted] (b) (4) to lactose monohydrate in the list of inactive ingredients to be consistent with the information provided in your Quality submission.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB

are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

1.3 POST-APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	10 mg, 20 mg, 40 mg, and 80 mg bottles of 90s	1/4/2022	Revise
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Pending	1/4/2022	Revise
Medication Guide	N/A	N/A		
Patient Information	Draft	Pending	1/4/2022	Revise
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? This entry in Drug Facts is expired so no longer applicable: (b) (4) [redacted]
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** NDA020702 / S-077 **Supplement Approval Date:** 11/16/2020 **Proprietary Name:** Lipitor **Established Name:** Atorvastatin Calcium Tablets **Description of Supplement:**

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

This Prior Approval sNDA provides for revisions in the Prescribing Information (PI) with information regarding potential drug interactions between atorvastatin and HCV NS5A/NS5B inhibitors. In addition, the Warnings and Precautions for Myopathy and Rhabdomyolysis and Drug Interactions sections were updated to more clearly communicate the risk and mitigation information.

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
LIPITOR	ATORVASTATIN CALCIUM	EQ 10MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
LIPITOR	ATORVASTATIN CALCIUM	EQ 20MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
LIPITOR	ATORVASTATIN CALCIUM	EQ 40MG BASE	TABLET;ORAL	Prescription	AB	Yes	No
LIPITOR	ATORVASTATIN CALCIUM	EQ 80MG BASE	TABLET;ORAL	Prescription	AB	Yes	Yes

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4701571_4290112_090140af805ad954_NDA020702_3105282

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

BPCA carve-out expired (see Regulatory Information section 4.1 above)

S-079 is pending (5/24/2021) and will impact labeling; no recent activity on this supplement so this approval does not appear to be imminent; goal date per DARRTS is 11/24/2021
This supplemental application proposes the following updates to the prescribing information for Lipitor:
- Revisions to Section 8 – Use in Special Populations
- Revisions to Section 17 – Patient Counseling Information

S-080 is a CMC supplement with no impact to labeling

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:
Proposed ANDA model labeling from RLD NDA 020702 S-077 (approved 11/16/2020); also note that there have been some additional changes to the RLD's current in-use labeling that are annual reportable in nature and the ANDA has incorporated those changes as well.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 05/12/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA020702) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 05/12/2022

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes	[redacted]	Atorvastatin Calcium Tablets	ADDITIONAL REQUIREMENTS • (b) (4) [redacted]
Not Yet Official	No	[redacted]	N/A	N/A

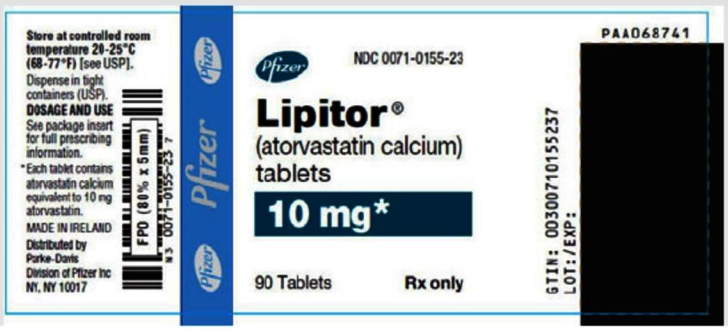
Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☒	☐	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☒	☐	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments:		

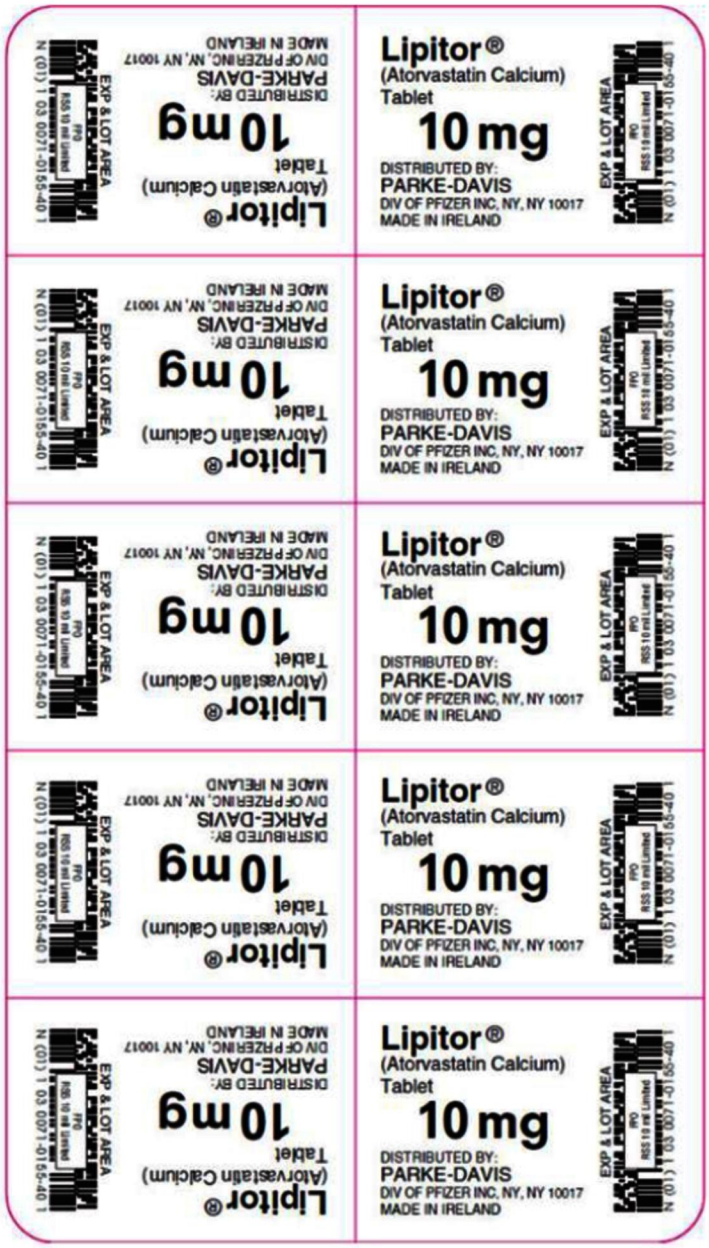
The DESCRIPTION section [redacted] (b) (4) As the Biopharmaceutics Review is still pending, we will issue the following Standard Comment at this time.	
Deficiency Comments: Deficiency # 1 Created in C1 Prescribing Information Response / Assessment:	DESCRIPTION: [redacted] (b) (4) "FDA approved dissolution test specifications differ from USP" at the end of the DESCRIPTION section. We refer you to the USP monograph for your drug product.
Deficiency # 2 Created in C1 Container Label Response / Assessment:	Add the "USP" descriptor to the end of the established name on all container labels (i.e. Atorvastatin Calcium Tablets, USP).
Deficiency # 3 Created in C1 Prescribing Information Response / Assessment:	GENERAL: [redacted] (b) (4)).

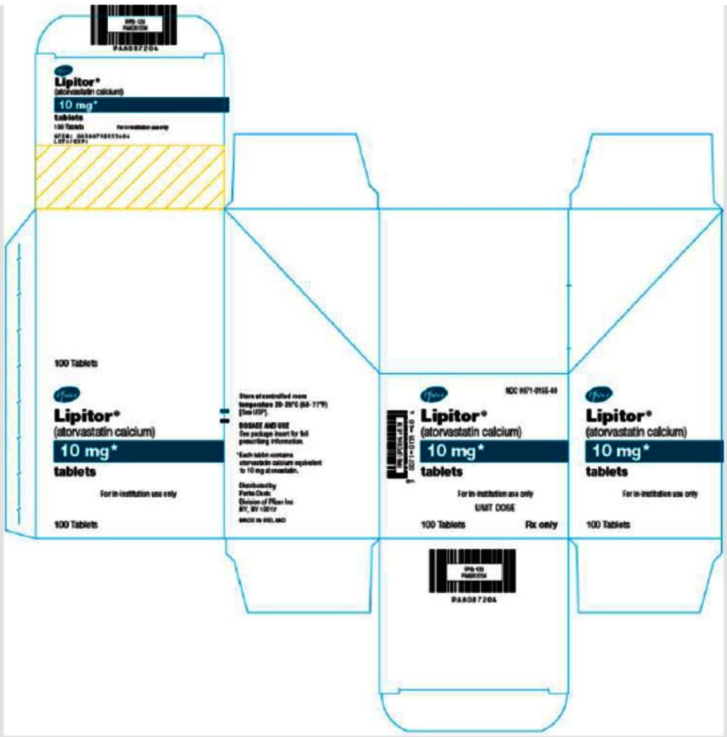
4.5 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: annual report-27, dated 12/20/2021, SPL link from Summary of labeling changes document; included only 90-count container labels for each strength and one representative foil blister and carton labeling)




Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.
MADE IN IRELAND
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
Pfizer
NDC 0071-0156-23
Lipitor®
(atorvastatin calcium)
tablets
20 mg*
90 Tablets
Rx only
PAA068743
GTIN: 00300710156234
LOT:/EXP:
Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
MADE IN IRELAND
Pfizer
NDC 0071-0157-23
Lipitor®
(atorvastatin calcium)
40 mg*
tablets
90 Tablets
Rx only
PAA056783
GTIN: 00300710157231
LOT:/EXP:
Store at controlled room temperature 20-25°C (68-77°F) [see USP].
Dispense in tight containers (USP).
DOSAGE AND USE
See package insert for full prescribing information.
*Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.
MADE IN IRELAND
Pfizer
NDC 0071-0158-23
Lipitor®
(atorvastatin calcium)
80 mg*
tablets
90 Tablets
Rx only
Distributed by
Parke-Davis
Division of Pfizer Inc
NY, NY 10017
PAA054393
GTIN: 00300710158238
LOT:/EXP:


Lipitor®
(Atorvastatin Calcium)
Tablet
10 mg
DISTRIBUTED BY:
PARKE-DAVIS
DIV OF PFIZER INC, NY, NY 10017
MADE IN IRELAND
EXP & LOT AREA



5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

5.1.2 DESCRIPTION

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	LIPITOR Tablets for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.
Previous ANDA Labeling	N/A
Current ANDA Labeling	(b) (4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
(b) (4)	
	Reviewer Assessment: • differences are allowable between inactive ingredients (b) (4) included in RLD vs. ANDA. • (b) (4) included in this list of inactive ingredients for ANDA labeling should be included as "lactose monohydrate" as is included in quality submission. I've included as a deficiency in Prescribing Information section 5.3 and will also provide an FYI comment to CMC.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 10 mg tablets (10 mg of atorvastatin): coded "PD 155" on one side and "10" on the other. NDC 0071-0155-23 bottles of 90 NDC 0071-0155-34 bottles of 5000 NDC 0071-0155-40 10 x 10 unit dose blisters NDC 0071-0155-10 bottles of 1000 20 mg tablets (20 mg of atorvastatin): coded "PD 156" on one side and "20" on the other. NDC 0071-0156-23 bottles of 90 NDC 0071-0156-40 10 x 10 unit dose blisters NDC 0071-0156-94 bottles of 5000 NDC 0071-0156-10 bottles of 1000 40 mg tablets (40 mg of atorvastatin): coded "PD 157" on one side and "40" on the other. NDC 0071-0157-23 bottles of 90 NDC 0071-0157-73 bottles of 500 NDC 0071-0157-88 bottles of 2500 NDC 0071-0157-40 10 x 10 unit dose blisters 80 mg tablets (80 mg of atorvastatin): coded "PD 158" on one side and "80" on the other. NDC 0071-0158-23 bottles of 90 NDC 0071-0158-73 bottles of 500 NDC 0071-0158-88 bottles of 2500 NDC 0071-0158-92 8 x 8 unit dose blisters Storage Store at controlled room temperature 20 -25°C (68 -77°F) [see USP].
Previous ANDA Labeling	N/A
Current ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 10 mg tablets (10 mg of atorvastatin): NDC 82137-016-01 bottles of 90, coded "l" on one side. 20 mg tablets (20 mg of atorvastatin): NDC 82137-017-01 bottles of 90, coded "l l" on one side. 40 mg tablets (40 mg of atorvastatin): NDC 82137-018-01 bottles of 90, coded "l l l" on one side. 80 mg tablets (80 mg of atorvastatin): NDC 82137-019-01 bottles of 90, coded "l l l l" on one side. Storage Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP]. Reviewer assessment: The differences in package size and configuration are allowable differences.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	N/A
Name and Address on ANDA Container/Carton	N/A
Name and Address on ANDA Prescribing Information	N/A
Current ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Lepu Pharmaceutical Technology Co., Ltd. No. 27 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province. P.R. China (3.2.P.3.1.1)
Name and Address on ANDA Container/Carton	Manufactured by: Lepu Pharmaceutical Technology Co., Ltd. (b) (4)
Name and Address on ANDA Prescribing Information	(b) (4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	**Dosage** statement.
☒	☐	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Title case is used in expressing the established/proprietary name.

(b) (4)

[redacted]

How Supplied: The differences in package size and configuration are allowable differences.

(b) (4)

[redacted]

(b) (4)

The proposed container label is inadequate and I have included several recommendations below.

Deficiency Comments:

Deficiency # 1 Created in C1 Container Label Response / Assessment:	Increase the prominence of the middle digits of the NDC numbers by increasing their size in comparison to the remaining digits or putting them in bold type to help minimize the risk for medication error (e.g., XXXX-**XXXX**-XX). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf
Deficiency # 2 Created in C1 Container Label Response / Assessment:	Product strength: Use a method to better distinguish the 40 mg and 80 mg strengths of the drug product (e.g., boxing, contrasting colors, and/or some other means) as currently presented the proposed colors appear similar. Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf
Deficiency # 3 Created in C1 Container Label Response / Assessment:	Include a statement of the place of business per 21 CFR 201.1(i).
Deficiency # 4 Created in C1 Container Label Response / Assessment:	Bar code: Revise the bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

5.3 PRESCRIBING INFORMATION

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☒	☐	**Contact information** for applicant and FDA are listed correctly.
☒	☐	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☒	☐	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☒	☐	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Deficiency Comments:
Deficiency # 1 [redacted] (b) (4)

Created in C1

Prescribing Information
Response / Assessment:

Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	DRUG INTERACTIONS, section 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets, Table 4, last sentence in Clinical Impact section: Revise [redacted] (b) (4) to "atorvastatin".
Deficiency # 3 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4)
Deficiency # 4 Created in C1 Prescribing Information Response / Assessment:	CLINICAL STUDIES, section 14.1 Prevention of Cardiovascular Disease, Figure 3: Revise [redacted] (b) (4) to "Atorvastatin 80 mg" and "Atorvastatin 10 mg" in accordance with the RLD.
Deficiency # 5 Created in C1 Prescribing Information Response / Assessment:	CLINICAL STUDIES, section 14.1 Prevention of Cardiovascular Disease, Table 8, column 1, last row: Add a space between "othertraumatic" (i.e. other traumatic).
Deficiency # 6 Created in C1 Prescribing Information Response / Assessment:	CLINICAL STUDIES, section 14.1 Prevention of Cardiovascular Disease, Table 8, footnotes section: Add the statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" to a new line below "CABG: coronary artery bypass graft" in accordance with the RLD.
Deficiency # 7 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4)
Deficiency # 8 Created in C1 Prescribing Information Response / Assessment:	HIGHLIGHTS, ADVERSE REACTIONS: Revise the contact phone number (e.g. 86-0576-88812311) to a U.S. phone number.
Deficiency # 9	HIGHLIGHTS: Revision date: Include a revision date at the end of the HIGHLIGHTS section per 21 CFR 201.57(a)(15).

Created in C1 Prescribing Information Response / Assessment:	
Deficiency # 10 Created in C1 Prescribing Information Response / Assessment:	HOW SUPPLIED/ STORAGE AND HANDLING: Add the product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).
Deficiency # 11 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4) .
Deficiency # 12 Created in C1 Prescribing Information Response / Assessment:	GENERAL: Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the Prescribing Information.
Deficiency # 13 Created in C1 Prescribing Information Response / Assessment:	GENERAL: Ensure there is adequate space between text, symbols and numerals throughout the Prescribing Information. For example, in subsection 1.2, revise "≥190 mg/dL" to "≥ 190 mg/dL" and in the subsection 2.2 heading, revise "to17 Years" to "to 17 Years".
Deficiency # 14 Created in C1 Prescribing Information Response / Assessment:	HIGHLIGHTS: Remove the established name and manufacturer information included above the Limitation statement so that the Highlights are in accordance with the PLR format requirements within 21 CFR 201.56(d) and 201.57(a).
Deficiency # 15 Created in C1 Prescribing Information	HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the Limitation statement and Title (as shown below) to be in accordance with the Guidance for Industry – Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements: **These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.**

Response / Assessment:	**ATORVASTATIN CALCIUM tablets, for oral use** **Initial U.S. Approval: 1996**
Deficiency # 16 Created in C1 Prescribing Information Response / Assessment:	[redacted] (b) (4)
Deficiency # 17 Created in C1 Prescribing Information Response / Assessment:	HIGHLIGHTS OF PRESCRIBING INFORMATION, DRUG INTERACTIONS table, 2nd column, 4th row: Add a space between the numerical dose and unit of measure (i.e. change "40mg" to "40 mg").

5.4 OTHER PATIENT LABELING

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:	
Deficiency Comments: Deficiency # 1 Created in C1 Patient Information Leaflet Response / Assessment:	Patient Information, section entitled What is Cholesterol?, 4th sentence: Revise [redacted] (b) (4) to "…or if heart disease starts early in your family." in accordance with the RLD.
Deficiency # 2 Created in C1 Patient Information Leaflet Response / Assessment:	1. "How Should I Take Atorvastatin Calcium Tablets?", 2. Add a bullet to the first paragraph in accordance with the RLD. 3. [redacted] (b) (4) 4. Create a line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." in accordance with the RLD.
Deficiency # 3 Created in C1	Patient Information, section entitled "How do I store Atorvastatin Calcium Tablets?", 3rd bullet: Bold the statement "**Keep Atorvastatin Calcium Tablets and all medicines out of the reach of children**." in accordance with the RLD.

Patient Information Leaflet Response / Assessment:	
Deficiency # 4 Created in C1 Patient Information Leaflet Response / Assessment:	[redacted] (b) (4) [redacted].
Deficiency # 5 Created in C1 Patient Information Leaflet Response / Assessment:	Patient Information, section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?", Inactive Ingredients section: Revise [redacted] (b) (4) to lactose monohydrate in the list of inactive ingredients to be consistent with the information provided in your Quality submission.

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

[redacted] (b) (4)

(b) (4)

Deficiency Comments:

Cameron Clark

Digitally signed by Cameron Clark
Date: 5/27/2022 12:16:28PM
GUID: 5a4fa1f0001c26bc28df0e20df234537

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 5/27/2022 12:54:28PM
GUID: 5256bdc00002af3bc3fa942a9512a891

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216848

CHEMISTRY REVIEW(s)

ANDA 216848 | Executive Summary

Recommendation | Approval

1. Application/Product Information

ANDA Number.	[redacted]
Review Cycle #	[redacted]
Applicant Name	[redacted]
Drug Product Name	[redacted]
Dosage Form. (click (+) for more than one)	[redacted]
Proposed Strength(s)	[redacted]
Route of Administration (click (+) for more than one)	Oral
Maximum Daily Dose	
Rx/OTC Dispensed	[redacted]
Proposed Indication	(b) (4) [redacted]
Drug Product Description	[redacted] (b) (4) [redacted]

	(b) (4) [redacted]
Co-packaged product information	[redacted]
Device information, if any:	[redacted]
Storage Temperature/ Conditions	Store at controlled room temperature 20 - 25˚C (68 - 77˚F) [see USP].
Review Team	**Discipline** / **Primary** / **Secondary** [redacted]
Consults	[redacted]

2. Submission Document(s) Reviewed

Submission(s) Assessed	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

3. Related/Supporting Documents

a. DMFs:

[redacted]	Holder	Item [redacted]	Status	[redacted]
02602	[redacted]	[redacted]	Adequat	[redacted]

b. Other Documents: IND, RLD, RS, Approved ANDA

[redacted]	[redacted]	[redacted]
[redacted]	N02207([redacted]	[redacted]

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

✓ **Overall Quality Deficiencies – Optional**
(*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)
None

✓ **Drug Substance Deficiencies**
None

✓ **Drug Product Deficiencies**
None

✓ **Labeling Deficiencies** (*Please contact OGD if you identify any Labeling deficiencies with your comments)*
None

✓ **Manufacturing Deficiencies**
None

✓ **Biopharmaceutics Deficiencies**

None

✓ **Microbiology Deficiencies**

None

✓ **Other Deficiencies** *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: **Pharm/Tox consult for Drug Product**)*

None

✓ **Additional Comments:**

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

(*Include summary of issues and benefit-risk considerations according to recommendation. Not intended to be a summary of review.*)

All the disciplines indicated below are adequate. All the issues — found in disciplines covered by executive summary — are resolved satisfactorily. Refer to the reviews of these disciplines in Panorama and KASA-nexus.

b. Recommendation by Subdiscipline:

Drug Substance | ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

Drug Product | ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

Quality Labeling | ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

Manufacturing | ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

Biopharmaceutics | ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

Microbiology | N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

Environmental | ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

[redacted]

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Comments:

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	216848
RLD/RS No.	020702 / 020702
Applicant	LEPU PHARMACEUTICAL TECHNOLOGY CO., LTD.
Dosage	Tablet IR
Route	Oral
DP Name	ATORVASTATIN CALCIUM
Primary Assessor	Vijay Sharma
Secondary Assessor	Laxma Nagavelli

Discipline Executive Summary

RECOMMENDATION: From a DP review perspective, ANDA 216848 for the proposed drug product, Atorvastatin Calcium IR Tablets, is ADEQUATE.

Drug substance – Atorvastatin calcium trihydrate – has a current USP monograph (official: January 2022). [redacted] (b) (4) [redacted]. Related DMF 026022 is adequate (Panorama, September 16, 2022).

Drug product – Atorvastatin Calcium Tablets, USP: ANDA 216848 proposes four dose-proportional strengths including 10 mg, 20 mg, 40 mg, and 80 mg – which are intended for immediate release via oral-administration. Drug product has a current USP monograph (official: December 2020). (b) (4) [redacted] The proposed drug product specification meet the requirements of USP monograph (official: Dec 2020). The drug product tablets of each strength are packaged in 90's counts (b) (4) bottles (b) (4) [redacted]

Drug Substance(s) and Drug Product

	DS Name	Strength Name (Active Moiety or Salt)	USP Monograph	DMF#	Status	Date of Complete
1	ATORVASTATIN CALCIUM TRIHYDRATE	Atorvastatin Calcium	USP-43	MF026022	Adequate	09/16/2022

USP Monograph for DP	Note
USP-43	The official date of USP monograph of drug product is December 01, 2020.

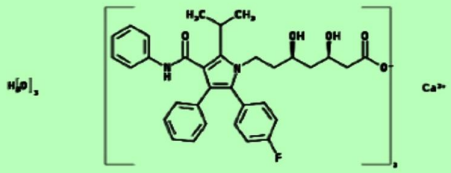
DP Strength List

	DS 1
	mg
Strength 1	80
Strength 2	20
Strength 3	40
Strength 4	10

Review Iteration						
Review Iteration		Assessor Decision	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	DRL	8/29/2022	Form 3674; New	1	1/4/2022
2	DRL Response	Adequate		Quality Filing Quality	2 5 3 6	2/18/2022 8/5/2022 2/25/2022 9/27/2022

Knowledge-aided Assessment and Structured Application

S4. Drug Substance

DMF	MF026022	ATORVASTATIN CALCIUM TRIHYDRATE
UNII	48A5M73Z4Q	
DMF Status	Adequate	

DS Specifications				
Specification	Release	Justification	Evaluation	AD
Description	White to off-white crystalline powder.		The description of API is adopted from DMF holder, thus considered acceptable. (b) (4)	Yes

10 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Knowledge-aided Assessment and Structured Application

P1 Drug Product Description

Tablet IR			
Comparison of Drug Product Design			
RLD/RS Product Design			
Configuration	(b) (4)		
Release Mechanism			
Functional Components			
Components		**Type**	**Brief Description**
#1	Tablet Core	IR	
Coatings	RLD - Lipitor tablets are white, elliptical, film-coated tablets in four approved strengths including 10 mg, 20 mg, 40 mg, and 80 mg. (b) (4) .		
CCS	**Counts**		
Bottles	90's counts for each strength		
Blister			
ANDA Product Design			
Configuration	(b) (4)		
Release Mechanism			
Functional Components			
Components		**Type**	**Description (Optional)**
#1	Tablet Core	IR	
Coatings	ANDA - Atorvastatin calcium tablets are white to off-white film-coated tablets in four proposed strengths including 10 mg, 20 mg, 40 mg, and 80 mg. (b) (4)		
CCS	**Counts**		
Bottles	90's counts for each strength		
AD	**Reviewer Evaluation**		
Yes	(b) (4) , it is acceptable. ; Comparison of excipients - ANDA vs RLD		

DP Component Composition of ANDA Drug Product
ANDA Product Design

Ingredient	Excipient Grade	Function	Quantity	Percentage	Function Location
Strength #1: Atorvastatin Calcium 80 mg					
IR Tablet Core					
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API			
CALCIUM CARBONATE	USP				
MICROCRYSTALLINE CELLULOSE	USP				
LACTOSE MONOHYDRATE	USP				
CROSCARMELLOSE SODIUM	USP				
POLYSORBATE 80	USP				
HYDROXYPROPYL CELLULOSE	USP				
MAGNESIUM STEARATE	USP				
Total:			1,200	100%	
OPADRY YS-1-7040 WHITE					
Total:				100%	
Strength #2: Atorvastatin Calcium 20 mg					
IR Tablet Core					
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API			
CALCIUM CARBONATE	USP				
MICROCRYSTALLINE CELLULOSE	USP				
LACTOSE MONOHYDRATE	USP				
CROSCARMELLOSE SODIUM	USP				
POLYSORBATE 80	USP				
HYDROXYPROPYL CELLULOSE	USP				
MAGNESIUM STEARATE	USP				
Total:			300	100%	
OPADRY YS-1-7040 WHITE					
Total:				100%	
Strength #3: Atorvastatin Calcium 40 mg					
IR Tablet Core					
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API			
CALCIUM CARBONATE	USP				
MICROCRYSTALLINE CELLULOSE	USP				
LACTOSE MONOHYDRATE	USP				
CROSCARMELLOSE SODIUM	USP				
POLYSORBATE 80	USP				
HYDROXYPROPYL CELLULOSE	USP				
MAGNESIUM STEARATE	USP				
Total:			600	100%	

[redacted]			(b) (4)
OPADRY YS-1-7040 WHITE			(b) (4)
Total:			100%
Strength #4: Atorvastatin Calcium 10 mg			
IR Tablet Core			
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API	(b) (4)
CALCIUM CARBONATE	USP		
MICROCRYSTALLINE CELLULOSE	USP		
LACTOSE MONOHYDRATE	USP		
CROSCARMELLOSE SODIUM	USP		
POLYSORBATE 80	USP		
HYDROXYPROPYL CELLULOSE (b) (4)	USP		
MAGNESIUM STEARATE	USP		
[redacted]			(b) (4)
Total:		150	100%
[redacted]			(b) (4)
OPADRY YS-1-7040 WHITE			
Total:			100%
Are there any DMFs with drug product intermediate (DPI)?			No

Overall Evaluation of Components Composition

Reviewer Evaluation	Drug product is proposed in 4 strengths including 10 mg, 20 mg, 40 mg, and 80 mg. Per package insert and the information in module 3.2.P.1, (b) (4) [redacted] The excipients in test-product and RLD product are comparable. (b) (4) [redacted] • Dimensions of tablets: The dimensions of tablets of test-product including width, length, and thickness are comparable with the corresponding dimensions of reference product. Per comparative tabulated data in Table-3 on the dimensions of tablets of generic product vs RLD products for four strengths in module 3.2.P.1 (Seq: 0001; January 04, 2022); the recommendations in FDA guidance, "Size, shape, and other physical attributes of generic tablets and tablets," are met. ; Composition of Drug Product; Comparative dimensions of Tablets - ANDA vs RLD

Patient-Product Interface

URL Description	URL	Init. Page
10 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-	2

	prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	
20 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	3
40 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	3
80 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	4

Strength #1: Atorvastatin Calcium 80 mg		
Property	**RLD**	**ANDA**
Length	19.1 mm	19.1 mm
Width	10.1 mm	10.1 mm
Thickness	7.63 mm	7.3-8.1 mm
Shape	Elliptical/Oval	Elliptical/Oval
Strength #2: Atorvastatin Calcium 20 mg		
Property	**RLD**	**ANDA**
Length	12.2 mm	12.2 mm
Width	6.4 mm	6.4 mm
Thickness	4.72 mm	4.1-4.9 mm
Shape	Elliptical/Oval	Elliptical/Oval
Strength #3: Atorvastatin Calcium 40 mg		
Property	**RLD**	**ANDA**
Length	15.4 mm	15.4 mm
Width	8 mm	8 mm
Thickness	5.92 mm	5.4-6.4 mm
Shape	Elliptical/Oval	Elliptical/Oval
Strength #4: Atorvastatin Calcium 10 mg		
Property	**RLD**	**ANDA**
Length	8.5 mm	8.5 mm
Width	5 mm	5 mm
Thickness	3.64 mm	3.3-4.1 mm
Shape	Elliptical/oval	Elliptical/oval
Reviewer Evaluation		
; Dimensions of four strengths (10 mg, 20 mg, 40 mg, and 80 mg)		

Color and Size	
For multiple strength drug products, do all strengths have the same color and size?	No
AD	**Reviewer Evaluation**
Yes	The color of all four proposed strengths is white to off-white. However, the size and coded sign on tablets of four strengths are different. Likewise, the tablets of RLD products of four strengths have same color with different sizes and coded signs. Refer to the images of four proposed strengths of generic products vs RLD products in module 3.2.P.1. ; Size of four strengths (10 mg, 20 mg, 40 mg, and 80 mg); Images of tablets - Color and shape of tablets
Tablet Split	
Does the ANDA meet the criteria per the Tablet Scoring Guidance?	N/A
AD	**Reviewer Evaluation**
Yes	

Unique Situations	
Any Unique Situations Not Covered by KASA?	No
Narrative	
AD	Reviewer Evaluation
Yes	NA

Labeling	
Description Section	
Is the information accurate?	No
Comment	
(b) (4)	

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Yes

For Solid Oral Drug Product:		
ANDA Strength	Length(mm)	Imprint Code
Atorvastatin Calcium 10mg	8.5	"I"
Atorvastatin Calcium 20mg	12.2	"II"
Atorvastatin Calcium 40mg	15.4	"III"
Atorvastatin Calcium 80mg	19.1	"IIII"
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	Yes
AD	Reviewer Evaluation
Yes	(b) (4)

	(b) (4) [redacted]

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

P.1.5 Unique Situations

L.1 Labeling

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	[Deficiency/IR]
			(b) (4) [redacted]
			[Summary of the applicant's response and reviewer comment]
DRL Response	Solved	1	[Summary of the applicant's response and reviewer comment]
			(b) (4) [redacted]
			[Deficiency/IR Previous Iteration]

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Knowledge-Aided Assessment and Structured Application

DEFICIENCIES

Drug Substance

ATORVASTATIN CALCIUM TRIHYDRATE

No deficiencies to display

Laxma Nagavelli

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Vijay Sharma

Digitally signed by Vijay Sharma
Date: 10/14/2022 08:10:56AM
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Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	216848
Drug Product Name	ATORVASTATIN CALCIUM
Drug Product Strength(s)	ATORVASTATIN CALCIUM TRIHYDRATE 80mg ; ATORVASTATIN CALCIUM TRIHYDRATE 20mg ; ATORVASTATIN CALCIUM TRIHYDRATE 40mg ; ATORVASTATIN CALCIUM TRIHYDRATE 10mg
RLD/RS Number.	020702
Applicant Name	LEPU PHARMACEUTICAL TECHNOLOGY CO., LTD.
Dosage Form	Tablet IR
Administration Route	Oral
Indication	[redacted] (b) (4)
Primary Assessor	Satheesh Podaralla
Secondary Assessor	Nathan Davis

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Adequate

Discipline Assessment Summary
Manufacturing process of Atorvastatin Tablets, 10, 20, 40 and 80 mg includes [redacted] (b) (4) . Drug substance manufacturing facility is approvable based on file history and facilities OMIR is approve recommendation.

Drug Substance(s) and Drug Product				
	Drug Substance Name	**Strength Name (Active Moiety or Salt)**	**DMF#**	**Note for Convenience**
1	ATORVASTATIN CALCIUM TRIHYDRATE	Atorvastatin	MF026022	

Drug Product Strength List	
	DS 1
	mg
Strength 1	80

Strength 2	20
Strength 3	40
Strength 4	10

Review Iteration							
Review Iteration		**Process**	**Facility**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	Inadequate Minor	Pending	6/16/2022	Other - Original Form 3674; New	 2 1	 2/18/2022 1/4/2022
2	DRL Response	Adequate	Adequate	10/4/2022	Quality	5	8/5/2022

Highlight Key Issues from Last Cycle and Their Resolution
N/A

Concise Description of Outstanding Issues
N/A

Lifecycle Management Considerations	
Post-approval inspection?	No
Lifecycle Consideration	No

Facilities Table

Facilities			
Facility name and address	**FEI**	**Responsibilities and profile code(s)**	**Status**
Lepu Pharmaceutical Technology Co., Ltd. No. 27 Binhai Road, Jiaojiang District, Taizhou,Zhejiang, China,318000	3013738987	(b) (4)	Approve - Based on PAI
Zhejiang Lepu Pharmaceutical Co.,Ltd. No.29 Binhai Road Jiaojiang District, Taizhou,Zhejiang, China,318000	3004414647		Approve - Based on Previous History
		(b) (4)	Approve - Based on Previous History

II. Drug Product Manufacturing

1. Batch Formula

Batch Formula				
Strength	**Max Exhibit Batch Size**	**Commercial Batch Size**	**Scale-Up Factor**	**URL**
Atorvastatin 10mg	[redacted] (b) (4)		1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Atorvastatin 20mg			1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Atorvastatin 40mg			1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Atorvastatin 80mg			1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Assessment of Batch Formula				
Did the applicant provide adequate information of Batch Formula and is overall scale up in a reasonable range?	Yes			
Reviewer Evaluation				

Deficiencies

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	[redacted] (b) (4)
			[Deficiency/IR]
			[redacted] (b) (4)
			[Summary of the applicant's response and reviewer comment]
DRL Response	Solved	1	**[Summary of the applicant's response and reviewer comment]**
			[redacted] (b) (4). response acceptable. ; DRL response
			[Deficiency/IR Previous Iteration]

2. Commercial Process Flow Diagram

Manufacturing Flow Diagram	
Short Description	**URL**
Commercial Manufacturing process flow diagram	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\manuf-process-and-controls-1.pdf

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Evaluation of Commercial Testing Facility	
Facility Status Assessment	Approve - Based on Previous History
Reviewer Evaluation	03/02/2022, During recent Pre-approval inspection of this testing laboratory minor observations were identified, corrective actions for the Observations adequately corrected. Approval of the testing facility was recommended.

Evaluation of Any Missing Facilities

Evaluation of Any Missing Facilities

V. List of outstanding Information Request/Deficiencies

No deficiencies to display

Satheesh Podaralla

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Nathan Davis

Digitally signed by Nathan Davis
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Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	216848
RLD/RS No.	020702 / 020702
Applicant	LEPU PHARMACEUTICAL TECHNOLOGY CO., LTD.
Dosage	Tablet IR
Route	Oral
DP Name	ATORVASTATIN CALCIUM
Primary Assessor	Vijay Sharma
Secondary Assessor	Laxma Nagavelli

Discipline Executive Summary

RECOMMENDATION: From a DP review perspective, ANDA 216848 for the proposed drug product, Atorvastatin Calcium IR Tablets, is ADEQUATE.

Drug substance – Atorvastatin calcium trihydrate – has a current USP monograph (official: January 2022). (b) (4) Applicant's API specification meets the requirements of current USP monograph of drug substance. Related DMF 026022 is adequate (Panorama, September 16, 2022).

Drug product – Atorvastatin Calcium Tablets, USP: ANDA 216848 proposes four dose-proportional strengths including 10 mg, 20 mg, 40 mg, and 80 mg – which are intended for immediate release via oral-administration. Drug product has a current USP monograph (official: December 2020). (b) (4) The proposed drug product specification meet the requirements of USP monograph (official: Dec 2020). The drug product tablets of each strength are packaged in 90's counts (b) (4) bottles (b) (4)

Drug Substance(s) and Drug Product						
	DS Name	Strength Name (Active Moiety or Salt)	USP Monograph	DMF#	Status	Date of Complete
1	ATORVASTATIN CALCIUM TRIHYDRATE	Atorvastatin Calcium	USP-43	MF026022	Adequate	09/16/2022

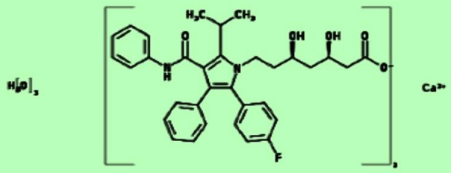
USP Monograph for DP	Note
USP-43	The official date of USP monograph of drug product is December 01, 2020.

DP Strength List	
	DS 1
	mg
Strength 1	80
Strength 2	20
Strength 3	40
Strength 4	10

Review Iteration						
Review Iteration		Assessor Decision	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	DRL	8/29/2022	Form 3674; New	1	1/4/2022
2	DRL Response	Adequate		Quality Filing Quality	2 5 3 6	2/18/2022 8/5/2022 2/25/2022 9/27/2022

Knowledge-aided Assessment and Structured Application

S4. Drug Substance

DMF	MF026022	ATORVASTATIN CALCIUM TRIHYDRATE
UNII	48A5M73Z4Q	
DMF Status	Adequate	

DS Specifications				
Specification	Release	Justification	Evaluation	AD
Description	White to off-white crystalline powder.		The description of API is adopted from DMF holder, thus considered acceptable. (b) (4) [redacted]	Yes

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Knowledge-aided Assessment and Structured Application

P1 Drug Product Description

Tablet IR			
Comparison of Drug Product Design			
RLD/RS Product Design			
Configuration	(b) (4)		
Release Mechanism			
Functional Components			
Components		**Type**	**Brief Description**
#1	Tablet Core	IR	
Coatings	RLD - Lipitor tablets are white, elliptical, film-coated tablets in four approved strengths including 10 mg, 20 mg, 40 mg, and 80 mg. (b) (4)		
CCS	**Counts**		
Bottles	90's counts for each strength		
Blister			
ANDA Product Design			
Configuration	(b) (4)		
Release Mechanism			
Functional Components			
Components		**Type**	**Description (Optional)**
#1	Tablet Core	IR	
Coatings	ANDA - Atorvastatin calcium tablets are white to off-white film-coated tablets in four proposed strengths including 10 mg, 20 mg, 40 mg, and 80 mg. (b) (4)		
CCS	**Counts**		
Bottles	90's counts for each strength		
AD	**Reviewer Evaluation**		
Yes	(b) (4) The excipients in test-product and RLD product are comparable (b) (4) , it is acceptable. ; Comparison of excipients - ANDA vs RLD		

DP Component Composition of ANDA Drug Product
ANDA Product Design

Ingredient	Excipient Grade	Function	Quantity	Percentage	Function Location
Strength #1: Atorvastatin Calcium 80 mg					
IR Tablet Core					
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API			
CALCIUM CARBONATE	USP				
MICROCRYSTALLINE CELLULOSE	USP				
LACTOSE MONOHYDRATE	USP				
CROSCARMELLOSE SODIUM	USP				
POLYSORBATE 80	USP				
HYDROXYPROPYL CELLULOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
Total:			1,200	100%	
OPADRY YS-1-7040 WHITE	YS-1-7040-CN				
Total:				100%	
Strength #2: Atorvastatin Calcium 20 mg					
IR Tablet Core					
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API			
CALCIUM CARBONATE	USP				
MICROCRYSTALLINE CELLULOSE	USP				
LACTOSE MONOHYDRATE	USP				
CROSCARMELLOSE SODIUM	USP				
POLYSORBATE 80	USP				
HYDROXYPROPYL CELLULOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
Total:			300	100%	
OPADRY YS-1-7040 WHITE					
Total:				100%	
Strength #3: Atorvastatin Calcium 40 mg					
IR Tablet Core					
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API			
CALCIUM CARBONATE	USP				
MICROCRYSTALLINE CELLULOSE	USP				
LACTOSE MONOHYDRATE	USP				
CROSCARMELLOSE SODIUM	USP				
POLYSORBATE 80	USP				
HYDROXYPROPYL CELLULOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
Total:			600	100%	

OPADRY YS-1-7040 WHITE			
Total:			100%
Strength #4: Atorvastatin Calcium 10 mg			
IR Tablet Core			
ATORVASTATIN CALCIUM TRIHYDRATE	USP	API	
CALCIUM CARBONATE	USP		
MICROCRYSTALLINE CELLULOSE	USP		
LACTOSE MONOHYDRATE	USP		
CROSCARMELLOSE SODIUM	USP		
POLYSORBATE 80	USP		
HYDROXYPROPYL CELLULOSE (90000 WAMW)	USP		
MAGNESIUM STEARATE	USP		
Total:		150	100%
OPADRY YS-1-7040 WHITE			
Total:			100%
Are there any DMFs with drug product intermediate (DPI)?			No
Overall Evaluation of Components Composition			
Reviewer Evaluation	Drug product is proposed in 4 strengths including 10 mg, 20 mg, 40 mg, and 80 mg.		

Patient-Product Interface		
URL Description	**URL**	**Init. Page**
10 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-	2

	prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	
20 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	3
40 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	3
80 mg - Generic tablet vs RLD	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p1-desc-comp\description-and-composition.pdf	4

Strength #1: Atorvastatin Calcium 80 mg		
Property	**RLD**	**ANDA**
Length	19.1 mm	19.1 mm
Width	10.1 mm	10.1 mm
Thickness	7.63 mm	7.3-8.1 mm
Shape	Elliptical/Oval	Elliptical/Oval
Strength #2: Atorvastatin Calcium 20 mg		
Property	**RLD**	**ANDA**
Length	12.2 mm	12.2 mm
Width	6.4 mm	6.4 mm
Thickness	4.72 mm	4.1-4.9 mm
Shape	Elliptical/Oval	Elliptical/Oval
Strength #3: Atorvastatin Calcium 40 mg		
Property	**RLD**	**ANDA**
Length	15.4 mm	15.4 mm
Width	8 mm	8 mm
Thickness	5.92 mm	5.4-6.4 mm
Shape	Elliptical/Oval	Elliptical/Oval
Strength #4: Atorvastatin Calcium 10 mg		
Property	**RLD**	**ANDA**
Length	8.5 mm	8.5 mm
Width	5 mm	5 mm
Thickness	3.64 mm	3.3-4.1 mm
Shape	Elliptical/oval	Elliptical/oval
Reviewer Evaluation		
; Dimensions of four strengths (10 mg, 20 mg, 40 mg, and 80 mg)		

Color and Size	
For multiple strength drug products, do all strengths have the same color and size?	No
AD	**Reviewer Evaluation**
Yes	The color of all four proposed strengths is white to off-white. However, the size and coded sign on tablets of four strengths are different. Likewise, the tablets of RLD products of four strengths have same color with different sizes and coded signs. Refer to the images of four proposed strengths of generic products vs RLD products in module 3.2.P.1. ; Size of four strengths (10 mg, 20 mg, 40 mg, and 80 mg); Images of tablets - Color and shape of tablets
Tablet Split	
Does the ANDA meet the criteria per the Tablet Scoring Guidance?	N/A
AD	**Reviewer Evaluation**
Yes	

Unique Situations	
Any Unique Situations Not Covered by KASA?	No
Narrative	
AD	Reviewer Evaluation
Yes	NA

Labeling	
Description Section	
Is the information accurate?	No
Comment	
[redacted] (b) (4)	

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Yes

For Solid Oral Drug Product:		
ANDA Strength	Length(mm)	Imprint Code
Atorvastatin Calcium 10mg	8.5	"I"
Atorvastatin Calcium 20mg	12.2	"II"
Atorvastatin Calcium 40mg	15.4	"III"
Atorvastatin Calcium 80mg	19.1	"IIII"
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	Yes
AD	Reviewer Evaluation
Yes	[redacted] (b) (4)

	(b) (4) [redacted]

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

P.1.5 Unique Situations

L.1 Labeling

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	[Deficiency/IR] (b) (4) [redacted] [Summary of the applicant's response and reviewer comment]
DRL Response	Solved	1	[Summary of the applicant's response and reviewer comment] (b) (4) [redacted] [Deficiency/IR Previous Iteration]

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Knowledge-Aided Assessment and Structured Application

DEFICIENCIES

Drug Substance

ATORVASTATIN CALCIUM TRIHYDRATE

No deficiencies to display

Laxma Nagavelli

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Vijay Sharma

Digitally signed by Vijay Sharma
Date: 10/14/2022 08:10:56AM
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Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	216848
Drug Product Name	ATORVASTATIN CALCIUM
Drug Product Strength(s)	ATORVASTATIN CALCIUM TRIHYDRATE 80mg ; ATORVASTATIN CALCIUM TRIHYDRATE 20mg ; ATORVASTATIN CALCIUM TRIHYDRATE 40mg ; ATORVASTATIN CALCIUM TRIHYDRATE 10mg
RLD/RS Number.	020702
Applicant Name	LEPU PHARMACEUTICAL TECHNOLOGY CO., LTD.
Dosage Form	Tablet IR
Administration Route	Oral
Indication	[redacted] (b) (4)
Primary Assessor	Satheesh Podaralla
Secondary Assessor	Nathan Davis

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Adequate

Discipline Assessment Summary
Manufacturing process of Atorvastatin Tablets, 10, 20, 40 and 80 mg includes [redacted] (b) (4) . Drug substance manufacturing facility is approvable based on file history and facilities OMIR is approve recommendation.

Drug Substance(s) and Drug Product				
	Drug Substance Name	**Strength Name (Active Moiety or Salt)**	**DMF#**	**Note for Convenience**
1	ATORVASTATIN CALCIUM TRIHYDRATE	Atorvastatin	MF026022	

Drug Product Strength List	
	DS 1
	mg
Strength 1	80

Strength 2	20
Strength 3	40
Strength 4	10

Review Iteration							
Review Iteration		**Process**	**Facility**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	Inadequate Minor	Pending	6/16/2022	Other - Original Form 3674; New	 2 1	 2/18/2022 1/4/2022
2	DRL Response	Adequate	Adequate	10/4/2022	Quality	5	8/5/2022

Highlight Key Issues from Last Cycle and Their Resolution
N/A

Concise Description of Outstanding Issues
N/A

Lifecycle Management Considerations	
Post-approval inspection?	No
Lifecycle Consideration	No

Facilities Table

Facilities			
Facility name and address	**FEI**	**Responsibilities and profile code(s)**	**Status**
Lepu Pharmaceutical Technology Co., Ltd. No. 27 Binhai Road, Jiaojiang District, Taizhou,Zhejiang, China,318000	3013738987	(b) (4)	Approve - Based on PAI
Zhejiang Lepu Pharmaceutical Co.,Ltd. No.29 Binhai Road Jiaojiang District, Taizhou,Zhejiang, China,318000	3004414647		Approve - Based on Previous History
		(b) (4)	Approve - Based on Previous History

II. Drug Product Manufacturing

1. Batch Formula

Batch Formula				
Strength	**Max Exhibit Batch Size**	**Commercial Batch Size**	**Scale-Up Factor**	**URL**
Atorvastatin 10mg	(b) (4)		1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Atorvastatin 20mg			1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Atorvastatin 40mg			1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Atorvastatin 80mg			1	\\CDSESUB1\EVSPROD\anda216848\0005\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\batch-formula.pdf
Assessment of Batch Formula				
Did the applicant provide adequate information of Batch Formula and is overall scale up in a reasonable range?	Yes			
Reviewer Evaluation				

Deficiencies

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	(b) (4) **[Deficiency/IR]** (b) (4) **[Summary of the applicant's response and reviewer comment]**
DRL Response	Solved	1	**[Summary of the applicant's response and reviewer comment]** (b) (4). response acceptable. ; DRL response **[Deficiency/IR Previous Iteration]**

2. Commercial Process Flow Diagram

Manufacturing Flow Diagram	
Short Description	**URL**
Commercial Manufacturing process flow diagram	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatin calciumtablets-tablet\32p3-manuf\manuf-process-and-controls-1.pdf

10 Pages have been withheld in full as b4 (CCI/TS) immedaitely following this page

III. [redacted]

[redacted]							
Facility Name	Zhejiang Lepu Pharmaceutical Co.,Ltd.	**FEI**	3004414647	**Profile Code**	CSN	**DMF**	MF026022
Any Special manufacturing/storage condition?	No						
Previous OPMA evaluation?	Relevant and acceptable N/A						
Is there any additional information since the last facility evaluation?	No						
Initial Risk Assessment							
Initial Risk Ranking	Low						
PAI Recommendation							
PAI/704(a)(4)	No						
Reviewer Evaluation							
Evaluation of DS Facility							
Facility Status Assessment	Approve - Based on Previous History						
Reviewer Evaluation	[redacted]						

Evaluation of Any Missing Facilities

IV. [redacted]

[redacted]	
Facility Name	[redacted]
Previous OPMA evaluation?	Relevant and acceptable N/A
Is there any additional information since the last facility evaluation?	No
Initial Risk Assessment	
Initial Risk Ranking	Low
PAI Recommendation	
PAI/704(a)(4)	No
Reviewer Evaluation	

Evaluation of Commercial Testing Facility	
Facility Status Assessment	Approve - Based on Previous History
Reviewer Evaluation	[redacted] (b) (4)

Evaluation of Any Missing Facilities

Evaluation of Any Missing Facilities

V. List of outstanding Information Request/Deficiencies

No deficiencies to display

Satheesh Podaralla

Digitally signed by Satheesh Podaralla
Date: 10/04/2022 01:26:37PM
GUID: 5b2a8bde0035075366df872da22f1d4a

Nathan Davis

Digitally signed by Nathan Davis
Date: 10/04/2022 01:30:38PM
GUID: 58a215b40087202b10a1561e3a515709

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/30/2022

TO: Office of Bioequivalence (OB)
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE:

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

ANDA (b) (4)
ANDA
ANDA
ANDA
ANDA

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Record Review (RRR) for the site in May 2021, which falls within the surveillance interval. The RRR was conducted under the following submission: ANDA (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
		(b) (4)

Folaremi K. Adeyemo -S
Digitally signed by Folaremi K. Adeyemo -S
Date: 2022.05.30 08:18:35 -04'00'

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/30/2022

TO: Office of Bioequivalence (OB)
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE:

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

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in March 2022, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b) (4)

The following objectionable condiction was discussed with the site:

- (b) (4)

After receiving a written response from the site, OSIS determined that the observation impacted the reliability of data for study (b) (4) but that the observation was isolated in nature. OSIS recommended that data from (b) (4) was not reliable for Agency review but that data from the other reviewed studies were reliable for Agency review.Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
(b) (4)		

Folaremi K. Adeyemo -S
Digitally signed by Folaremi K. Adeyemo -S
Date: 2022.05.30 08:20:55 -04'00'

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 216848

Drug Product: ATORVASTATIN CALCIUM, Tablet

DMF#: 026022

DMF Subject (API name): ATORVASTATIN CALCIUM

DMF Holder: ZHEJIANG LEPU PHARMACEUTICAL CO LTD

Note: If the DMF is for a mixture of the API and excipient(s) (e.g. stabilizer, buffer), email DMF OGD Mailbox (DMFOGD@fda.hhs.gov) and include the URL to the project; example "this TCIR is for an API excipient mixture".). Note to reviewer: Do not archive the TCIR document as changes may need to be made.

1. Are there any **secondary DMFs** referenced by this DMF? ☐Yes ☒No
   If yes, fill in the following table.

Secondary DMF #	Subject of the DMF	Intermediate/Starting material?

Note: If the secondary DMF is for a regulatory starting material, a review of the secondary DMF may not be needed.

2. **For original DMFs only: Is the regulatory starting material appropriately designated as per ICH Q11 guidelines? ☐Yes ☐No ☒N/A**

   If No, has the firm provided complete facility information?

   ☐Yes. Fill in the following table and send a directed update to the RBPM under the most recent DMF project in Panorama. Use IR comment #1 in TCIR-IR Comments template (SharePoint: DLAPI/TCIR/TCIR-IR Comments).

   ☐No. Fill in what has been provided and send a directed update to the RBPM under the most recent DMF project in Panorama for missing information. Use IR comment in #2 in TCIR-IR Comments template (SharePoint: DLAPI/TCIR/TCIR-IR Comments).

Facility Name and Address#	FEI/DUNS	Intermediate critical (Y/N)**	Justification*

* Re-designation of the KSM may result in a starting material facility becoming an intermediate manufacturing facility, therefore please select a justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

Note: Add "Pending Evaluation" as the initial assessment. Update this once the response to IR is received.

Note: If intermediate facility is not deemed critical, the facility IR comment is NOT issued to the ANDA applicant.

3. Are there any intermediate facilities **listed in the 356h**? ☐Yes ☒No

If yes, determine if the intermediate facility is critical.

Facility Name and Address	FEI/DUNS	Intermediate critical (Y/N)	Justification*

* If an intermediate facility is identified, please select justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

4. Does the Type II API DMF list any manufacturing facilities, intermediate facilities, or testing facilities for routine release or stability testing that are **not listed in the facility profile and/or on the 356h** form for the referencing ANDA? ☐Yes ☒No

If yes, include the information identifying each facility and its function below:

Facility Name and Address#	**Function$**	**Justification if Intermediate facility***	**FEI/DUNS#**

* If an intermediate facility is identified, please select justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

Note: If intermediate facility is not deemed critical, the facility IR comment is NOT issued to the ANDA applicant.

[$] Facility function codes for hidden and critical intermediate facilities:

CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
LCP: Laboratory, Chemical/Physical Testing
LBI: Laboratory, Biological Testing
LMS: Laboratory, Microbiological – Sterility Testing
LMN: Laboratory, Microbiological – Non-Sterility Testing
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation
CRU: API Non-Sterile/Intermediate (***Note: The only code to be used for the intermediate facilities***)

[#]***Note:*** *Not for FOI boxes (refer to SOP for format) need to be used if the facility information is submitted in a secondary DMF.*

Note to Reviewer: Do not alter this language beyond providing the specifics for the yellow and blue text.

DMF hidden facility language to be issued to ANDA applicant if the site is in primary or secondary DMF:

n/a

5. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?
☐Yes ☒No

   If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

   Consult form date:

6. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☐No ☒N/A

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☒No

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:

ANDA	**216848**
Applicant	Lepu Pharmaceutical Technology Co., Ltd.
Drug	Atorvastatin Calcium Tablets, USP
Strength	10 mg, 20 mg, 40 mg, and 80 mg
RLD | N210259	**Lipitor** (*Approved on Apr 07, 2000 for Upjohn Manufacturing Ireland Ltd*)
Risk Profile Performed By	Vijay Sharma, PhD

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	COMMENT
Physical stability (solid state)	3-1 = 2	3	4	24	(b) (4)
Chemical stability	4	3	4	48	
Assay	2	3	3	18	
Content uniformity	3-1 = 2	3	4	24	
Microbial limits	3	3	3	27	

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	COMMENT
					(b) (4)
Dissolution	4	3	4	48	

- Product properties or CQAs | RPN of <25 | Low risk
- Product properties or CQAs | RPN of ≥25 | Moderate risk
- Product properties or CQAs | RPN ≥60 | High risk

Drug Product CQAs	Initial Risk	Comments	Updated Risk Cycle #1	Comments
Physical stability	24	(b) (4)		
Chemical stability	48			

Drug Product CQAs	Initial Risk	Comments	Updated Risk Cycle #1	Comments
Assay	18	(b) (4)		
Content uniformity	24			
Microbial limits	27			
Dissolution	48			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216848

BIOEQUIVALENCE REVIEW(s)

Knowledge-Aided Assessment and Structured Application Biopharmaceutics Assessment

Overview

ANDA Basic Information	
ANDA No.	216848
DP Name[1]	Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 mg and 80 mg
RLD/RS No.	020702
Applicant	LEPU PHARMACEUTICAL TECHNOLOGY CO., LTD.
Dosage	Tablet IR
Route	Oral
Primary Assessor	Annie Fomene, Pharm.D.
Secondary Assessor	Anitha Govada, Ph.D.
USP Revision to the Official Monograph	Pending Monograph process
Overall Review Outcome	Adequate

Biopharmaceutics Executive Summary

This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed in-vitro dissolution method as a quality control test (QC) and the acceptance criterion for the proposed drug product. The Applicant originally conducted dissolution testing using (b) (4) the dissolution method described in the FDA Dissolution Methods Database, and in the USP monograph as dissolution test 1. The Applicant provided data shows that the drug substance (DS), atorvastatin calcium has (b) (4) solubility. The initial risk was ranked as medium based (b) (4) The proposed drug product exhibits (b) (4) using the proposed dissolution method. To assess the suitability of the proposed dissolution testing parameters/conditions, for the proposed drug product, additional data to support the proposed method's discriminating ability and (b) (4) In the response submitted on 08/05/2022, the Applicant provided dissolution data using (b) (4)

Based on the totality of the information, the final dissolution method with (b) (4) [using USP Apparatus 2 (paddle) at 60 RPM, 900 mL of 0.05 M phosphate buffer, pH 6.8] with an acceptance criterion of Q=(b) (4)% in 30 minutes] was recommended for the proposed product in an IR on 9/23/2022.

The Applicant accepted FDA's recommendations in the response submitted on 09/27/2022. In addition, the Applicant has committed to submit updated stability data in the post approval stability period for the shelf-life (b) (4) using the revised dissolution method and acceptance criterion. The Applicant submitted updated drug product batch release and stability specifications. The recommended dissolution method for the drug product, differs from the method described in the USP monograph for *Atorvastatin Calcium Tablets*. *Therefore, the Applicant was notified on 9/28/2022 to petition USP for the revision of official monograph.*

Recommendation: From a Biopharmaceutics perspective, **ANDA 216848** for the proposed Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 mg and 80 mg is recommended for **APPROVAL**.

Has OGD deemed the drug product BE to the RLD?	Yes[2]

[1] **IR comments were issued by the Labelling Reviewer for the Applicant to update the drug product's name to include USP in the description, refer to the Labelling review below for more details:**
https://panorama.fda.gov/internal/document/preview?versionID=629102a7003560aeec6f9ba3559da43a&ID=6290f90a002025f1a4bb10990336f13a

[2] **BE Assessor Review**
https://panorama.fda.gov/internal/document/preview?versionID=62b9a4e2002066254aba5bb72f63fab4&ID=629537d0001e8fc3e5060eb175192b62

Drug Substance	The method in USP
ATORVASTATIN CALCIUM TRIHYDRATE (Tablet IR)	Refer to Reviewer's comments in the Executive summary additional comments section above.

Drug Substance(s) and Drug Product				
DS Name		Strength Name (Active Moiety or Salt)	Therapeutic Area	Therapeutic Sub-Category
1	ATORVASTATIN CALCIUM TRIHYDRATE	Atorvastatin Calcium	Diabetes, Lipid Disorders, and Obesity	Lipid altering agents

DP Strength List	
	DS 1
	mg
Strength 1	80
Strength 2	20
Strength 3	40
Strength 4	10

Additional Notes
The DP is an immediate-release film-coated tablet without a score manufactured by [redacted] (b) (4)

Review Iteration				
Review Iteration		Assessor Decision	Comments	Submission Date
1	Original Review	DRL-Inadequate minor	The Applicant will be requested to clearly update the drug specification test for proposed the acceptance criterion and resolve the OLDP Reviewer deficiency comments regarding the control of the PSD and polymorphic form of the API.	06/13/2022
1	Original review	DRL-Response	After reviewing the Applicant's newly submitted comparative dissolution data between [redacted] (b) (4) new IR comment were sent to the Applicant to implement a new dissolution method and acceptance criterion.	08/05/2022
1	Original review	IR Biopharm comments-Adequate	The Applicant accepted FDA's recommendations for the dissolution method and acceptance criterion.	09/27/2022

Lifecycle Management for ANDA 216848	
Biopharmaceutics Risk Mitigation Strategy	Adequate in vitro dissolution specifications
Supportive BA/BE	Adequate BE
Other Relevant Comment	None

Approved Dissolution Specification						
ATORVASTATIN CALCIUM TRIHYDRATE - Tablet IR						
	Strengths	Apparatus	Rotation Speed	Temperature	Medium / Volume (ml)	Acceptance Criterion
1	10 mg 20 mg 40 mg 80 mg	2-Paddle	60 rpm	37 °C	900 mL of 0.05 M phosphate buffer, pH 6.8 - Volume: 900 ml	Q= (b) (4) % in 30 minutes

Reference Biopharmaceutics Properties

RLD Basic Information	
NDA No.	020702
Non-proprietary DP Name	ATORVASTATIN CALCIUM
Proprietary DP Name	LIPITOR

RLD (NDA 020702) Reference Information	
Dosage and Administration	(b) (4)
Equilibrium Solubility	(b) (4)
pKa	(b) (4)
Bioavailability	The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability is approximately 30%.
Pharmacokinetics	Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The low systemic availability is attributed to pre systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
BCS Classification	BCS class II (low solubility and high permeability) compound
DS/DP Characterization	N/A
Other Relevant Biopharm Information	N/A

Reference Documents		
URL Description	URL	Init. Page
RLD Labeling	https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020702s077lbl.pdf	1
Composition-10mg	\\CDSESUB1\evsprod\nda020702\0000\m3\32-body-data\32p-drug-prod\lipitor\32p-desc-comp\dfm-37010a.pdf	1
Composition- 20mg	\\CDSESUB1\evsprod\nda020702\0000\m3\32-body-data\32p-drug-prod\lipitor\32p-desc-comp\dfm-37020a.pdf	1
Composition-40mg	\\CDSESUB1\evsprod\nda020702\0000\m3\32-body-data\32p-drug-prod\lipitor\32p-desc-comp\dfm-370040a.pdf	1
Composition-80mg	\\CDSESUB1\evsprod\nda020702\0000\m3\32-body-data\32p-drug-prod\lipitor\32p-desc-comp\dfm-37080.pdf	1

RLD Drug Substance(s) and Drug Product		
	DS Name	Strength Name (Active Moiety or Salt)
1	ATORVASTATIN CALCIUM TRIHYDRATE	Atorvastatin calcium

RLD DP Strength List	
	DS 1
	mg
Strength 1	40
Strength 2	80
Strength 3	20
Strength 4	10

Pilot BE Studies

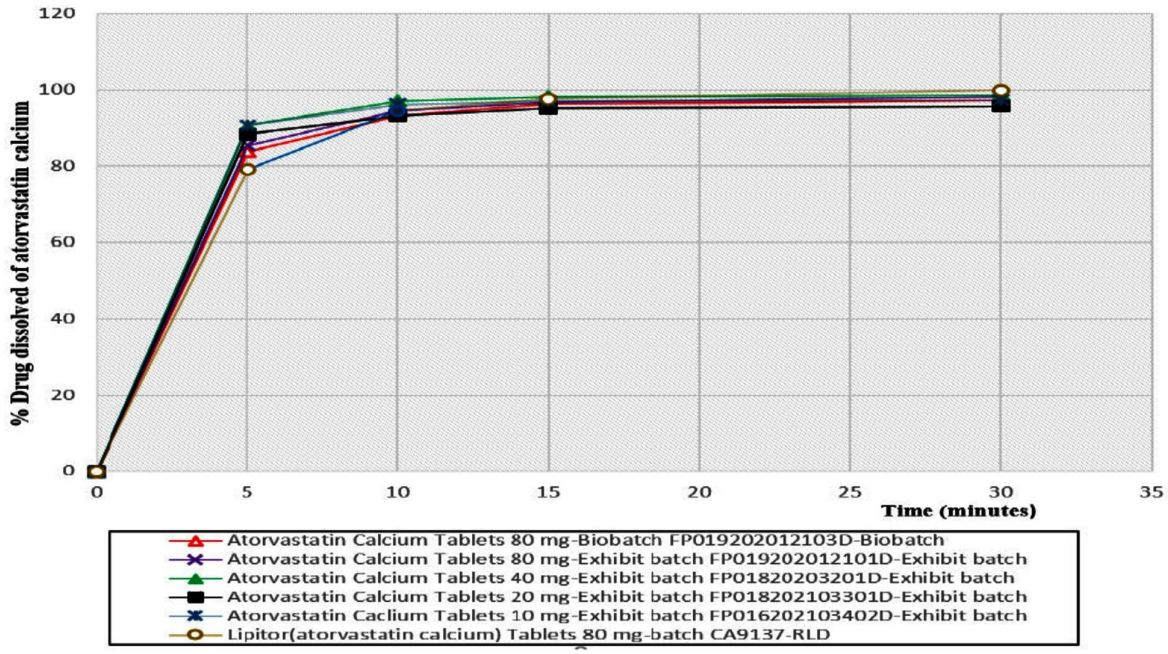
Are there any submitted pilot studies evaluating the BE of several formulation variants for the test product?	No
Reviewer Evaluation	The Applicant did not submit any pilot BE studies.

Drug Substance Information

ATORVASTATIN CALCIUM TRIHYDRATE (IR)	
Drug Substance Information	
High Risk drug substance	Medium – DS solubility is low
BCS Solubility	Low
BCS Class Reported by Applicant	II
BCS Class Reported by WHO	n/a
Is the Cmax Critical to Ensure Safety?	No
Is Tmax Critical?	No

Dissolution Plot(s)

Figure 1: Dissolution data : Dissolution of atorvastatin calcium from Atorvastatin Calcium Tablets, 10 mg, 20, 40 and 80 mg using the proposed dissolution method, (b) (4)



Note: The Reviewer has plotted 1 strength of each exhibit batch vs. Biobatch vs. RLD and that the f2 similarity factor was not calculated between the bio-batch and exhibit batch of each proposed strength because (b) (4)

Table 1 -Solubility data of the drug substance atorvastatin calcium in different pH medium 1.0-~7.4

Media	Solubility (mg/ml)
[redacted]	(b) (4)

Note: The solubility data was calculated based on the highest single daily dose of 80 mg

Solubility link:
\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p2-pharm-dev\pharmaceutical-development-1.pdf, refer to page 19

Figure 2: Dissolution data of RLD batch CA9137 for Lipitor (atorvastatin calcium) 80 mg in multi-media pH

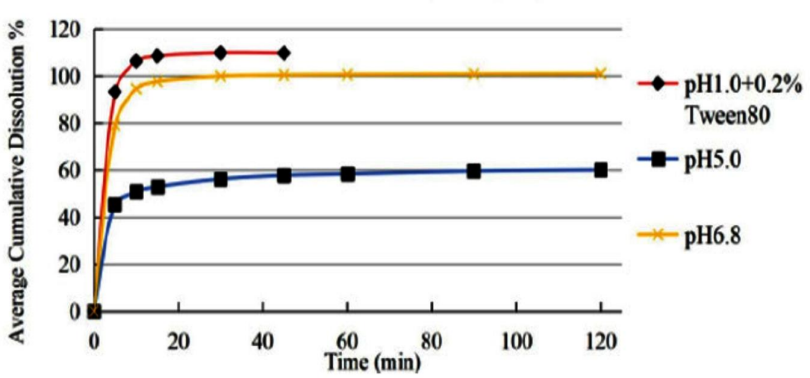
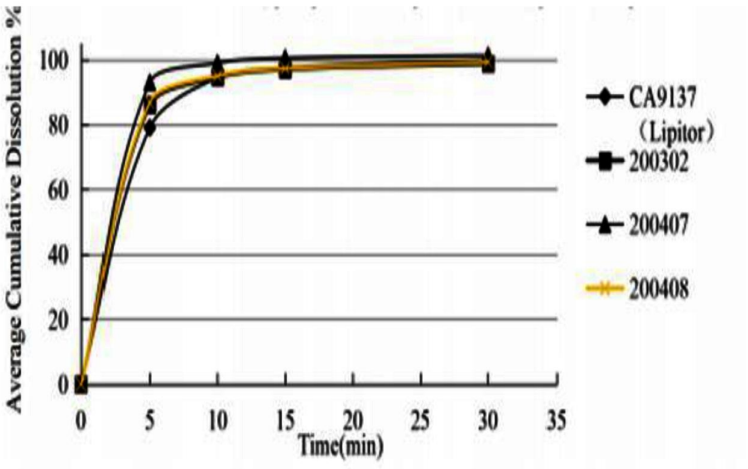


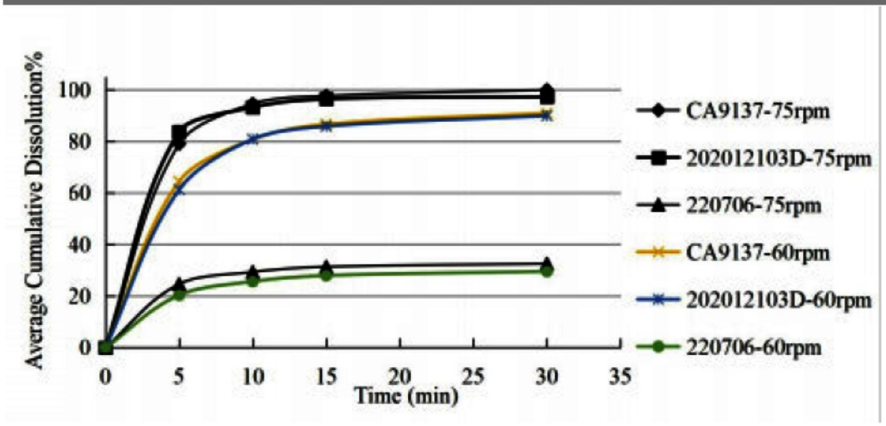
Figure 3: Discriminating ability data studies of the effect of the changes in the amount of the CFV, disintegrant croscarmellose Na on dissolution



RLD:CA9137 (Lipitor)

(b) (4)

(b) (4)



Assessor comments: The dissolution profiles in the above plot indicate that the proposed dissolution method (b) (4)

Table 2: Dissolution data (N=12) of the proposed drug product using 900 mL of 0.05 M phosphate buffer, pH 6.8 using USP Apparatus 2 at 60 rpm for new exhibit batches of the proposed drug product, Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 mg and 80 mg

(b) (4)

(b) (4)

Assessor comments: After evaluation of the dissolution data submitted on 8/5/2022 per table 2 above, a revision of the dissolution method (b) (4) was found as most suitable for the proposed drug product.

Reviewer Evaluation	This Reviewer evaluated Tmax as not critical because the drug product is an immediate-release formulation and used for non-acute indications. This Reviewer noted that per the Prescribing Information, the package insert, the usual recommended starting dose range is 10 or 20 mg up to a maximum daily dose of 80 mg once daily. The highest strength which is the same as the highest dose is 80 mg. The highest single daily dose (80 mg)/250 mL =0.32 mg/mL (b) (4) based on BCS classification. Hence, based on the totality of information, the Reviewer agrees with the Applicant's classification of atorvastatin calcium as low solubility per BCS class. (b) (4) Solubility link **Packet insert link:** \\CDSESUB1\evsprod\anda216848\0004\m1\us\114-labeling\114a-draft-label\draft-labeling-text-in-pdf.pdf, refer to page 1

Are there supportive BE studies (i.e. pilot BE studies evaluating formulation variants) to support the in vivo relevance of the dissolution test?	No
Reviewer Evaluation	The Applicant did not provide any pilot BE studies.

Initial Risk Assessment

ATORVASTATIN CALCIUM TRIHYDRATE (IR) / BCS Solubility: Low	
Is drug substance's permeability high?	Yes
Does the in vitro dissolution of the highest strength show rapid dissolution in a medium in the pH range 4.5-6.8 (without surfactant)?	No
Could Critical Bioavailability Attribute(s) be clearly identified, detected and controlled?	No
Could IVIVC/R be established with PBBM and/or any available in vitro and in vivo data?	No
Initial Risk Ranking	Medium
Rationale for Risk Update	Since the Applicant submitted solubility data that shows that atorvastatin calcium is low soluble by BCS class, this Reviewer classified the initial dissolution risk as medium due to [redacted] (b) (4) . Solubility link

Mitigation Strategies

ATORVASTATIN CALCIUM TRIHYDRATE (IR) / BCS Solubility: Low / Initial Risk: Medium	
Are the dissolution method development and validation reports submitted?	Yes
Reviewer Evaluation	The Applicant submitted a dissolution method report for justification of the proposed dissolution method and criterion. Original validation report Updated validation report Pharmaceutical development report
Is the proposed dissolution method discriminating to identified critical BA attributes that has potential to affect in vitro/in vivo dissolution?	No
Reviewer Evaluation	[redacted] (b) (4)

[3] **Discriminating studies**
\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatincalciumtablets-tablet\32p2-pharm-dev\pharmaceutical-development-1.pdf, refer to page 69

	in CFV. Refer to this link[4] below for more details on the updated discriminating ability data and figure 4 above. Discriminating ability link Updated discriminating ability link on 8/5/2022
Are there other information/data supporting the proposed dissolution method? (Yes/No) (required) (e.g., Justification for the lack of discriminating ability; controls on identified critical BA attributes as supported by clinical/PK/BE batches - refer to drug product/process review; interaction is encouraged as needed*)	Yes
Reviewer Evaluation	The Applicant's data show that 12 validated batches were manufactured [redacted] (b) (4) with satisfactory dissolution data. This Reviewer notes the OLDP reviewers have found the dissolution analytical method is suitable for atorvastatin calcium drug product. Refer to OLDP Assessor review for more details

Recommended Biopharmaceutics Mitigation Strategies (Pertinent Critical Bioavailability Attribute(s) CBAs)

Attributes	Strength(s)	Control Strategy	Proposed Control Limit	Comment
[redacted] (b) (4)				

Mitigated Biopharmaceutics Risk Level	Reviewer Evaluation
Low	This Reviewer considers that the dissolution risk will be mitigated from medium risk to low (b) (4) [redacted]

Drug Substance

Dissolution Method and Acceptance Criterion

ATORVASTATIN CALCIUM TRIHYDRATE (Tablet IR)

Originally Proposed Dissolution Method and Acceptance Criterion

Strength	Apparatus	Rotation Speed	Temp (°C)	Medium/Volume (mL)	Acceptance Criterion	Adequate
[redacted] (b) (4)						

[4] **Updated discriminating ability link on 8/5/2022**
\\CDSESUB1\EVSPROD\anda216848\0005\m1\us\12-cover-letter\dissolution-profile-investigation-report-of-atorvastatin-cal.pdf, refer pages 1-12

	[redacted] (b) (4)
Unique Situations	
Any unique situations not covered by KASA?	Yes, due to space limitations, this Reviewer's comments were cut in KASA in some sections. Refer to the Panorama word review for the full comments of this ANDA review approved by the Secondary.
Adequate	Yes
Reviewer Evaluation	After the Applicant's response date 9/27/2022, both the dissolution test method and acceptance criterion are now adequate. Refer to Reviewer's evaluation above for more detail.
Proposed Dissolution Testing	
• In the original submission dated 1-04-2022, the Applicant conducted dissolution testing using [redacted] (b) (4) . • On 9/27/2022, the Applicant updated to a recommended dissolution method 900 mL of 0.05 M phosphate buffer, pH 6.8 using USP Apparatus 2 (paddle) at 60 rpm and acceptance criterion of Q= [redacted] (b) (4) % drug dissolved in 30 minutes.	
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Yes[7]

[5] **Dissolution data using 50 pm in the Applicant's response dated 08/05/2022**
\\CDSESUB1\EVSPROD\anda216848\0005\m2\27-clin-sum\summary-biopharm.pdf, refer to page 10
[6] **Applicant's retesting of all exhibit batches using 60 rpm in the response dated 9/27/2022**
\\CDSESUB1\EVSPROD\anda216848\0006\m1\us\12-cover-letter\response-to-ir-quality.pdf, refer to page 2
[7] **OLDP Assessor Reviewer review**
https://panorama.fda.gov/internal/document/preview?versionID=62a75ced0042fd547a4f68028d7c3f61&ID=62a75b800042dbf98f89f93195804d22, refer to page 40

Description of Links for Dissolution Methods	URL Link
Dissolution test method	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatncalciumtablets-tablet\32p5-contr-drug-prod\32p52-analyt-proc\analyt-proc.pdf Updated dissolution method on 9/27/2022 Updated dissolution test specifications 9/27/2022
Multimedia dissolution profiles	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32s-drug-sub\atorvastati calcium-lepu\32s7-stab\stability-summary.pdf
Drug product release specification for the proposed dissolution acceptance criterion	\\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastatncalciumtablets-tablet\32p5-contr-drug-prod\32p51-spec\specifications.pdf
Discriminating ability link	\CDSESUB1\evsprod\anda216848\0001\m3\32-body-data\32p-drug-prod\atorvastaticalciumtablets-tablet\32p2-pharm-dev\pharmaceutical-development-1.pdf
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	Yes
Number of units tested meets the requirements (e.g. 12 units)	Yes
Source of Dissolution Test Method	Proposed in-house method
Is method development report provided?	Yes, Updated dissolution method on 9/27/2022 Updated specification test specification 9/27/2022
Does the proposed drug product meet the USP Monograph standards?	No it does not meet the official USP Monograph standards (b) (4) [redacted]
Actions requested of the Applicant	Initiate USP Monograph revision
Reviewer Evaluation	This Reviewer notes that there are currently 6 dissolution test methods described in the USP Monograph for Atorvastatin Calcium Tablets. (b) (4) [redacted]

Drug Product Exhibit Batch Dissolution Testing

Commercial batch size is within a factor of ten times the size of the biobatch	Yes
Testing was conducted using unexpired and/or fresh lots	Yes
Reviewer Evaluation	This Reviewer notes that all the batches tested were approximately 1 month of age at the time of dissolution. The biobatch (80 mg strength) is FD19202012103D; Information of batches
Is the RLD drug product scored?	No

DEFICIENCY

The following Biopharmaceutics Information Request (IR) comments were conveyed to the Applicant:

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	Acceptance criterion specifications
			[Deficiency comments in DRL[8] dated 07/08/2022]
			(b) (4) . To demonstrate the suitability of your proposed dissolution method for the proposed drug product, submit additional information listed below, including complete dissolution profiles for the proposed drug product, Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 mg and 80 mg: 1. Provide dissolution data for all strengths of the proposed drug product, (b) (4) 2. (b) (4) a. It is noted that various variables like the change in the levels of the Particle Size Distribution and Polymorphism may significantly impact dissolution of your proposed drug product. Demonstrate the discriminating ability of the dissolution method with regards to these formulation variables, as per the above recommendations. b. Provide a) the manufacturing date, storage conditions and the age of the batches used in the above studies, b) the number of dosage units used to generate the dissolution data, c) table number and separate table heading for each table, and d) graphic presentation for the mean dissolution data for each table. 3. The adequacy of the proposed dissolution acceptance criterion will be determined after assessing the above requested information and upon acceptability of the proposed dissolution method.
			[Summary of the applicant's response and reviewer comment]
			In their response on 08/05/2022, (b) (4) this Reviewer finds the dissolution method using 60 rpm and the acceptance criterion of Q=(b) (4)% in 30 minutes most optimal for QC testing of the proposed drug product. Refer to new IR comments dated 09/24/2022. Response to Biopharmaceutics DRL comments
DRL Response		1	**[Summary of the applicant's response to new biopharmaceutics comments[9] dated 9/23/2022 and Reviewer comments]**

[8] **Biopharmaceutics comments in DRL dated 7/08/2022**
https://panorama.fda.gov/internal/document/preview?versionID=62c8575000201692ca80b851dd8de5db&ID=62a97d19006081f572fad6a213b9435b, **refer to page 6**
[9] **Biopharmaceutics IR comments dated 9/23/2022**

	Solved pending SEC		In their response on 09/27/2022, the Applicant explained that FDA's recommendations were accepted (b) (4) [redacted]. This Reviewer finds the Applicant's updates for the drug product batch release and stability specifications acceptable. This Reviewer finds the Applicant's response acceptable and notes that USP revision comments were conveyed on 09/27/2022 for the Applicant to acknowledge, refer to executive summary section for more details. This Reviewer notes that the adequacy of the update to USP revision comments in the description section of the label is under the purview of the Labelling Reviewer. Response to Biopharmaceutics comments dated 9/23/2022 **[Deficiency IR comments dated 9/23/2022 below /IR Previous Iteration]** We have reviewed your response dated 8/05/2022. (b) (4) [redacted] Therefore, based on the totality of the information provided, we recommend that you implement the following dissolution method and acceptance criterion for your proposed Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 and 80 mg Dissolution method: 900 mL of 0.05 M phosphate buffer, pH 6.8 using USP Apparatus 2 (paddle) at 60 rpm Acceptance criterion: Q= (b) (4) % drug dissolved in 30 minutes Note that the dissolution acceptance criterion is set based on the mean value. Therefore, some batches may require Stage 2 and occasionally Stage 3 testing. Update your drug product batch release and stability specifications accordingly. In addition, be advised, that all proposed exhibit batches are expected to meet the revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed. In the response submitted on 9/27/2022, The Applicant accepted the FDA recommended dissolution method and acceptance criterion and submitted updated drug product batch release and stability specifications.

https://panorama.fda.gov/internal/document/preview?versionID=632e7d3a01435aa547e5952f637b9ba6&ID=632e7c0c0143555388e04e84e4a761af

Annie Fomene

Digitally signed by Annie Fomene
Date: 9/30/2022 12:10:59PM
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Anitha Palamakula Govada

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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	216848
Drug Product Name	Atorvastatin Calcium Tablets USP
Strength(s)	EQ 10 mg base, EQ 20 mg base, EQ 40 mg base, and EQ 80 mg base
Applicant Name	Lepu Pharmaceutical Technology Co. Ltd.
Applicant Address	No. 27 Binhai Road, Jiaojiang District Taizhou, Zhejiang 318000 China
US Contact Name and US Mailing Address	Saxon International Associated 10 DeBary Place Summit, NJ 07901
US Contact Telephone Number	1-908-273-1303
US Contact Email	Petersaxon@psaxon.com
Original Submission Date(s)	01/04/2022
Submission Date(s) of Amendment(s) Under Review	N/A
Primary Reviewer	Taylor Smith, Ph.D.
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.

Study Number(s)	325-20	326-20
Study Type(s)	Fasting	Fed
Strength(s)	80 mg	80 mg
Clinical Site	(b) (4)	
Clinical Site Address		
Analytical Site		
Analytical Site Address		

Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**

	☐ N/A (Waiver/Deem Bioequivalent)	☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is Adequate)	
Major Deficiency Theme	N/A	
Justification for Major Designation	N/A	
Overall Review Result	☒ Adequate ☐ Inadequate	
Product Specific Guidance (PSG) Referenced in Review	***Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)*** ☒ Recommended/Latest Revision Date: Oct 2010_ RS Number: NDA 020702 ☐ N/A (no PSG available at time of review)	
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO	

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1,2,3	**Fasting**	80 mg	☒ Adequate ☐ Inadequate
1,2,3	**Fed**	80 mg	☒ Adequate ☐ Inadequate
1,2,3	**Waiver/Deem Bioequivalent**	10 mg, 20 mg, and 40 mg	☒ Adequate ☐ Inadequate

* EQ 10 mg base, EQ 20 mg base, EQ 40 mg base, and EQ 80 mg base will be 10 mg, 40 mg and 80 mg within review.

1 EXECUTIVE SUMMARY

This application contains the results of a fasting (study # 325-20) and fed (study # 326-20) bioequivalence (BE) studies comparing a test product, Lepu Pharmaceutical Technology Co. Ltd's Atorvastatin Calcium Tablets, USP, EQ 80 mg base to the corresponding reference product, Pfizer Inc.'s Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg base. Each of the BE studies was designed as a single-dose, 3-period, 3-sequence, partial replicated crossover study in healthy subjects. The assessor calculated results are summarized in the tables below.

Atorvastatin

Atorvastatin Calcium Tablets, EQ 80 mg base (No. of subjects completed=48) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 325-20							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	359.93	48	355.00	48	1.01	96.19	106.87
AUC∞ (hr *ng/ml)	362.88	48	357.93	48	1.01	96.22	106.83
Cmax (ng/ml)	90.36	48	88.75	48	1.00	90.87	114.08

Fasting Bioequivalence Study (Study No. 325-20)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT	1.02	96.19	106.87	0.0323677	0.1799103	-0.017517	Unscaled	PASS
LAUCI	1.02	96.22	106.83	0.0321482	0.1792992	-0.017436	Unscaled	PASS
LCMAX	1.02	90.87	114.08	0.1306727	0.3614868 (>0.294)	-0.072329	Scaled/PE	PASS

Atorvastatin

Atorvastatin Calcium Tablets, EQ 80 mg base (No. of subjects completed=51) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. 326-20							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	335.54	51	339.35	51	0.99	92.88	105.27
AUC∞ (hr *ng/ml)	339.40	51	343.11	51	0.99	92.98	105.24
Cmax (ng/ml)	62.79	51	66.81	51	0.94	85.35	103.51

Fed Bioequivalence Study (Study No. 326-20)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT	0.98	92.88	105.27	0.0170619	0.1306211	-0.005574	Unscaled	PASS
LAUCI	0.98	92.98	105.24	0.0166679	0.1291044	-0.005566	Unscaled	PASS
LCMAX	0.91	85.35	103.51	0.0704956	0.2655101	-0.015222	Unscaled	PASS

The reference scaled average bioequivalence approach is applied for both fasting and fed studies following the recommendation in the PSG[1]. For atorvastatin, S_{WR} is less than 0.294 for $LnAUC_t$, and $LnAUC_\infty$ in the fasting and fed studies, and for Cmax in the fed study. Thus, average bioequivalence approach is applied for these PK parameters. The 90% confidence intervals (CIs) of the test/reference ratios for LnCmax, LnAUCt, and LnAUC∞ were all within the acceptable range of 80.00-125.00%. Since S_{WR} is greater than 0.294 for Cmax in the fasting study, the reference scaled average bioequivalence approach is applied for Cmax. In the BE studies, the PK parameters of the test and reference in the fasting and fed studies for the active metabolites (ortho-hydroxylated Atorvastatin and para-hydroxylated Atorvastatin) were comparable. Therefore, the metabolite data are supportive, and the fasting and fed BE studies are acceptable.

The test product formulations of 10 mg, 20 mg, 40 mg are proportionally similar to the 80 mg of the test product. The applicant conducted comparative dissolution testing using the FDA-recommended method. The dissolution testing is currently being reviewed by the Office of Pharmaceutical Quality (OPQ) and is inadequate pending applicant's response to deficiencies[2]. The dissolution data are adequate with respect to supporting waiver requests under 21 CFR 320.22 (d)(2) for the lower immediate release strength(s). The Division of Bioequivalence III (DBIII) grants the waiver requests for in vivo BE study requirements for the following strengths (10 mg, 20 mg and 40 mg) based on the criteria set forth in 21 CFR 320.22 (d)(2).

OSIS Status "Complete"

Per GDRP, OSIS inspection(s) at both clinical [redacted (b) (4)][3] and analytical [redacted (b) (4)][4] sites are classified as No Action Indicated (NAI). In addition, the study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is complete.

The application is adequate.

[1] Product Specific Guidances for Generic Drug Development
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Atorvastatin_tabs_20702_RC5-08.pdf
[2] GDRP. Search ANDA-216848-ORIG-1. Drug Product Quality Review.
https://panorama.fda.gov/internal/document/preview?versionID=62a75ced0042fd547a4f68028d7c3f61&ID=62a75b800042dbf98f89f93195804d22

[redacted (b) (4)]

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[5]

Test Drug Product and Strength(s)	Atorvastatin Calcium Tablets USP, EQ 10 mg base, EQ 20 mg base, EQ 40 mg base, and EQ 80 mg base
Reference Standard (RS) and Strength(s)	Lipitor® (atorvastatin calcium) Tablets, EQ 80 mg base
RS Holder; NDA/ANDA Number; Approval Date	Pfizer Inc. NDA 020702 Approved Apr 7, 2000
Reference Listed Drug (RLD) and Strength(s)	Lipitor® (atorvastatin calcium) Tablets, EQ 10 mg base, EQ 20 mg base, EQ 40 mg base, and EQ 80 mg base
RLD Holder; NDA/ANDA Number; Approval Date	Pfizer Inc. NDA 020702 Apr 7, 2000 (EQ 80 mg base) Dec 17, 1996 (EQ 40 mg base, EQ 20 mg base and EQ 10 mg base)

3.2 PK/PD Information

Most recent RLD label (provide embedded document)[6] Please check if an NG/G/J tube study is needed.	RLD LBL.pdf Last updated 11/16/2020; Last accessed 05/09/2022. No NG/G/J tube study is indicated in the label.
Indication	LIPITOR is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to: • Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors. • Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors. • Reduce the risk of no-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD. • 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.

[5] Per Orange Book. https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
[6] Drugs @FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020702s077lbl.pdf; Last updated 11/16/2020; Last accessed 05/09/2022.

	• Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia. • Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH). • Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy. Limitations of Use: • LIPITOR has not been studied in Fredrickson Types I and V dyslipidemias
Boxed warning	Not Applicable (N/A)
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 pre-systemic 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 LIPITOR is given with or without food. 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. 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.
Tmax	1 to 2 hours
Metabolism	LIPITOR is extensively metabolized to ortho-and para-hydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho-and para-hydroxylated metabolites is equivalent to that of LIPITOR. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR metabolism by cytochrome

	P450 3A4, consistent with increased plasma concentrations of LIPITOR in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxylated 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. 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. Less than 2% of a dose of LIPITOR is recovered in urine following oral administration.
Half-life	Approximately 14 hours
Maximum Daily Dose	80 mg

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	PSG Atorvastatin_tabs_2((Recommended May 2008; Revised Oct 2010)	
Summary of OGD or DB History	Approved ANDAs:[7]	ANDA 213853, ANDA 076477, ANDA 077575, ANDA 091226, ANDA 090548, ANDA 091650, ANDA 202357, ANDA 091624, ANDA 205519, ANDA 204846, ANDA 205300, ANDA 207687, ANDA 209912, ANDA 206536, ANDA 209288, ANDA 211933, ANDA 204991, ANDA 205945,
	Pending ANDAs:[8]	ANDA 214513, ANDA 216848, (b) (4) ANDA 211886, ANDA 208480 Complete Response: ANDA 214344, (b) (4) ANDA 212103

[7] Orange Book Online. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
[8] DAARTS; Search Atorvastatin. https://darrts.fda.gov/darrts/faces/ApplicationSearchResultTF/applicationSearchResults?_afrRedirect=833208701354082&_afrPage=3

	Controls:	None from the current applicant
	Protocols:	None from the current applicant
	Pending Citizen Petitions and other legal and regulatory issues: If yes, please comment below.	☐ Yes ☒ No

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data		
Bioanalytical method validation report location	m5\53-clin-stud-rep\531-rep-biopharm-stud\\5314-bioanalyt-analyt-met\stud-rep-325-20-fasting\325-20-fasting-5314-bio-ana-report\Annexure-I\ Method Validation Reports High Performance Liquid Chromatography – Mass Spectrometric Method Validation Report of Atorvastatin, o-Hydroxy Atorvastatin, p-Hydroxy Atorvastatin and Total Ezetimibe in K2EDTA Human Plasma		
Analyte (s)	Atorvastatin	o-Hydroxy Atorvastatin	p-Hydroxy Atorvastatin
Internal standard (IS)	Atorvastatin D5	o-Hydroxy Atorvastatin-d5	p-Hydroxy Atorvastatin-d5
Method description	Analytical Technique: LC–MS/MS Detection: Electro Spray Ionization in Multiple Reaction Monitoring mode Analytical Column: Discovery® C18, 5µm, 250 X 4.6mm Mobile Phase: 0.1% Formic acid: acetonitrile; 40:60 v/v Biological Matrix: Human Plasma Anticoagulant: K_2EDTA Sample Extraction Method: Solid Phase Extraction Sample Processing Volume: 300 µL Quantification Method: Peak Area Ratios Regression, Weighting Factor: Linear Regression, $1/X^2$		
Limit of Quantitation	0.100 ng/mL	0.200 ng/mL	0.100 ng/mL
Average Recovery of drug (%)	MV-491-00 Atorvastatin: 90.01%, %CV=1.0 HQC: 90.7%, MQC: 90.4%, LQC: 89% MV-491-00 (Addendum-1)	MV-491-00 o-Hydroxy Atorvastatin: 89.97%, %CV=0.6 HQC:89.7%, MQC: 90.6%, LQC: 89.6% MV-491-00 (Addendum-1)	MV-491-00 p-Hydroxy Atorvastatin: 91.46%, %CV=2.0 HQC: 89.7%, MQC: 91.2%, LQC: 93.4% MV-491-00 (Addendum-1)

	Atorvastatin: 99.08%, %CV=2.5 HQC: 100.7%, MQC: 100.3%, LQC: 96.3%	o-Hydroxy Atorvastatin: 99.09%, %CV=1.8 HQC: 99.6%, MQC: 100.5%, LQC: 97.2%	p-Hydroxy Atorvastatin:98.04%, %CV=0.8 HQC: 98.2%, MQC: 97.2%, LQC: 98.8%
Average Recovery of IS (%)	MV-491-00 Atorvastatin D5: 91.8%, %CV=1.7 MV-491-00 (Addendum-1) Atorvastatin D5: 100.0%, %CV=2.3	MV-491-00 o-Hydroxy Atorvastatin D5: 92.1%, %CV=1.4 MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin D5: 100.2%, %CV=2.4	MV-491-00 p-Hydroxy Atorvastatin D5: 92.3%, %CV=1.6 MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin D5: 102.3%, %CV=2.0
Standard curve concentrations (ng/mL)	MV-491-00 Atorvastatin: 0.100, 0.200, 1.000, 6.004, 30.021, 150.107, 240.171 & 300.214 ng/mL MV-491-00 (Addendum-1) Atorvastatin: 0.100, 0.201, 1.003, 6.021, 30.105, 150.527, 240.843 & 299.184 ng/mL	MV-491-00 o-Hydroxy Atorvastatin: 0.200, 0.400, 3.997, 19.986, 49.966, 128.283, 160.354 & 200.442 ng/mL MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin: 0.200, 0.400, 4.000, 20.001, 50.002, 128.210, 160.263 & 200.328 ng/mL	MV-491-00 p-Hydroxy Atorvastatin: 0.100, 0.200, 1.002, 3.001, 7.502, 15.003, 24.083 & 30.103 ng/mL MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin: 0.100, 0.200, 1.002, 3.001, 7.503, 15.005, 24.055 & 30.069 ng/mL
QC concentrations (ng/mL)	MV-491-00 Atorvastatin: 0.100, 0.299, 90.711 & 226.778 ng/mL for LLOQQC, LQC, MQC & HQC respectively MV-491-00 (Addendum-1) Atorvastatin: 0.100, 0.299, 90.459 & 226.147 ng/mL for LLOQQC, LQC,	MV-491-00 o-Hydroxy Atorvastatin: 0.200, 0.594, 61.244 & 153.111 ng/mL for LLOQQC, LQC, MQC & HQC respectively MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin:	MV-491-00 p-Hydroxy Atorvastatin: 0.100, 0.298, 9.917 & 23.897 ng/mL for LLOQQC, LQC, MQC & HQC respectively MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin: 0.100, 0.298, 9.687 & 23.342 ng/mL for LLOQQC,

	MQC & HQC respectively	0.200, 0.596, 61.408 & 153.521 ng/mL for LLOQQC, LQC, MQC & HQC respectively	LQC, MQC & HQC respectively
QC Intraday precision range (%)	MV-491-00 Atorvastatin: LLOQQC: 3.0 to 5.4% LQC, MQC & HQC: 1.4 to 5.4% DIQC: 1.4 to 1.9% MV-491-00 (Addendum-1) Atorvastatin: LLOQQC: 3.3 to 17.1% LQC, MQC & HQC: 0.8 to 4.7% DIQC: 1.1 to 2.1%	MV-491-00 o-Hydroxy Atorvastatin: LLOQQC: 3.1 to 5.7% LQC, MQC & HQC: 1.5 to 4.9% DIQC: 1.0 to 2.0% MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin: LLOQQC: 3.7 to 11.4% LQC, MQC & HQC: 1.4 to 5.8% DIQC: 1.1 to 3.0%	MV-491-00 p-Hydroxy Atorvastatin: LLOQQC: 4.7 to 10.6% LQC, MQC & HQC: 1.6 to 5.7% DIQC: 2.7 to 3.1% MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin: LLOQQC: 7.3 to 14.2% LQC, MQC & HQC: 1.1 to 4.9% DIQC: 1.5 to 4.9%
QC Intraday accuracy range (%)	MV-491-00 Atorvastatin: LLOQQC: 95.5 to 105.3% LQC, MQC & HQC: 100.9 to 107.6% DIQC: 96.5 to 98.8% MV-491-00 (Addendum-1) Atorvastatin: LLOQQC: 88.0 to 103.3% LQC, MQC & HQC: 90.9 to 103.3% DIQC: 98.6 to 102.6%	MV-491-00 o-Hydroxy Atorvastatin: LLOQQC: 88.5 to 100.3% LQC, MQC & HQC: 95.5 to 103.6% DIQC: 94.3 to 97.3% MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin: LLOQQC: 88.4 to 111.5% LQC, MQC & HQC: 94.4 to 108.9% DIQC: 99.2 to 102.5%	MV-491-00 p-Hydroxy Atorvastatin: LLOQQC: 92.3 to 108.2% LQC, MQC & HQC: 93.6 to 99.2% DIQC: 104.2 to 107.3% MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin: LLOQQC: 91.3 to 107.8% LQC, MQC & HQC: 98.5 to 107.8% DIQC: 99.5 to 106.8%
QC Inter day precision range (%)	MV-491-00 Atorvastatin: LLOQQC: 5.5%	MV-491-00 o-Hydroxy Atorvastatin:	MV-491-00 p-Hydroxy Atorvastatin: LLOQQC: 10.0%

	LQC, MQC & HQC: 1.8 to 4.5% DIQC: 1.9% MV-491-00 (Addendum-1) Atorvastatin: LLOQQC: 10.2% LQC, MQC & HQC: 3.3 to 4.6% DIQC: 2.1%	LLOQQC: 6.9% LQC, MQC & HQC: 3.1 to 4.6% DIQC: 2.1% MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin: LLOQQC: 10.5% LQC, MQC & HQC: 2.8 to 6.6% DIQC: 2.7%	LQC, MQC & HQC: 2.1 to 4.3% DIQC: 3.1% MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin: LLOQQC: 11.4% LQC, MQC & HQC: 2.8 to 4.0% DIQC: 4.2%
QC Inter day accuracy range (%)	MV-491-00 Atorvastatin: LLOQQC: 100.3% LQC, MQC & HQC: 103.0 to 107.0% DIQC: 97.4% MV-491-00 (Addendum-1) Atorvastatin: LLOQQC: 97.3% LQC, MQC & HQC: 96.5 to 101.2% DIQC: 100.1%	MV-491-00 o-Hydroxy Atorvastatin: LLOQQC: 95.0% LQC, MQC & HQC: 97.8 to 99.8% DIQC: 96.2% MV-491-00 (Addendum-1) o-Hydroxy Atorvastatin: LLOQQC: 100.8% LQC, MQC & HQC: 99.1 to 107.7% DIQC: 100.7%	MV-491-00 p-Hydroxy Atorvastatin: LLOQQC: 101.2% LQC, MQC & HQC: 94.1 to 98.2% DIQC: 106.2% MV-491-00 (Addendum-1) p-Hydroxy Atorvastatin: LLOQQC: 100.7% LQC, MQC & HQC: 101.8 to 103.7% DIQC: 102.8%
Bench-top stability (hrs)	MV-491-00 18.63 hrs at below 7°C in wet-ice water bath MV-491-00 (Addendum-1) 17.47 hrs at below 7°C in wet-ice water bath	MV-491-00 18.63 hrs at below 7°C in wet-ice water bath MV-491-00 (Addendum-1) 17.47 hrs at below 7°C in wet-ice water bath	MV-491-00 18.63 hrs at below 7°C in wet-ice water bath MV-491-00 (Addendum-1) 17.47 hrs at below 7°C in wet-ice water bath
Stock stability (days) (Long term)	MV-491-00 19.77 days at 1-10°C	MV-491-00 19.77 days at 1-10°C	MV-491-00 19.77 days at 1-10°C
Processed stability (hrs)	MV-491-00 94.75 hrs at 10°C, in autosampler	MV-491-00	MV-491-00 94.75 hrs at 10°C, in autosampler

	MV-491-00 (Addendum-1) 118.57 hrs at 10°C, in autosampler	94.75 hrs at 10°C, in autosampler MV-491-00 (Addendum-1) 118.57 hrs at 10°C, in autosampler	MV-491-00 (Addendum-1) 118.57 hrs at 10°C, in autosampler
Freeze-thaw stability (cycles)	MV-491-00 9 Cycles, at -70 ± 15°C MV-491-00 (Addendum-1) 7 cycles, at -70 ± 15°C	MV-491-00 9 Cycles, at -70 ± 15°C MV-491-00 (Addendum-1) 7 cycles, at -70 ± 15°C	MV-491-00 9 Cycles, at -70 ± 15°C MV-491-00 (Addendum-1) 7 cycles, at -70 ± 15°C
Long-term storage stability (days) (In Matrix) (Addendum-3)	68.86 days at -70 ± 15°C & -20 ± 5°C	68.86 days at -70 ± 15°C & -20 ± 5°C	68.86 days at -70 ± 15°C & -20 ± 5°C
Dilution integrity	Dilution integrity was evaluated using DIQC with 1/4 Dilution factor as a part of precision and accuracy batches. Atorvastatin DIQC: 576.90 to 590.58 ng/mL Precision: 1.4 to 1.9% Accuracy (% Nominal): 96.5 to 98.8% o-Hydroxy Atorvastatin DIQC: 377.36 to 388.36 ng/mL Precision: 1.0 to 2.0% Accuracy (% Nominal): 94.3 to 97.3% p-Hydroxy Atorvastatin DIQC: 62.24 to 64.09 ng/mL Precision: 2.7 to 3.1% Accuracy (% Nominal): 104.2 to 107.3%		
Selectivity	No significant interfering peaks were observed at the RT of Atorvastatin & Atorvastatin D5, o-Hydroxy Atorvastatin & o-Hydroxy Atorvastatin D5, p-Hydroxy Atorvastatin & p-Hydroxy Atorvastatin D5.		

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No SOP no.: (b) (4)
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K2 EDTA

Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Adequate

- The applicant submitted multiple addendums for the method validations.
  - The addendum 01, partial validation to method validation report No. MV-491-00, Version: 00 was partially validated for the determination of Atorvastatin, o-Hydroxy Atorvastatin, and p-Hydroxy Atorvastatin. As part of partial validation, the method selectivity, specificity, precision and accuracy, signal to noise ratio, recovery, matrix effect, extended precision and accuracy, re-injection reproducibility and all stabilities (matrix and processed samples stabilities) were evaluated in absence of Total Ezetimibe.
  - The addendum 02 to method validation report No. MV-491-00, Version: 00 was evaluated for long term stability of analytes. The instrument precision and accuracy run on instrument [redacted] (b) (4) was evaluated.
  - The addendum 03 to method validation report No. MV-491-00, Version: 00 was evaluated to assess the presence of concomitant medication.
  - The addendum 04, MV-491-00 (Addendum-4), Version: 00 and MV-491-00 (Addendum-5), Version: 00, evaluated the instrument precision and accuracy run on instrument ID: [redacted] (b) (4) The long-term stability in matrix was also evaluated.
  - The addendum 06, MV-491-00 (Addendum-6), Version: 00 evaluated the presence of Diclofenac and Levocetirizine at concentration of [redacted] (b) (4)

- The percent recovery of drug is consistent for Atorvastatin, o-Hydroxy Atorvastatin and p-Hydroxy Atorvastatin across all QC levels and are comparable to the percent recovery of the corresponding internal standards.

- The precision and accuracy at all QC levels are acceptable.

- Pre-Study Method Validation is **adequate.**

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Fasting Study: Atorvastatin

Study Ref. No	Study Objectives	Study Design	Treatments (Dose, Dosage form, Route) [product ID]	Subjects No. Type (M/F) Age: Mean (range)	Mean parameters(+/-SD) Atorvastatin							Study report location
					C_{max} (ng/mL)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	AUC% Extrapolation	T_{max} (hr)	Kel (hr^{-1})	Thalf (hr)	
325-20	**Primary Objective:** To demonstrate the bioequivalence between Test product (T): Atorvastatin calcium Tablets 80	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate,	Test Product: Atorvastatin calcium Tablets 80 mg Oral [Batch No.: 202012103D]	48 male subjects were completed Mean age: 34.0 (20-44)	106.5581 ± 77.79300 (73.0)	393.3639 ± 178.99910 (45.5)	396.0286 ± 179.00088 (45.2)	0.8179 ± 0.58217 (71.2)	1.00 (0.33-3.50)	0.08719 ± 0.031094 (35.7)	8.829 ± 2.7538 (31.2)	ANDA Submitted page No:

	mg of Lepu Pharmaceutical Technology Co., Ltd, China with that of Reference product (R): Lipitor® (atorvastatin calcium) 80 mg tablets of Parke-Davis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fasting conditions. **Secondary objective: :** To monitor the subject's safety and tolerability of single oral dose of investigational products (IPs).	cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fasting conditions	Reference Product: Lipitor® (atorvastatin calcium) 80 mg tablets Oral [LOT No:-CA9137]		107.3837± 82.94432 (77.2)	390.6769± 190.07933 (48.7)	393.4903± 190.21563 (48.3)	0.8573± 0.56361 (65.7)	1.25 (0.33-5.00)	0.09162± 0.036615 (40.0)	8.658±3.0052 (34.7)	

Fasting Study: ortho-hydroxylated

Study Ref. No	Study Objectives	Study Design	Treatments (Dose, Dosage form, Route) [product ID]	Subjects No. Type (M/F) Age: Mean (range)	Mean parameters(+/-SD) Ortho-hydroxylated atorvastatin							Study report location
					C_{max} (ng/mL)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	AUC% Extrapolation	T_{max} (hr)	Kel (hr^{-1})	thalf (hr)	
325-20	**Primary Objective:** To demonstrate the bioequivalence between Test product (T): Atorvastatin calcium Tablets 80	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over,	Test Product: Atorvastatin calcium Tablets 80 mg Oral [Batch No.: 202012103D]	48 male subjects were completed Mean age: 34.0 (20-44)	53.1773 ± 29.32241 (55.1)	357.8682 ± 160.79611 (44.9)	363.4101 ± 161.20829 (44.4)	1.7674 ± 1.16559 (65.9)	1.50 (0.50 - 7.00))	0.08367 ± 0.028883 (34.5)	9.136 ± 2.7375 (30.0)	ANDA Submitted page No:

	mg of Lepu Pharmaceutical Technology Co., Ltd, China with that of Reference product (R): Lipitor® (atorvastatin calcium) 80 mg tablets of Parke-Davis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fasting conditions. **Secondary objective: :** To monitor the subject's safety and tolerability of single oral dose of investigational products (IPs).	single-dose, oral bioequivalence study in healthy, adult, human subjects under fasting conditions	Reference Product: Lipitor® (atorvastatin calcium) 80 mg tablets Oral [LOT No:-CA9137]		54.0898 ± 31.8432 8 (58.9)	362.3511 ± 155.5270 3 (42.9)	366.9296 ± 156.6105 9 (42.7)	1.6490 ± 0.97079 (58.9)	1.75 (0.67 - 5.00)	0.08558 ± 0.02917 0 (34.1)	8.977 ± 2.880 0 (32.1)	

Fasting Study: para-hydroxylated

Study Ref. No	Study Objectives	Study Design	Treatments (Dose, Dosage form, Route) [product ID]	Subjects No. Type (M/F) Age: Mean (range)	Mean parameters(+/-SD) Para-hydroxylated atorvastatin							Study report location
					C_{max} (ng/mL)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	AUC% Extrapolation	T_{max} (hr)	Kel (hr^{-1})	thalf (hr)	
325-20	**Primary Objective:** To demonstrate the bioequivalence between Test product (T): Atorvastatin calcium Tablets 80	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over,	Test Product: Atorvastatin calcium Tablets 80 mg Oral [Batch No.: 202012103D]	48 male subjects were completed Mean age: 34.0 (20-44)	3.8428 ±2.71753 (70.7)	74.3345 ± 34.34623 (46.2)	82.8338 ± 38.87113 (46.9)	9.8172 ± 4.34484 (44.3)	5.00 (0.50 - 18.00)	0.03579 ± 0.009582 (26.8)	20.764 ± 5.6454 (27.2)	ANDA Submitted page No:

	mg of Lepu Pharmaceutical Technology Co., Ltd, China with that of Reference product (R): Lipitor® (atorvastatin calcium) 80 mg tablets of Parke-Davis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fasting conditions. **Secondary objective:** To monitor the subject's safety and tolerability of single oral dose of investigational products (IPs).	single-dose, oral bioequivalence study in healthy, adult, human subjects under fasting conditions	Reference Product: Lipitor® (atorvastatin calcium) 80 mg tablets Oral [LOT No:-CA9137]		4.0330 ± 3.30037 (81.8)	75.9896 ± 37.96368 (50.0)	86.4028 ± 45.13873 (52.2)	11.4481 ± 7.78308 (68.0)	6.00 (0.50 - 18.00	0.03418 ± 0.012805 (37.5)	22.970 ± 10.8637 (47.3)	

Fed BE Study Atorvastatin

Study Ref. No	Study Objectives	Study Design	Treatments (Dose, Dosage form, Route) [product ID]	Subjects No. Type (M/F) Age: Mean (range)	Mean (+/-SD) Atorvastatin						Study report location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	thalf (hr)	Kel (hr^{-1})	
326-20	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study of	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral	Test Product: Atorvastatin calcium Tablets 80 mg Oral [Lot No.: 202012103D]	48 male subjects were completed Mean age: 34.6 (24-44)	73.2025 ± 45.61875 (62.3)	2.25 (0.75 - 5.00)	363.8826 ± 150.38697 (41.3)	367.5330 ± 150.67757 (41.0)	11.364 ± 2.7372 (24.1)	0.06479 ± 0.016614 (25.6)	ANDA Submitted page No:

	Atorvastatin calcium tablets 80 mg (Test) of Lepu Pharmaceutical Technology Co., Ltd, China and Lipitor® (Atorvastatin calcium) tablets 80 mg (Reference) of Parke-Davis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fed conditions.	bioequivalence study in healthy, adult, human subjects under fed conditions.	Reference Product: Lipitor® (atorvastatin calcium) 80 mg tablets Oral [LOT No:-CA9137]		77.7323 ± 46.53294 (59.9)	2.00 (0.75 - 6.00)	367.4362 ± 142.35392 (38.7)	371.0496 ± 142.72063 (38.5)	11.181 ± 3.0802 (27.5)	0.06830 ± 0.026573 (38.9)	

Fed Study: ortho-hydroxylated

Study Ref. No	Study Objectives	Study Design	Treatments (Dose, Dosage form, Route) [product ID]	Subjects No. Type (M/F) Age: Mean (range)	Mean parameters(+/-SD) Ortho-hydroxylated atorvastatin						Study report location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	thalf (hr)	Kel (hr^{-1})	

326-20	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study of Atorvastatin calcium tablets 80 mg (Test) of Lepu Pharmaceutical Technology Co., Ltd, China and Lipitor® (Atorvastatin calcium) tablets 80 mg (Reference) of Parke-Davis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fed conditions.	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Test Product: Atorvastatin calcium Tablets 80 mg Oral [Lot No.: 202012103D]	48 male subjects were completed Mean age: 34.6 (24-44)	23.7663 ± 10.93221 (46.0)	3.50 (1.00 - 7.00)	212.9627 ± 72.75837 (34.2)	219.9271 ± 72.55071 (33.0)	10.964 ± 2.8856 (26.3)	0.06836 ± 0.021904 (32.0)	ANDA Submitted page No:
			Reference Product: Lipitor® (atorvastatin calcium) 80 mg tablets Oral [LOT No:- CA9137]		23.9853 ± 11.41176 (47.6)	4.00 (1.00 - 7.00)	209.5323 ± 70.70357 (33.7)	216.3092 ± 71.04640 (32.8)	11.067 ± 3.2820 (29.7)	11.067 ± 3.2820 (38.9)	

Fed Study: para-hydroxylated

Study Ref. No	Study Objectives	Study Design	Treatments (Dose, Dosage	Subjects No.	Mean parameters(+/-SD) Para-hydroxylated atorvastatin	Study report location

			form, Route) [product ID]	Type (M/F) Age: Mean (range)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	thalf (hr)	Kel (hr^{-1})	
326-20	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study of Atorvastatin calcium tablets 80 mg (Test) of Lepu Pharmaceutical Technology Co., Ltd, China and Lipitor® (Atorvastatin calcium) tablets 80 mg (Reference) of Parke-Davis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fed conditions.	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Test Product: Atorvastatin calcium Tablets 80 mg Oral [Lot No.: 202012103D]	48 male subjects were completed Mean age: 34.6 (24-44)	2.8035 ± 1.90309 (67.9)	5.00 (1.25 - 15.00)	59.7987 ± 27.46506 (45.9)	72.0476 ± 34.16150 (47.4)	26.104 ± 8.7030 (33.3)	0.02919 ± 0.008646 (29.6)	ANDA Submitted page No:
			Reference Product: Lipitor® (atorvastatin calcium) 80 mg tablets Oral [LOT No:- CA9137]		2.8367 ± 1.81897 (64.1)	6.00 (1.00 - 15.00)	60.4065 ± 27.24190 (45.1)	75.2654 ± 34.76588 (46.2)	29.219 ± 15.0525 (51.5)	0.02785 ± 0.010463 (37.6)	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	325-20
Study Title	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study of Atorvastatin calcium tablets 80 mg (Test) of Lepu Pharmaceutical Technology Co., Ltd, China and Lipitor® (Atorvastatin calcium) tablets 80 mg (Reference) of Parke-Devis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fasting conditions.
Clinical Site (Name & Address)	(b) (4)
Principal Clinical Investigator	
Dosing Dates	Period 1: 03/18/2021 Period 2: 04/03/2021 Period 3: 04/19/2021
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	
Principal Analytical Investigator	
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)**	(a) 99 days
(b) Temperature Range (e.g., -20°C to -80°C)	(b) -70°C ± 15°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	138.82 days at -70°C ± 15°C temperature and at -20°C±5°C temperature

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference

Treatment ID	T	R
Product Name	Atorvastatin Calcium Tablets	Lipitor
Distributed by	Lepu Pharmaceutical Technology Co., Ltd.	Parke-Davis Division of Pfizer Inc NY, NY 10017
Manufactured by	Lepu Pharmaceutical Technology Co., Ltd.	(b) (4)
Manufactured for	Process Validation and BE	For Sale
Batch No.	FP019202012103D*	CA9137
Manufacture Date	29th Dec, 2020	N/A
Expiry date	Nov. 2022	28th Feb, 2022
Strength	80mg	80mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	101.1%	100.0%
Content Uniformity (mean, %CV)	1.8	1.2
Dose Administered	One tablet once	One tablet once
Route of Administration	Oral	Oral

*Note: In release COA, the material code was deleted from the internal Batch No. based on the requirement of Lepu's SOP, e.g. for the internal Batch No. FP019202012101D, the batch No. will be 202012101D in the release COA, but actually they are the same batch.

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled:54 Dosed: 54 (Period I); 53 (Period II); 48 (Period III) Completed: 48; 54 (Period I); 52 (Period II); 48(Period III) Samples Analyzed: 48 Statistically Analyzed: 48

No. of Sequences	3: R1, R2, T
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	16 days
Randomization	☒ Yes ☐ No RTR, TRR or RRT
Blood Sampling Times	25 post-dose blood samples of 5 mL each were collected at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 9.00, 12.00, 15.00, 18.00, 24.00, 48.00 and 72.00 hours in each period.
IRB Approval	☒ Yes Date: 21/Jan/2021 ☐ No
Informed Consent	☒ Yes Date: 21/Jan/2021 ☐ No
Length of Fasting	10 hours
Length of Confinement	Subjects were housed in the clinic from at least 11 hours prior to dosing until at least 48 hours post dose in each study period.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Assessor's Note

Subjects that were excluded from study per protocol included: (b) (6) Subject (b) (6) did not report to the facility for period II and period III check-in. The assessor agrees with the exclusions of the subjects.

Comments on Study Design: Adequate

- The study was designed as a single dose of 80 mg, a two-treatment, three-sequence, three-period, partial replicate, cross-over BE study.
- As recommended in the PSG, the applicant used reference scaled average bioequivalence approach (RSABE).

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No.: 325-20			
Parameter		**Treatment Groups**	
		Test Product N = 48	**Reference Product N = 48**
Age (years)	Mean ± SD	34.0 ± 6.4	34.0 ± 6.4
	Range	20-44	20-44

Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	40 (83.33%)	40 (83.33%)
	41 – 64	8 (16.67%)	8 (16.67%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	48 (100%)	48 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	48 (100%)	48 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	24.99 ± 2.54	24.99 ± 2.54
	Range	19.73-29.98	19.73-29.98
Other Factors	-	Not applicable	

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. 325-20				
Subject No.	**Reason for Drop-out/Replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	**Reason:** Dropped out as subject was absent for check in of Period-II only. **Last Treatment received:** Reference Product-R **Time & Date**: 23:05 hrs & (b) (4)	II	Not Applicable	Not Applicable
	Reason: Withdrawn due to adverse event (Pyrexia) after dosing in Period-II. **Last Treatment received:** Test Product-T **Time & Date**: 16:40 hrs & (b) (6)	II	Not Applicable	Not Applicable
	Reason: Withdrawn due to Failure to comply with the requirement of the study (Urine alcohol test Positive) in check in of Period-III. **Last Treatment received:** Reference Product-R **Time & Date**: 22:35 hrs & (b) (6)	III	Not Applicable	Not Applicable
	Reason: Dropped out as subject was absent for check in of Period-III. **Last Treatment received:** Reference Product-R **Time & Date**: 23:00 hrs & (b) (6)	III	Not Applicable	Not Applicable
	Reason: Dropped out as subject was absent for check in of Period-III. **Last Treatment received:** Test Product-T **Time & Date**: 23:00 hrs & (b) (6)	III	Not Applicable	Not Applicable
	Reason: Dropped out as subject was absent for check in of Period-III. **Last Treatment received:** Reference Product-R **Time & Date**: 23:00 hrs & (b) (6)	III	Not Applicable	Not Applicable
	Reason: Dropped out as subject was absent for check in of Period-III. **Last Treatment received:** Reference Product-R **Time & Date**: 23:00 hrs & (b) (6)	III	Not Applicable	Not Applicable

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.1.2.3 Study Adverse Events

Body system/adverse event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study No.: 325-20	
	Treatment T (1) N = 50	Treatment R (1) N = 54
General disorders and administration site conditions		
Body ache	01 (2%)	-
Pyrexia	02 (4%)	-
Gastrointestinal disorders		
diarrhea	01 (2%)	03 (5.56%)
Abdominal Pain	01 (2%)	-
Infections and infestations		
Pharyngitis	-	01 (1.85%)
Eye Disorders		
Subconjunctival Hemorrhage	-	01 (1.85%)
Total	**05 (*10%)**	**05 (*9.26%)**
Post-study Abnormalities N = 53 (100%)		
Gastrointestinal disorders		
Vomiting	01 (1.89%)	
Investigations		
Decreased Hemoglobin Count	02 (3.77%)	
Increased White Blood Cell Count	03 (5.66%)	
Decreased White Blood Cell Count	01 (1.89%)	
Increased Blood Bilirubin Count	01 (1.89%)	
Increased Creatine Phosphokinase	02 (3.77%)	
Total	**10 (*18.90%)**	

*Total is sum percentage of each AE

(1) N = Number of subjects dosed for each treatment

Note:

Post-study safety assessments were performed for 53 subjects.

Subject No. (b) (6) was absent for check-in period-III hence he was considered as dropped out from the study for period- III. He did not report to the clinical facility for his post-study evaluations after repeated efforts and hence he was considered as lost to follow-up on (b) (6)

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis
(b) (6)	Reference	Post Study	09:16 (b) (6)	11:00	3 days

Were subjects who experienced vomiting included in statistical analysis?	☒ Yes ☐ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☒ Yes ☐ No ☐ N/A subject experience vomiting during post study.
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No. 325-20		
Type	**Test Product (T) (N =54)**	**Reference Product (R) (N=54)**
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-I, which was delayed due to late arrival of the subject.	(b) (6)	
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-II, which was delayed due to late arrival of the subject.		

Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.	(b) (6)
Missed Samples	
Protocol deviation was recorded for missed samples in Period-I at 72.00 hours [i.e. total 01 (original) + 01 (duplicate) missed sample] as the subject was absent for ambulatory blood visit.	
Protocol deviation was recorded for missed samples in Period-II from 00.00 to 72.00 hours [i.e. total 26 (original) + 26 (duplicate) missed sample] as the subject was absent for check-in period-II & III hence he was considered as dropped out from the study for period-II & III.	
Protocol deviation was recorded for missed samples in Period-II for Subject No. S(b) (6) from 9.00 to 72.00 hours [i.e. total 07 (original) + 07 (duplicate) missed samples] as the subject was withdrawn due to adverse event (Pyrexia) after dosing of Period-II hence he was considered as withdrawn from the study.	
Protocol deviation was recorded for missed samples in Period-II for Subject No. S(b) (6) at 72.00 hours [i.e. total 01 (original) + 01 (duplicate) missed sample] as the subject was absent for ambulatory visit	

Protocol deviation was recorded for missed samples in Period-II for Subject No. S[redacted] at 72.00 hours [i.e. total 01 (original) + 01 (duplicate) missed sample] as the subject was absent for ambulatory visit.	(b) (6)
Protocol deviation was recorded for missed samples in Period-III for Subject No. S[redacted] from 00.00 to 72.00 hours [i.e. total 26 (original) + 26 (duplicate) missed samples] as the subject was withdrawn due to failure to comply with the requirement of the study (Urine alcohol test Positive) in check-in of Period-III hence he was considered as withdrawn from the study.	
Protocol deviation was recorded for missed samples in Period-III for Subject No. S[redacted] from 00.00 to 72.00 hours [i.e. total 26 (original) + 26 (duplicate) missed samples] as the subject was absent for check-in period-II & III hence he was considered as dropped out from the study for period-II & III.	
Protocol deviation was recorded for missed samples in Period-III for Subject No. S[redacted] from 00.00 to 72.00 hours [i.e. total 26 (original) + 26 (duplicate) missed samples] as the subject was withdrawn due to adverse event	

Protocol deviation was recorded for missed samples in Period-III for Subject No. S(b) (6) from 00.00 to 72.00 hours [i.e. total 26 (original) + 26 (duplicate) missed samples] as the subject was absent for check-in period-III hence he was considered as dropped out from the study for period-III.	(b) (6)
Protocol deviation was recorded for missed samples in Period-III for Subject No. S(b) (6) from 00.00 to 72.00 hours [i.e. total 26 (original) + 26 (duplicate) missed samples] as the subject was absent for check-in period-III hence he was considered as dropped out from the study for period-III.	
Unplanned Deviation	
Unplanned Deviation (Period-I) As per protocol section 10.9.3 Handling of blood samples "collected blood samples will be kept at below 7°C in wet-ice water bath until centrifugation and up to storage after plasma separation."	(b) (6)

Unplanned Deviation (Period-I) As per protocol section 10.1.4 Inclusion criteria, Sr. No. 09. Normal levels of serum creatine phosphokinase (CPK) test during screening. Volunteer registration number (b) (6) has CPK value 200.19 at the time of screening, which was out of normal range (24.00-195.00 U/L). As this value is clinically non-significant and very high from the normal range, volunteer was enrolled in the study based on the discretion of principle investigator.	(b) (6)
Unplanned Deviation (Period-II) As per protocol section 10.10 (Admission and Stay), 'Subjects will be admitted and housed in the clinical facility at least 11.00 hours before the administration of the dose during each period of the study'. However, housing requirement was not fulfilled for subject no. S(b) (6) in period-II.	

Unplanned Deviation (Period-Not Applicable) As per protocol section 10.11.4 (Post-study Evaluations), "All subjects will have a post study evaluation. Subjects completing all periods of the study should have post study evaluation & end-of-study tests may be done on the last blood collection day of period-III or at any stage if the subject is withdrawn or dropped from the study for any reason /on discretion of Clinical Investigator/designee." However, same has not been followed for subject no. S (b) (6) hence he is considered as lost to follow-up for post study safety assessment on (b) (6)	(b) (6)
Unplanned Deviation (Period-I) As per Protocol Section 10.9.3 Handling of Blood Samples, The time interval between sample collection and the start time of centrifugation should not exceed 45 minutes.	

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

- There was a total of 20 Adverse events in 15 subjects during the fasting study. Sixteen (16) adverse events were mild in intensity and four (04) adverse events were moderate in intensity. There was one (1) subject who experienced vomiting during post study. The subject was included within analysis and had no impact on the safety of the study.
- No deaths or serious adverse events were reported during the study.

Overall, the applicant's dropouts, adverse reactions and protocol deviations are considered adequate.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Repeat Analysis
		Bioanalytical Method Validation
		Study Sample Analysis and Recording of Raw Data
		Chromatography Acceptance Criteria
		Reanalysis of Incurred Samples
		Investigation and Reporting of Rejected Analytical Batch
		Preparation of Calibration Curve Standards and Quality Control Samples and their Acceptance Criteria

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Study No: 325-20 Analyte Name: Atorvastatin								
Parameter	**Standard Curve Samples**							
	STD 1	**STD 2**	**STD 3**	**STD 4**	**STD 5**	**STD 6**	**STD 7**	**STD 8**
Concentration (ng/mL)	**0.100**	**0.200**	**1.001**	**6.009**	**30.046**	**150.230**	**239.220**	**299.025**
Inter day Precision (%CV)	**2.3**	**4.3**	**2.7**	**2.6**	**2.1**	**2.5**	**2.2**	**2.3**
Inter day Accuracy (%Actual)	**99.3**	**101.0**	**102.1**	**101.2**	**100.6**	**98.2**	**98.1**	**99.5**
Linearity (Range of r values)	0.9984 to 0.9999							
Linearity Range (ng/mL)	0.100 to 299.025 ng/mL							
Sensitivity/LOQ (ng/mL)	0.100 ng/mL							

Study No: 325-20 Analyte Name: Atorvastatin	
Parameter	**Quality Control Samples**

	LQC	LMQC	MQC	HQC
Concentration (ng/mL)	0.298	17.949	90.654	226.634
Inter day Precision (%CV)	4.9	8.3	3.8	9.6
Inter day Accuracy (%Actual)	104.2	101.0	99.5	101.4

Study No: 325-20 Analyte Name: o-Hydroxy Atorvastatin								
Parameter	Standard Curve Samples							
	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8
Concentration (ng/mL)	0.200	0.400	4.002	20.012	50.031	128.153	160.192	200.240
Inter day Precision (%CV)	2.3	4.6	2.7	2.5	2.7	2.4	2.8	2.1
Inter day Accuracy (%Actual)	100.6	98.8	98.6	100.2	99.8	99.7	99.5	102.8
Linearity (Range of r values)	0.9968 to 0.9999							
Linearity Range (ng/mL)	0.200 to 200.240 ng/mL							
Sensitivity/LOQ (ng/mL)	0.200 ng/mL							

Study No: 325-20 Analyte Name: o-Hydroxy Atorvastatin				
Parameter	Quality Control Samples			
	LQC	LMQC	MQC	HQC
Concentration (ng/mL)	0.598	12.106	61.453	153.633
Inter day Precision (%CV)	5.3	9.1	4.4	10.3
Inter day Accuracy (%Actual)	93.8	99.5	97.7	100.8

Study No: 325-20 Analyte Name: p-Hydroxy Atorvastatin								
Parameter	Standard Curve Samples							
	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8
Concentration (ng/mL)	0.100	0.200	1.002	3.000	7.501	15.001	24.013	30.016
Inter day Precision (%CV)	2.6	5.4	3.0	3.0	2.8	2.9	3.1	2.8
Inter day Accuracy (%Actual)	101.1	98.5	96.8	99.2	101.4	99.6	100.9	102.5
Linearity (Range of r values)	0.9967 to 0.9998							

Linearity Range (ng/mL)	0.100 to 30.016 ng/mL
Sensitivity/LOQ (ng/mL)	0.100 ng/mL

Study No: 325-20 Analyte Name: p-Hydroxy Atorvastatin				
Parameter	**Quality Control Samples**			
	LQC	**LMQC**	**MQC**	**HQC**
Concentration (ng/mL)	**0.299**	**1.803**	**9.691**	**23.352**
Inter day Precision (%CV)	**6.5**	**9.7**	**4.4**	**10.2**
Inter day Accuracy (%Actual)	**103.9**	**99.0**	**98.3**	**103.9**

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☒ Yes ☐ No Subject sample [redacted] and subject [redacted] (please see comment below in section 4.1.1.3.3)
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Study No: 325-20 Analyte Name: Atorvastatin Additional information in Volume(s), 325-20-bioanalytical-report, Page(s) 89 of 117								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Code C: Poor Chromatography	1	0	0.1	0.0	1	0	0.1	0.0
Code D: Value above upper limit	6	8	0.5	0.3	6	8	0.5	0.3

Code I: Interference in subject zero samples	0	1	0.0	0.0	0	1	0.0	0.0
Code H1: Interference at analyte RT	0	1	0.0	0.0	0	1	0.0	0.0
Code G: ISTD variation	8	14	0.6	0.5	8	14	0.6	0.5
Code JL: Value below the truncated calibration range	3	7	0.2	0.3	3	7	0.2	0.3
Total	18	31	1.4	1.1	18	31	1.4	1.1

Study No: 325-20
Analyte Name: o-Hydroxy Atorvastatin
Additional information in Volume(s), 325-20-bioanalytical-report, Page(s)92 of 117

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Code B: Lost in processing /	0	1	0.0	0.0	0	1	0.0	0.0
Code C: Poor Chromatography	1	0	0.1	0.0	1	0	0.1	0.0
Code D: Value above upper limit	1	1	0.1	0.0	1	1	0.1	0.0
Code G: ISTD variation	5	15	0.4	0.6	5	15	0.4	0.6
Code H1: Interference at analyte RT	0	1	0.0	0.0	0	1	0.0	0.0
Code JL: Value below the truncated calibration range	11	4	0.9	0.1	11	4	0.9	0.1
Total	18	22	1.4	0.8	18	22	1.4	0.8

Study No: 325-20
Analyte Name: p-Hydroxy Atorvastatin
Additional information in Volume(s), 325-20-bioanalytical-report, Page(s)94 of 117

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Code G: ISTD variation	5	5	0.4	0.2	5	5	0.4	0.2
Total	5	5	0.4	0.2	5	5	0.4	0.2

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No

If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate.

Atorvastatin:

- There were 49 samples repeated for Atorvastatin, including repeats, rejected runs, re-injected runs and ISR runs. There were 2 re-injected and rejected runs reported in the fasting study for Atorvastatin. The repeated values were found acceptable and reported.
- One sample (reference, S4) was reanalyzed due to interference in subject zero samples (Code I). Per the applicant's SOP No. (b) (4) "Repeat Analysis", subject zero sample was repeated. The repeated values were below LLOQ and therefore reported as BLQ.
- One sample (reference, S(b) (6)) was reanalyzed due to interference at analyte RT (Code H1). Per the SOP, the sample was repeated for confirmation. The repeated value was reported based on the concentration observed in subject zero sample. The assessor checked and verified the raw data for the original and repeated sample, and determined that the repeats are acceptable.
- Quality control samples (Sample ID: (b) (6) to (b) (6)) along with (Sample ID: (b) (6) to (b) (6)) were re-injected due to missing vial error and check valve error, respectively during the run.

- The applicant used 269 (out of 4019 samples, 10% of the first 1000 samples + 5.6% of the remaining samples) selected samples for ISR for Atorvastatin. During the ISR, 94.8 % of the samples for Atorvastatin met the acceptance criteria (within ±20% of the original results) and thus, ISR was found to be within acceptance criteria, demonstrating reproducibility.

o-Hydroxy Atorvastatin:

- There were 40 samples repeated for o-hydroxy atorvastatin, including repeats, rejected runs, re-injected runs and ISR runs. There were 1 rejected and 2 re-injected

runs were reported in the fasting study for o-hydroxy atorvastatin. The repeated values were found acceptable and reported.

- The applicant used 269 (out of 4019 samples, 10% of the first 1000 samples + 5.6% of the remaining samples) selected samples for ISR for o-hydroxy atorvastatin. During the ISR, 91.8 % of the samples for o-hydroxy atorvastatin met the acceptance criteria (within ±20% of the original results) and thus, ISR was found to be within acceptance criteria, demonstrating reproducibility.

p-Hydroxy Atorvastatin:

- There were 10 samples repeated for p-hydroxy atorvastatin, including repeats and ISR runs. There were 1 rejected and 2 re-injected runs were reported in the fasting study for p-hydroxy atorvastatin. The repeated values were verified and found acceptable.
- The applicant used 263 (out of 4019 samples, 10% of the first 1000 samples + 5.4% of the remaining samples) selected samples for ISR for p-hydroxy atorvastatin. During the ISR, 87 % of the samples for p-hydroxy atorvastatin met the acceptance criteria (within ±20% of the original results) and thus, ISR was found to be within acceptance criteria, demonstrating reproducibility.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters (Assessor Calculated)

Atorvastatin

Fasting Bioequivalence Study No. 325-20					
Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC0-t (hr *ng/ml)	393.364	45	394.179	49.1	0.99
AUC∞ (hr *ng/ml)	396.029	44.7	396.877	48.8	0.99
Cmax (ng/ml)	106.558	72.3	109.887	76.5	0.96
Tmax* (hr)	1.33	68	1.465	74.4	0.90
Kel (hr^{-1})	0.087	32.6	0.091	39.6	0.96
T1/2 (hr)	8.83	30.9	8.71	34.2	1.01

Ortho-hydroxylated

Fasting Bioequivalence Study No. 325-20					
Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC0-t (hr *ng/ml)	357.868	44.5	359.906	44	0.99

AUC∞ (hr *ng/ml)	363.41	43.9	365.063	43.5	0.99
Cmax (ng/ml)	53.177	54.6	54.333	59.1	0.97
Tmax* (hr)	1.825	66.8	2.039	60.6	0.89
Kel (hr^{-1})	0.084	34.5	0.086	34.9	0.97
T1/2 (hr)	9.135	29.7	8.994	32.5	1.01

Para-hydroxylated

Fasting Bioequivalence Study No. 325-20					
Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC0-t (hr *ng/ml)	74.334	45.7	75.895	51	0.97
AUC∞ (hr *ng/ml)	83.601	45.6	86.236	52.8	0.97
Cmax (ng/ml)	3.843	70	4.015	83.1	0.96
Tmax* (hr)	6.813	73	7.321	65.3	0.93
Kel (hr^{-1})	0.035	28.6	0.034	38.2	1.03
T1/2 (hr)	21.556	34.2	22.961	47.8	0.94

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Assessment of BE using Unscaled Average BE Approach- Atorvastatin

Reference Scaled Average Bioequivalence Approach Used	☑ Yes ☐ No					
Atorvastatin calcium Tablets, 80 mg (No. of subjects completed=48) Dose: 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals of Atorvastatin						
Fasting Bioequivalence Study No. 325-20						
Parameter (Units)	Test	N	RLD	N	Ratio	90% C.I.
C_{max} (ng/mL)	90.3599	48	88.7511	48	101.81	90.87-114.08
AUC_{0-t} (hr. ng/mL)	359.9302	48	354.9708	48	101.40	96.19-106.88
$AUC_{0-\infty}$ (hr. ng/mL)	362.8820	48	357.9618	48	101.37	96.21-106.82

Assessment of BE using Reference Scaled Average BE Approach

Fasting Bioequivalence Study (Study No. 325-20)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2wr	S_{WR}	Criteria Bound	Method Used	Outcome
LCMAX	101.86	90.87	114.08	0.133	0.365 (>0.294)	-0.0746 (<0)	SABE Proc GLM	Bioequivalent

$LAUC_{0-t}$	101.40	96.19	106.88	0.031	0.177 (<0.294)	-0.0171	ABE Proc mixed	Bioequivalent
$LAUC_{0-\infty}$	101.37	96.21	106.82	0.031	0.177 (<0.294)	-0.0170	ABE Proc mixed	Bioequivalent

Ortho-hydroxylated Atorvastatin

Reference Scaled Average Bioequivalence Approach Used	☑ Yes ☐ No

Atorvastatin calcium Tablets 80 mg
(No. of subjects completed=48)
Dose: 80 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals of Ortho-hydroxylated atorvastatin

fasting Bioequivalence Study No. 325-20

Parameter (Units)	Test-T	N	RLD	N	Ratio	90% C.I.
C_{max} (ng/mL)	46.7119	48	47.4189	48	98.51	89.58-108.32
AUC_{0-t} (hr. ng/mL)	326.7295	48	325.9618	48	100.24	95.40-105.31
$AUC_{0-\infty}$ (hr. ng/mL)	332.6040	48	331.4595	48	100.35	95.57-105.35

Assessment of BE using Reference Scaled Average BE Approach- Ortho hydroxylated Atorvastatin

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2_{WR}	S_{WR}	Criteria Bound	Method Used	Outcome
LCMAX	98.49	89.58	108.32	0.103	0.322 (>0.294)	-0.0588 (<0)	SABE Proc mixed	Bioequivalent
$LAUC_{0-t}$	100.16	95.40	105.31	0.028	0.168 (<0.294)	-0.0164	ABE Proc mixed	Bioequivalent
$LAUC_{0-\infty}$	100.53	95.57	105.35	0.027	0.165 (<0.294)	-0.0155	ABE Proc mixed	Bioequivalent

Para hydroxylated Atorvastatin

Reference Scaled Average Bioequivalence Approach Used	☑ Yes ☐ No

Atorvastatin calcium Tablets 80 mg
(No. of subjects completed=48)
Dose: 80 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals of Para-hydroxylated atorvastatin

fasting Bioequivalence Study No. 325-20

Parameter (Units)	Test-T	N	RLD	N	Ratio	90% C.I.
C_{max} (ng/mL)	3.2418	48	3.1280	48	103.64	94.69-113.43
AUC_{0-t} (hr. ng/mL)	67.4969	48	66.6401	48	101.29	96.17-106.68
$AUC_{0-\infty}$ (hr. ng/mL)	76.0540	48	75.2512	48	101.07	96.01-106.39

Assessment of BE using Reference Scaled Average BE Approach- Para hydroxylated Atorvastatin

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2wr	S_{WR}	Criteria Bound	Method Used	Outcome
LCMAX	103.30	94.69	113.43	0.110	0.332 (>0.294)	-0.0606 (<0)	SABE Proc mixed	Bioequivalent
$LAUC_{0-t}$	101.46	96.17	106.68	0.021	0.145 (<0.294)	-0.0105	ABE Proc mixed	Bioequivalent
$LAUC_{0-\infty}$	101.82	96.01	106.39	0.020	0.141 (<0.294)	-0.0094	ABE Proc mixed	Bioequivalent

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Assessment of BE using Unscaled Average BE Approach- Atorvastatin

Atorvastatin Calcium Tablets, 80 mg (No. of subjects completed=48) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 325-20							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	359.93	48	355.00	48	1.01	96.19	106.87
AUC∞ (hr *ng/ml)	362.88	48	357.93	48	1.01	96.22	106.83
Cmax (ng/ml)	90.36	48	88.75	48	1.00	90.87	114.08

Assessment of BE using Reference Scaled Average BE Approach- Atorvastatin

Fasting Bioequivalence Study (Study No. 325-20)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.02	96.19	106.87	0.0323677	0.1799103	-0.017517	Unscaled	PASS
LAUCI	1.02	96.22	106.83	0.0321482	0.1792992	-0.017436	Unscaled	PASS
LCMAX	1.02	90.87	114.08	0.1306727	0.3614868 (>0.294)	-0.072329	Scaled/PE	PASS

Assessment of BE using Unscaled Average BE Approach- Ortho-hydroxylated Atorvastatin

Atorvastatin Calcium Tablets, 80 mg

(No. of subjects completed=48) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (Study No. 325-20)							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	326.73	48	325.96	48	1.00	95.40	105.31
AUC∞ (hr *ng/ml)	332.60	48	331.31	48	1.00	95.65	105.37
Cmax (ng/ml)	46.71	48	47.42	48	0.99	89.58	108.32

Assessment of BE using Reference Scaled Average BE Approach-Ortho-hydroxylated Atorvastatin

Fasting Bioequivalence Study (Study No. 325-20)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.00	95.40	105.31	0.0284085	0.1685483	-0.016432	Unscaled	PASS
LAUCI	1.00	95.65	105.37	0.0270004	0.1643181	-0.0155	Unscaled	PASS
LCMAX	0.98	89.58	108.32	0.1001367	0.3164439	-0.056269	Scaled/PE	PASS

Assessment of BE using Unscaled Average BE Approach-Para hydroxylated Atorvastatin

Atorvastatin Calcium Tablets, 80 mg (No. of subjects completed=48) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (Study No. 325-20)							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	76.07	48	75.56	48	1.01	95.68	105.93
AUC∞ (hr *ng/ml)	67.50	48	66.64	48	1.01	96.17	106.68
Cmax (ng/ml)	3.24	48	3.13	48	1.04	94.69	113.43

Assessment of BE using Reference Scaled Average BE Approach- Para hydroxylated Atorvastatin

Fasting Bioequivalence Study (Study No. 325-20)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.01	95.68	105.93	0.0204558	0.1430239	-0.010923	Unscaled	PASS

Fasting Bioequivalence Study (Study No. 325-20)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCI	1.01	96.17	106.68	0.0216135	0.1470151	-0.010871	Unscaled	PASS
LCMAX	1.03	94.69	113.43	0.1075235	0.3279078	-0.058547	Scaled/PE	PASS

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	**Atorvastatin** AUC_{0-t}: 0.1799 AUC_i:0.1793 Cmax: 0.3615 **O-hydroxy Atorvastatin** AUC_{0-t}: 0.1685 AUC_i: 0.1643 Cmax: 0.3164 **P-hydroxy Atorvastatin** AUC_{0-t}: 0.1430 AUC_i: 0.1470 Cmax: 0.3279
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No **Atorvastatin** T/R ratio=0.90 **O-hydroxy Atorvastatin** T/R ratio=0.89 **P-hydroxy Atorvastatin** T/R ratio=0.93
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Comments on PK results: Adequate

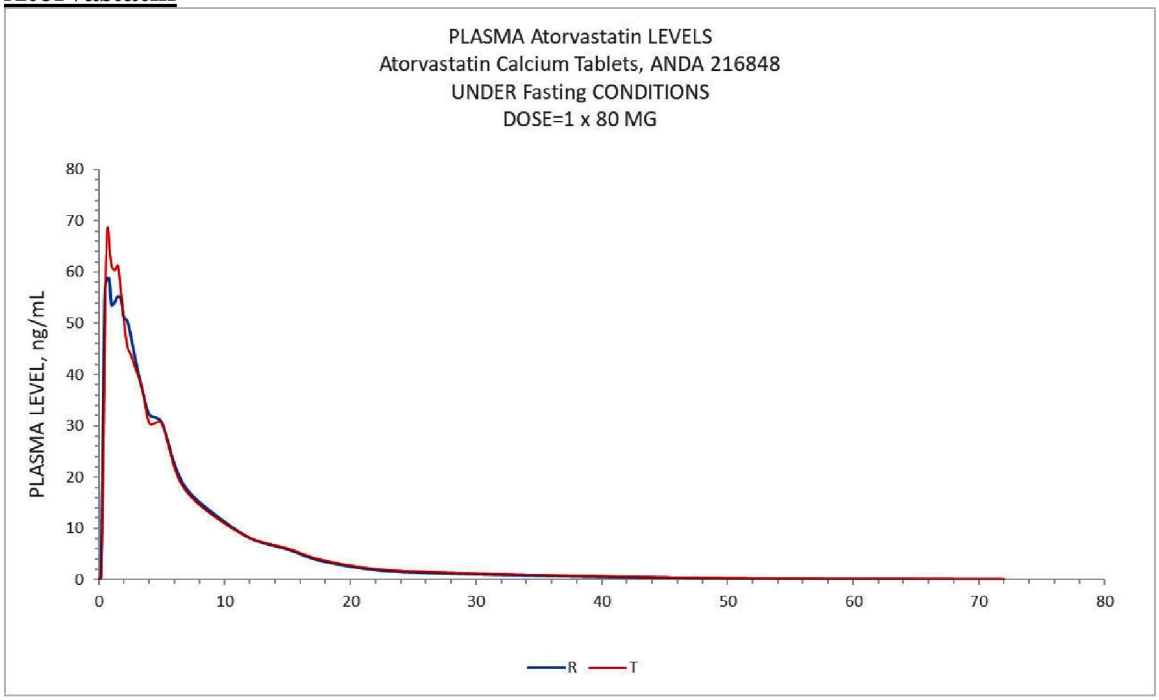
- The assessor performed the PK and statistical analysis to verify the applicant's result using SAS software (SAS 9.4). The SAS code: Highly Variable Reference Scaled 3-period.SAS was used for the analysis.
- 54 (Fifty-four) enrolled participants were included for PK analysis. As mentioned in section 4.1.1.2.2 table, six subjects were withdrawn/dropped out during fasting study. 48 (Forty-eight) completed subjects were included for reference scaled average bioequivalence (RSABE) analysis per applicant's protocol section 13.3, and 51 subjects completed at least two periods were included for within subject standard deviation of reference product (S_{WR}) analysis. The assessor agrees with the sufficient number of subjects included in the analysis.
- In the BE analysis, S_{WR} was found to be greater than (>) 0.294 for Cmax, therefore RSABE approach was used for Cmax. The reference-scaled average BE criteria limits were acceptable. The confidence bound was ≤ to 0 and the point estimate falls within 0.8-1.25.
- S_{WR} < 0.294 for pharmacokinetic parameters AUC0-t and AUCi. Therefore, BE criteria is based on unscaled average BE. The unscaled average BE limits results in 90% confidence interval for the geometric least squares mean ratio that falls within 90.00 – 125.00%.
- Altogether, the assessor's calculated statistical results were similar to those calculated by the applicant as both analysis met BE acceptance criteria. Therefore, the assessor considers BE study acceptable.

4.1.1.5 Overall Comment

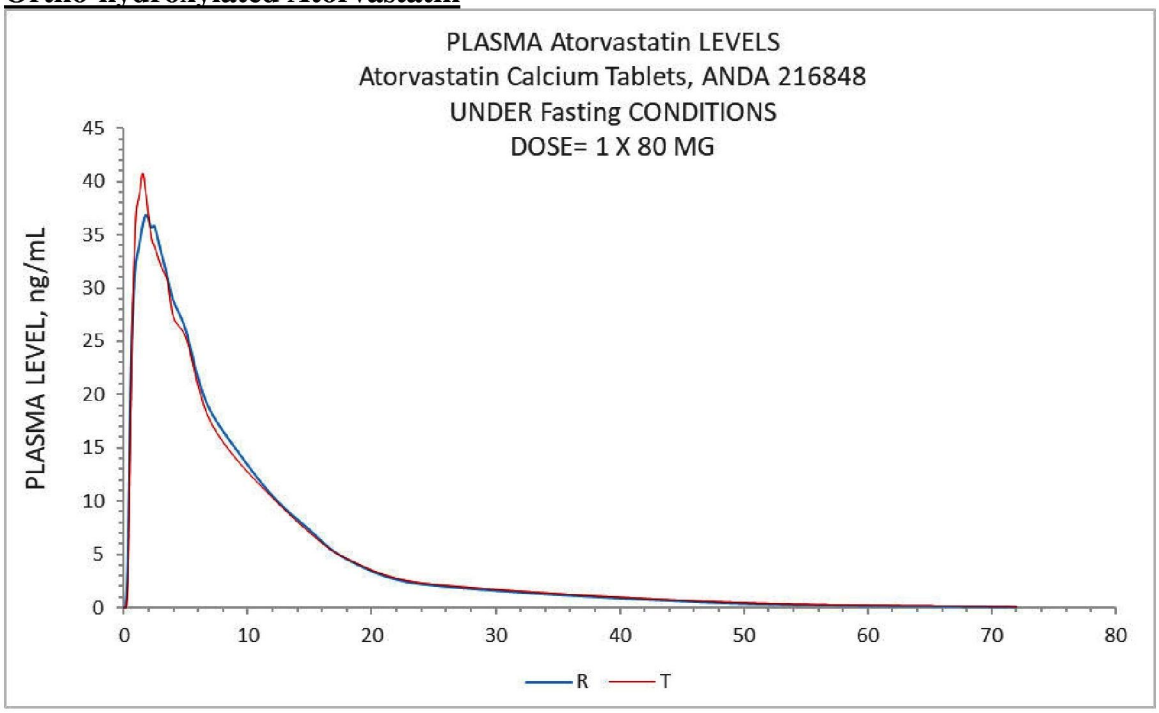
Was the fasting bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

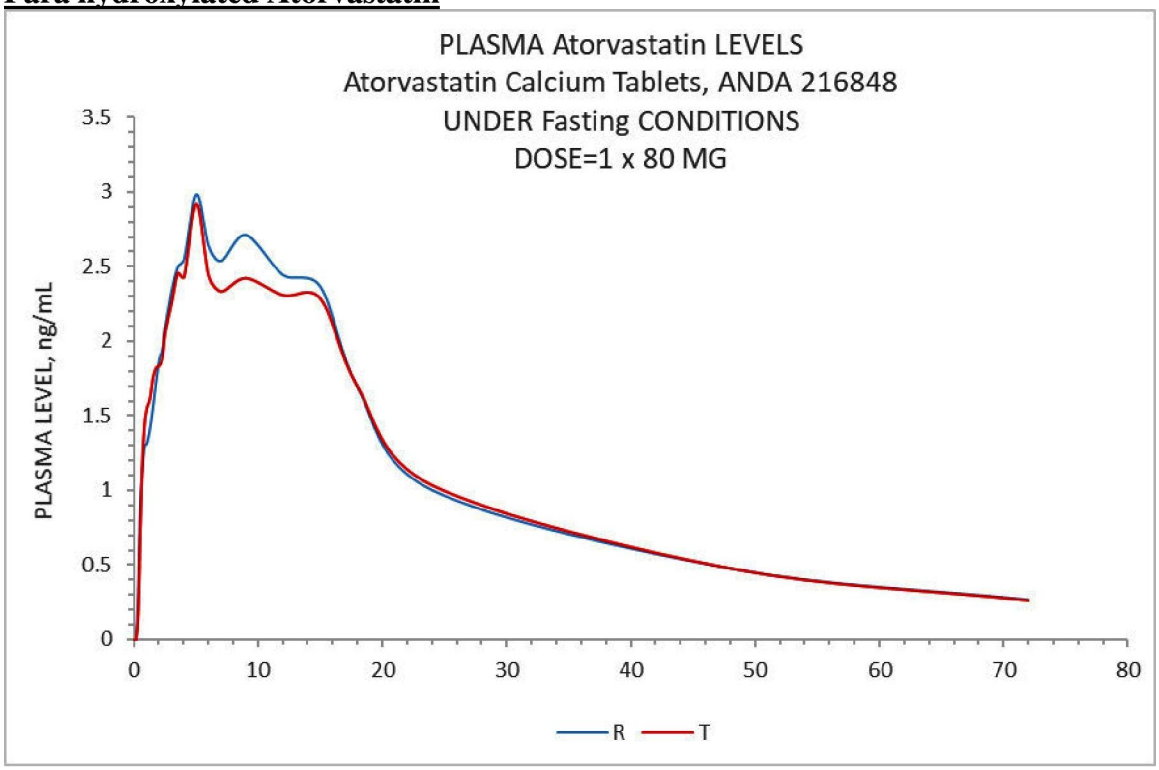
Atorvastatin



Ortho-hydroxylated Atorvastatin



Para hydroxylated Atorvastatin



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	326-20
Study Title	An open label, balanced, randomized, two-treatment, three-sequence, three-period, partial replicate, cross-over, single-dose, oral bioequivalence study of Atorvastatin calcium tablets 80 mg (Test) of Lepu Pharmaceutical Technology Co., Ltd, China and Lipitor® (Atorvastatin calcium) tablets 80 mg (Reference) of Parke-Devis, Division of Pfizer Inc, NY, NY 10017, USA in healthy, adult, human subjects under fed conditions.
Clinical Site (Name & Address)	(b) (4)
Principal Clinical Investigator	
Dosing Dates	Period 1: 06/22/2021 Period 2: 07/02/2021 Period 3: 07/13/2021
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	09/01/2021 – 09/22/2021
Principal Analytical Investigator	(b) (4)
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	(a) 92 days (b) -70°C ± 15°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	138.82 days at -70°C ± 15°C temperature and at -20°C±5°C temperature

4.1.2.1.2 Product Information

Please see section 4.1.1.1.2.

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 55 (54 + 01 stand by) Dosed: 54 (Period I); 52 (Period II); 49(Period III) Completed: 54 (Period I); 50 (Period II); 48(Period III) Samples Analyzed:51 Statistically Analyzed: 51
No. of Sequences	3: R1, R2, T
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	A washout period of 10 days between period-I and II, and 11 days between Period-II and III was maintained between each treatment schedule.
Randomization	☒ Yes ☐ No RTR, TRR or RRT
Blood Sampling Times	post-dose blood samples of 5 mL each were collected at at 0.17, 0.33, 0.50, 0.75, 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, 7.00, 9.00, 12.00, 15.00, 18.00, 24.00, 48.00 and 72.00 hours in each period.
IRB Approval	☒ Yes Date: 21/Jan/2021 ☐ No
Informed Consent	☒ Yes Date: 21/Jan/2021 ☐ No
Length of Fasting	Fasting of at least 10 hours
Length of Confinement	Subjects were housed in the clinic from at least 11 hours prior to dosing until at least 48 hours post dose in each study period.
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study						
Food Items	**Ingredients**	**Amount (gm/ml.)**	**Energy (kcal.)**	**Protein (kcal.)**	**Fat (kcal.)**	**Carbohydrate (kcal.)**
Fried Eggs	**Eggs**	**80**	107.84	42.48	65.88	0.00
	Butter	**10**	72.90	0.00	72.90	0.00
Total			**180.74**	**42.48**	**138.78**	**0.00**
Chicken Fry	**Chicken Breast**	**40**	67.30	34.88	32.40	0.00
	Corn flour	**6**	20.05	2.12	2.07	15.56
	Oil	**13**	117.00	0.00	117.00	0.00
Total			**204.35**	**37.00**	**151.47**	**15.56**
Bread Butter	**Bread**	**50**	122.50	15.60	3.15	103.80
	Butter	**10**	72.90	0.00	72.90	0.00

Total			**195.40**	**15.60**	**76.05**	**103.80**
Fried Potato	**Potato brown skin big**	**75**	52.34	4.64	1.53	44.68
	Oil	**10**	90.00	0.00	90.00	0.00
Total			**142.34**	**4.64**	**91.53**	**44.68**
Milk	**Milk whole buffalo**	**240**	257.54	35.32	142.11	80.56
	Sugar	**5**	19.90	0.04	0.00	19.88
Total			**277.44**	**35.36**	**142.11**	**100.44**
TOTAL			**1000.27**	**135.08**	**599.94**	**264.48**
PERCENTAGE				**13.50%**	**59.98%**	**26.44%**

Comments on Study Design: Adequate

The applicant enrolled 54 subjects for fed study. Subject (b) (6) was voluntarily withdrawn from the study and replaced with stand by subject SS1. Out of the 54 subjects enrolled, 48 subjects completed each period of the study and were considered for RSABE and SWR analysis. The number of subjects included for average BE analysis was 51 subjects, including subjects (b) (6) as they completed two periods.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No.: 326-20			
Parameter		**Treatment Groups**	
		Test Product N = 48	**Reference Product N = 48**
Age (years)	Mean ± SD	34.6 ± 5.3	34.6 ± 5.3
	Range	24-44	24-44
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	41 (85.42%)	41 (85.42%)
	41 – 64	7 (14.58%)	7 (14.58%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	48 (100%)	48 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	48 (100%)	48 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)

	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	24.49 ± 2.61	24.49 ± 2.61
	Range	19.56-29.93	19.56-29.93
Other Factors	-	Not applicable	

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No

4.1.2.2.2 Dropout Information

Study No. 326-20				
Subject No.	**Reason for Drop-out/Replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	**Reason:** Dropped out as subject was voluntarily withdrawn from the study and he is replaced with stand by subject SS1. **Last Treatment received:** Not Applicable **Time & Date**: 21:30 hrs & (b) (6)	I	YES	SS1
	Reason: Withdrawn due to adverse event (vomiting) after dosing. **Last Treatment received:** Reference Product-R **Time & Date**: 10:11hrs & (b) (6)	I	Not Applicable	Not Applicable
	Reason: Dropped out as subject was absent for check in of P-II only **Last Treatment received:** Reference Product-R **Time & Date**: 23:00 hrs & (b) (6)	II	Not Applicable	Not Applicable
	Reason: Withdrawn due to Adverse (Vomiting) & meets withdrawal criteria after dosing in in P-II. **Last Treatment received:** Test Product-T **Time & Date**: 09:10 hrs & (b) (6)	II	Not Applicable	Not Applicable
	Reason: Withdrawn due to Adverse (Vomiting) & meets withdrawal criteria after dosing in in P-II. **Last Treatment received:** Reference Product-R **Time & Date**: 09:46 hrs & (b) (6)	II	Not Applicable	Not Applicable
	Reason: Dropped out as subject was absent for check. **Last Treatment received:** Reference Product-R **Time & Date**: 23:10 hrs & (b) (6)	III	Not Applicable	Not Applicable
	Reason: Withdrawn due to subject did not complete HFHC breakfast before dosing. **Last Treatment received:** Reference Product-R **Time & Date**: 09:18 hrs & (b) (6)	III	Not Applicable	Not Applicable

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

Assessor's Note

The applicant reported within the table that subject (b) (6) experienced vomiting after administration of test product. The assessor confirms throughout the case report of the application that subject (b) (6) experienced vomiting after dosing of reference product[9].

4.1.2.2.3 Study Adverse Events

Body system/adverse event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No.: 326-20	
	Treatment T (1) N = 54	Treatment R (1) N = 54
Gastrointestinal Disorder		
Vomiting	-	03 (5.55%)
Diarrhea	01 (1.85 %)	-
Central Nervous system disorders		
Headache	-	01 (1.85 %)
Total	**01 (*1.85%)**	**04 (*7.40 %)**
Post-study Abnormalities N = 54 (100%)		
Investigations		
Increased Blood creatinine phosphokinase	01 (1.85%)	
Increased Blood alkaline phosphatase	01 (1.85%)	
Increased Blood Aspartate aminotransferase	01 (1.85%)	
Increased Blood Alanine aminotransferase	01 (1.85%)	
Total	**04 (*7.40%)**	

*Total is sum percentage of each AE

(1) N = Number of subjects dosed for each treatment

Subjects Experiencing Emesis (Include in eCTD)

[9] EDR. ANDA 216848. Module 5.3. Clinical Study Reports. \\CDSESUB1\evsprod\anda216848\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\326-20\crfs\fed\326-20-crf-sub-20.pdf

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	Reference	II	09:02	09:10 (b) (6)	0.13
	Reference	II	09:32	09:46 (b) (6)	0.23
	Reference	I	09:20	10:07 (b) (6)	0.78

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☒ No ☐ N/A Subject (b) (6) experienced vomiting 8 minutes after dosing in Period II and was not included within analysis for Period II and Period III. Subject (b) (6) experienced vomiting 14 minutes after dosing in Period II and was not included within analysis for Period II and Period III. Subject (b) (6) experienced vomiting 14 minutes after dosing in Period I and was not included within analysis for Period II and Period III.
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☐ Yes ☒ No (please see comment below in comment section)
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.2.2.4 Protocol Deviations

Study No.: 326-20			
Type	**Test Product (T) N= 54**	**Reference Product (R) N=54**	**Impact Assessment**
Blood sample collection deviations:			

Study No.: 326-20			
Type	**Test Product (T)** **N= 54**	**Reference Product (R)** **N=54**	**Impact Assessment**
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-I, which was delayed due to late arrival of the subject.	[redacted]	(b) (6) [redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-I, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-I, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-I, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-I, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-II, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-II, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-II, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-II, which was delayed due to late arrival of the subject.	[redacted]	[redacted]	No impact on the outcome of the study and safety of the subject.

Study No.: 326-20			
Type	**Test Product (T) N= 54**	**Reference Product (R) N=54**	**Impact Assessment**
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.	[redacted]	(b) (6)	No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.			No impact on the outcome of the study and safety of the subject.
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Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for 72.00 hours ambulatory blood sample time-point in Period-III, which was delayed due to late arrival of the subject.			No impact on the outcome of the study and safety of the subject.

Study No.: 326-20			
Type	**Test Product (T) N= 54**	**Reference Product (R) N=54**	**Impact Assessment**
Missed samples deviations:			
Protocol deviation was recorded for missed samples in Period-I for Subject No. (b) (6) for 1.00 to 72.00 hours [i.e., total 21 (original) + 21 (duplicate) missed sample] as withdrawn due to adverse event (vomiting) after dosing. Hence, he was considered as withdrawn from the study	(b) (6)		No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-II for Subject No. (b) (6) for 0.00 to 72.00 hours [i.e., total 26 (original) + 26 (duplicate) missed sample] as Dropped out as subject was absent for check in of P-II only.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-II for Subject No. (b) (6) for 0.17 to 72.00 hours [i.e., total 25 (original) + 25 (duplicate) missed sample] as Withdrawn due to Adverse (Vomiting) & meets withdrawal criteria after dosing in in P-II.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-II for Subject No. (b) (6) for 0.33 to 72.00 hours [i.e., total 24 (original) + 24 (duplicate) missed sample] as withdrawn due to Adverse (Vomiting) & meets withdrawal criteria after dosing in in P-II.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-II for Subject No. (b) (6) for 0.00 to 72.00 hours [i.e., total 26 (original) + 26 (duplicate) missed sample] as withdrawn due to adverse event (vomiting) after dosing in P-I.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-III for Subject No. (b) (6) for 0.00 to 72.00 hours [i.e., total 26 (original) + 26 (duplicate) missed sample] as withdrawn due to adverse event (vomiting) after dosing in P-I.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-III for Subject No. (b) (6) for 0.00 to 72.00 hours [i.e., total 26 (original) + 26 (duplicate) missed sample] as Withdrawn due to Adverse event (Vomiting) & meets withdrawal criteria after dosing in in P-II.			No impact on the outcome of the study and safety of the subject.

Study No.: 326-20			
Type	**Test Product (T) N= 54**	**Reference Product (R) N=54**	**Impact Assessment**
Protocol deviation was recorded for missed samples in Period-III for Subject No. [redacted] for 0.00 to 72.00 hours [i.e., total 26 (original) + 26 (duplicate) missed sample] as withdrawn due to Adverse event (Vomiting) & meets withdrawal criteria after dosing in in P-II.	[redacted] (b) (6)		No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-III for Subject No. [redacted] for 0.00 to 72.00 hours [i.e., total 26 (original) + 26 (duplicate) missed sample] as Dropped out as subject was absent for P-III check-in.			No impact on the outcome of the study and safety of the subject.
Protocol deviation was recorded for missed samples in Period-III for Subject No. [redacted] for 0.17 to 72.00 hours [i.e., total 25 (original) + 25 (duplicate) missed sample] as withdrawn due to subject did not complete HFHC breakfast before dosing of P-III.			No impact on the outcome of the study and safety of the subject.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

- As previously stated, there were three (3) subjects to experience vomiting after administration of reference product compared to one (1) subject to experience diarrhea after administration of test product. The 3 subjects were withdrawn from the study and therefore did not have an impact on the study outcome. The difference of the adverse events between the reference and test product did not have any effect on the safety and BE evaluation.

- There were no deaths or serious adverse events reported during the fed study.

- The protocol deviations will likely not have an impact on the study outcome as the actual time of sampling was used in the PK analysis and missing samples are not included in the statistical analysis.

Overall, the applicant's dropouts, adverse events and protocol deviations are considered adequate.

4.1.2.3 Bioanalytical Results

4.1.2.3.1 Sample Analysis Calibration and Quality Control

Study No: 326-20 Atorvastatin								
Parameter	**Standard Curve Samples**							
	STD 1	**STD 2**	**STD 3**	**STD 4**	**STD 5**	**STD 6**	**STD 7**	**STD 8**
Concentration (ng/mL)	**0.100**	**0.200**	**1.001**	**6.012**	**30.058**	**150.288**	**239.312**	**299.139**
Inter day Precision (%CV)	**31.0**	**6.0**	**3.1**	**2.2**	**2.3**	**2.0**	**3.1**	**2.0**
Inter day Accuracy (%Actual)	**105.6**	**97.6**	**96.8**	**98.6**	**99.7**	**102.0**	**102.3**	**101.4**
Linearity (Range of r values)	0.9973 to 1.0000							
Linearity Range (ng/mL)	0.100 to 299.139 ng/mL							
Sensitivity/LOQ (ng/mL)	0.100 ng/mL							

Study No: 326-20 Atorvastatin					
Parameter	**Quality Control Samples**				
	LQC	**LMQC**	**LMQC2**	**MQC**	**HQC**
Concentration (ng/mL)	**0.298**	**17.934**	**18.038**	**90.487**	**226.216**
Inter day Precision (%CV)	**6.8**	**2.7**	**2.8**	**2.9**	**2.9**
Inter day Accuracy (%Actual)	**98.8**	**100.3**	**107.7**	**101.9**	**101.2**

Assessor's Note

It is noted that the applicant experienced high %CV for STD1, run CCID: (b) (6) (Subject (b) (6), PI, PII and PIII). The STD1 run failed as high accuracy was identified. Per the SOP No. (b) (4), the applicant removed failed STD1 of CCID: (b) (6) for subject (b) (6) analysis. Overall, the calibration curve was found acceptable. The variability did not have any effect on the BE data.

Study No: 326-20 o-Hydroxy Atorvastatin								
Parameter	**Standard Curve Samples**							
	STD 1	**STD 2**	**STD 3**	**STD 4**	**STD 5**	**STD 6**	**STD 7**	**STD 8**

Concentration (ng/mL)	0.200	0.400	4.000	20.000	49.999	128.071	160.089	200.111
Inter day Precision (%CV)	10.5	3.2	2.2	2.3	2.1	2.8	2.0	1.7
Inter day Accuracy (%Actual)	102.1	98.7	99.3	100.3	100.3	100.4	99.7	100.6
Linearity (Range of r values)	0.9981 to 0.9999							
Linearity Range (ng/mL)	0.200 to 200.111 ng/mL							
Sensitivity/LOQ (ng/mL)	0.200 ng/mL							

Study No: 326-20 o-Hydroxy Atorvastatin					
Parameter	Quality Control Samples				
	LQC	LMQC	LMQC2	MQC	HQC
Concentration (ng/mL)	0.599	12.092	8.023	61.380	153.450
Inter day Precision (%CV)	4.9	3.7	2.9	3.4	3.5
Inter day Accuracy (%Actual)	100.1	99.2	93.7	100.0	98.5

Study No: 326-20 p-Hydroxy Atorvastatin								
Parameter	Standard Curve Samples							
	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8
Concentration (ng/mL)	0.100	0.200	1.001	2.998	7.496	14.992	23.999	29.999
Inter day Precision (%CV)	2.8	5.9	3.2	2.5	2.7	2.8	2.3	2.4
Inter day Accuracy (%Actual)	100.5	99.0	100.2	100.4	100.2	100.3	99.5	99.9
Linearity (Range of r values)	0.9971 to 0.9999							
Linearity Range (ng/mL)	0.100 to 29.999 ng/mL							
Sensitivity/LOQ (ng/mL)	0.100 ng/mL							

Study No: 326-20 p-Hydroxy Atorvastatin					
Parameter	Quality Control Samples				
	LQC	LMQC	LMQC2	MQC	HQC
Concentration (ng/mL)	0.299	1.799	0.604	9.674	23.310
Inter day Precision (%CV)	5.2	3.5	3.1	3.3	3.3
Inter day Accuracy (%Actual)	99.7	97.6	108.1	98.1	98.1

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions.	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☒ Yes ☐ No Subject sample (b) (6) and subject (b) (6) (please see comment below in section 4.1.2.3.2)
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.2.3.2 Reanalysis of Study Samples

Study No: 326-20 Analyte Name: Atorvastatin Additional information in Volume(s), Page(s): 326-20-bioanalytical-report: Page 100 of 125								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Code D: Value above upper limit of standard curve	0	1	0.0	0.0	0	1	0.0	0.0
Code G: ISTD variation	4	5	0.3	0.2	4	5	0.3	0.2
Code H1: Interference at analyte RT	0	1	0.0	0.0	0	1	0.0	0.0
Code I: Interference in subject zero samples	0	1	0.0	0.0	0	1	0.0	0.0
Code JL: Value below the truncated calibration range	0	3	0.0	0.1	0	3	0.0	0.1
Total	4	11	0.3	0.4	4	11	0.3	0.4

Study No: 326-20 Analyte Name: o-Hydroxy Atorvastatin Additional information in Volume(s), Page(s): 326-20-bioanalytical-report: Page 101 of 125		
Reason why assay was repeated	**Number of samples reanalyzed**	**Number of recalculated values used after reanalysis**

	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Code G: ISTD variation	8	10	0.6	0.4	8	10	0.6	0.4
Code JL: Value below the truncated calibration range	4	13	0.3	0.5	4	13	0.3	0.5
Total	12	23	0.9	0.9	12	23	0.9	0.9

Study No: 326-20 Analyte Name: p-Hydroxy Atorvastatin Additional information in Volume(s), Page(s): 326-20-bioanalytical-report: Page 103 of 125								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Code G: ISTD variation	2	1	0.1	0.0	2	1	0.1	0.0
Total	2	1	0.1	0.0	2	1	0.1	0.0

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

Atorvastatin:

- There were 15 samples repeated for atorvastatin, including repeats, rejected runs, re-injected runs and ISR runs. There were 2 rejected runs reported in the fed study for atorvastatin.
- One sample (reference, (b) (6)) was reanalyzed due to interference in subject zero samples (Code I). The repeated values were below LLOQ and therefore reported as BLQ.
- One sample (reference, (b) (6)) was reanalyzed due to interference at analyte RT (Code H1). The values were reported based on the concentration observed in subject zero sample. Per the SOP, the sample was repeated for confirmation. The repeated value was reported based on the concentration observed in subject zero sample. The assessor checked and verified the raw data for the original and repeated sample and determined that the repeats are acceptable.
- The applicant used 264 (out of 3961 samples, 10% of the first 1000 samples + 5.54% of the remaining samples) selected samples for ISR for Atorvastatin.

During the ISR, 87.1 % of the samples for Atorvastatin met the acceptance criteria (within ±20% of the original results) and thus, ISR was found to be within acceptance criteria, demonstrating reproducibility.

o-Hydroxy Atorvastatin:

- There were 35 samples repeated for o-hydroxy atorvastatin, including repeats, rejected runs, and re-injected runs. There was one rejected run reported in the fed study for o-hydroxy atorvastatin.
- The applicant used 264 (out of 3961 samples, 10% of the first 1000 samples + 5.54% of the remaining samples) selected samples for ISR for o-hydroxy atorvastatin. During the ISR, 82.6 % of the samples for o-hydroxy atorvastatin met the acceptance criteria (within ±20% of the original results) and thus, ISR was found to be within acceptance criteria, demonstrating reproducibility.

p-Hydroxy Atorvastatin:

- There were 3 samples repeated for p-hydroxy atorvastatin. There were no rejected and re-injected runs were reported in the fed study for p-hydroxy atorvastatin.
- The applicant used 263 (out of 4019 samples, 10% of the first 1000 samples + 5.4% of the remaining samples) selected samples for ISR for p-hydroxy atorvastatin. During the ISR, 84.8 % of the samples for p-hydroxy atorvastatin met the acceptance criteria (within ±20% of the original results) and thus, ISR was found to be within acceptance criteria, demonstrating reproducibility.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters (Assessor Calculated)

Atorvastatin

Fasting Bioequivalence Study No. 326-20					
Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC0-t (hr *ng/ml)	363.883	40.9	365.262	38.5	0.99
AUC∞ (hr *ng/ml)	367.533	40.6	371.05	38.3	0.99
Cmax (ng/ml)	73.202	61.7	77.732	59.6	0.94
Tmax* (hr)	2.378	51.5	2.316	53.5	1.02
Kel (hr^{-1})	0.065	24.6	0.068	38.2	0.95
T1/2 (hr)	11.364	23.8	11.181	27.4	1.01

Ortho-hydroxylated

Fasting Bioequivalence Study No. 326-20

Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC0-t (hr *ng/ml)	212.963	33.8	212.963	33	1.00
AUC∞ (hr *ng/ml)	219.927	32.7	216.309	32.7	1.01
Cmax (ng/ml)	23.766	45.5	23.985	47.3	0.99
Tmax* (hr)	3.608	43.2	3.639	45.6	0.99
Kel (hr^{-1})	0.068	32.4	0.07	38.6	0.97
T1/2 (hr)	10.964	26.1	11.067	29.5	0.99

Para-hydroxylated

Fasting Bioequivalence Study No. 326-20					
Parameter (units)	Test		Reference		T/R
	Mean	%CV	Mean	% CV	
AUC0-t (hr *ng/ml)	59.799	45.5	60.406	44.9	0.98
AUC∞ (hr *ng/ml)	72.048	46.9	75.265	45.9	0.95
Cmax (ng/ml)	2.803	67.2	2.837	63.8	0.98
Tmax* (hr)	6.525	43.2	6.672	39.4	0.97
Kel (hr^{-1})	0.029	31	0.028	35.7	1.03
T1/2 (hr)	26.104	33	29.219	51.2	0.89

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Assessment of BE using Unscaled Average BE Approach-Atorvastatin

Reference Scaled Average Bioequivalence Approach Used	☑ Yes ☐ No

Atorvastatin calcium Tablets 80 mg
(No. of subjects completed=51*)
Dose: 80 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals of Atorvastatin

Fed Bioequivalence Study No. 326-20						
Parameter (Units)	Test-T	N	RLD	N	Ratio	90% C.I.
AUC_{0-t} (hr. ng/mL)	335.5436	51	339.3492	51	98.88	92.88-105.27
$AUC_{0-\infty}$ (hr. ng/mL)	339.4030	51	343.1109	51	98.92	92.98-105.24
C_{max} (ng/mL)	62.7905	51	66.8054	51	93.99	85.35-103.51

*Subjects who complete at least two periods of the study of which at least one period with test and reference as per protocol section 13.3 "Statistical analysis"

Assessment of BE using Reference Scaled Average BE Approach-Atorvastatin

parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2wr	S_{WR}	Criteria Bound	Method Used	Outcome
$LAUC_{0-t}$	98.88	92.88	105.27	0.017	0.131 (<0.294)	-0.0056	ABE Proc mixed	Bioequivalent
$LAUC_{0-\infty}$	98.92	92.98	105.24	0.017	0.129 (<0.294)	-0.0056	ABE Proc mixed	Bioequivalent
LCMAX	93.99	85.35	103.51	0.070	0.266 (<0.294)	-0.0152	ABE Proc mixed	Bioequivalent

*Within-subject standard deviation of the reference product (S_{WR}) was found to be less than 0.294 for Cmax, AUC0-t and AUC0-∞ of Atorvastatin, ortho-hydroxylated atorvastatin and para-hydroxylated atorvastatin, hence average bioequivalence approach was used to determine the bioequivalence.

Ortho-hydroxylated Atorvastatin

Reference Scaled Average Bioequivalence Approach Used	☑ Yes ☐ No

Atorvastatin calcium Tablets 80 mg
(No. of subjects completed=51*)
Dose: 80 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals of Ortho-hydroxylated atorvastatin

Fed Bioequivalence Study No. 326-20

Parameter (Units)	Test-T	N	RLD	N	Ratio	90% C.I.
AUC_{0-t} (hr. ng/mL)	202.6143	51	198.9940	51	101.82	97.76-106.05
$AUC_{0-\infty}$ (hr. ng/mL)	209.9692	51	206.0358	51	101.91	97.99-105.99
C_{max}(ng/mL)	21.7227	51	21.5206	51	100.94	93.25-109.26

Assessment of BE using Reference Scaled Average BE Approach- Ortho hydroxylated Atorvastatin

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2wr	S_{WR}	Criteria Bound	Method Used	Outcome
$LAUC_{0-t}$	101.82	97.76	106.05	0.016	0.126 (<0.294)	-0.0083	ABE Proc mixed	Bioequivalent
$LAUC_{0-\infty}$	101.91	97.99	105.99	0.015	0.123 (<0.294)	-0.0076	ABE Proc mixed	Bioequivalent
LCMAX	100.94	93.25	109.26	0.049	0.221 (<0.294)	-0.0269	ABE Proc mixed	Bioequivalent

Para-hydroxylated Atorvastatin

Reference Scaled Average Bioequivalence Approach Used	☑ Yes ☐ No

Atorvastatin calcium Tablets 80 mg
(No. of subjects completed=51)
Dose: 80 mg
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals of Para-hydroxylated atorvastatin

Fed Bioequivalence Study No. 326-20						
Parameter (Units)	**Test-T**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr. ng/mL)	54.9663	51	55.4272	51	99.17	94.58-103.98
$AUC_{0-\infty}$ (hr. ng/mL)	66.0316	51	69.2356	51	95.37	91.44-99.47
C_{max} (ng/mL)	2.3176	51	2.3516	51	98.55	90.56-107.25

Assessment of BE using Reference Scaled Average BE Approach- Para-hydroxylated Atorvastatin

parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s^2wr	SWR	Criteria Bound	Method Used	Outcome
$LAUC_{0-t}$	99.17	94.58	103.98	0.015	0.122 (<0.294)	-0.0069	ABE Proc mixed	Bioequivalent
$LAUC_{0-\infty}$	95.37	91.44	99.47	0.023	0.152 (<0.294)	-0.0087	ABE Proc mixed	Bioequivalent
LCMAX	98.55	90.56	107.25	0.073	0.271 (<0.294)	-0.0379	ABE Proc mixed	Bioequivalent

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Assessment of BE using Unscaled Average BE Approach-Atorvastatin

Atorvastatin Calcium Tablets, 80 mg (No. of subjects completed=51) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. 326-20							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	335.54	51	339.35	51	0.99	92.88	105.27
AUC∞ (hr *ng/ml)	339.40	51	343.11	51	0.99	92.98	105.24
Cmax (ng/ml)	62.79	51	66.81	51	0.94	85.35	103.51

Assessment of BE using Reference Scaled Average BE Approach- Atorvastatin

Fed Bioequivalence Study (Study No. 326-20)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCT	0.98	92.88	105.27	0.0170619	0.1306211	-0.005574	Unscaled	PASS
LAUCI	0.98	92.98	105.24	0.0166679	0.1291044	-0.005566	Unscaled	PASS
LCMAX	0.91	85.35	103.51	0.0704956	0.2655101	-0.015222	Unscaled	PASS

Assessment of BE using Unscaled Average BE Approach- Ortho hydroxylated Atorvastatin

Atorvastatin Calcium Tablets, 80 mg (No. of subjects completed=51) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. 326-20							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	202.61	51	198.99	51	1.02	97.76	106.05
AUC∞ (hr *ng/ml)	209.97	51	206.04	51	1.02	97.99	105.99
Cmax (ng/ml)	21.72	51	21.52	51	1.01	93.25	109.26

Assessment of BE using Reference Scaled Average BE Approach- Ortho hydroxylated Atorvastatin

Fed Bioequivalence Study (Study No. 326-20)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.01	97.76	106.05	0.0159197	0.1261733	-0.00829	Unscaled	PASS
LAUCI	1.01	97.99	105.99	0.015066	0.1227438	-0.007636	Unscaled	PASS
LCMAX	0.99	93.25	109.26	0.0489939	0.2213456	-0.026933	Unscaled	PASS

Assessment of BE using Unscaled Average BE Approach-Para hydroxylated Atorvastatin

Atorvastatin Calcium Tablets, 80 mg (No. of subjects completed=51) Dose: 1 x 80 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. 326-20							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	54.97	51	55.43	51	0.99	94.58	103.98
AUC∞ (hr *ng/ml)	66.03	51	69.24	51	0.95	91.44	99.47
Cmax (ng/ml)	2.32	51	2.35	51	0.99	90.56	107.25

Assessment of BE using Reference Scaled Average BE Approach- Para hydroxylated Atorvastatin

Fed Bioequivalence Study (Study No. 326-20)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.99	94.58	103.98	0.0147714	0.1215375	-0.006852	Unscaled	PASS

Fed Bioequivalence Study (Study No. 326-20)								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
LAUCI	0.95	91.44	99.47	0.0230611	0.1518589	-0.008658	Unscaled	PASS
LCMAX	0.97	90.56	107.25	0.0734669	0.2710478	-0.037874	Unscaled	PASS

4.1.2.4.4 Additional Information for the Study

Root Mean Square Error	**Atorvastatin** AUC_{0-t}: 0.1306 AUC_i: 0.1291 Cmax: 0.2655 **O-hydroxy Atorvastatin** AUC_{0-t}: 0.1262 AUC_i: 0.1227 Cmax: 0.2213 **P-hydroxy Atorvastatin** AUC_{0-t}: 0.1215 AUC_i: 0.1519 Cmax: 0.2710
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☐ Yes ☒ No **Atorvastatin** T/R ratio=1.02 **O-hydroxy Atorvastatin** T/R ratio=0.99 **P-hydroxy Atorvastatin** T/R ratio=0.97
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Comments on PK results: Adequate

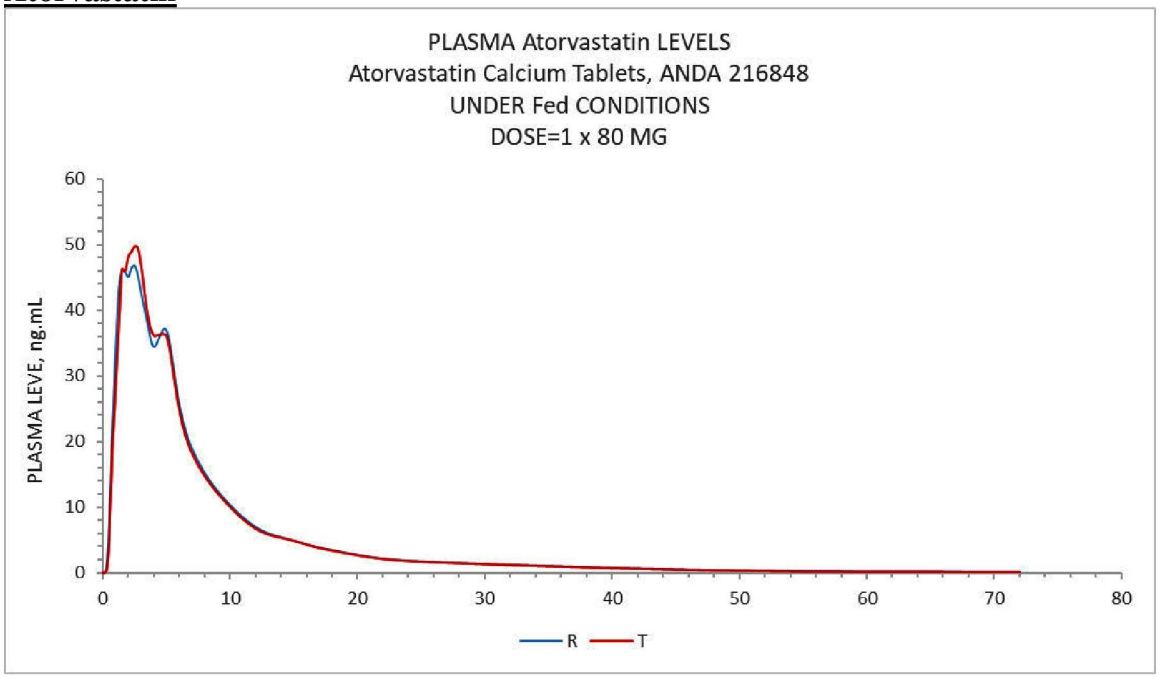
- The assessor performed the PK and statistical analysis to verify the applicant's result using the Highly Variable Reference Scaled 3-period.SAS program.
- The study design considered a reference-scaled average bioequivalence approach for this drug product. However, the S_{WR} was < 0.294, hence the unscaled average BE approach was used to assess BE.
- The unscaled average BE limits result in 90% confidence interval for the geometric least squares mean ratio that falls within 80.00 – 125.00%.
- The assessor's calculated statistical results were similar to those calculated by the applicant. Therefore, the assessor considers BE study acceptable.

4.1.2.5 Overall Comment

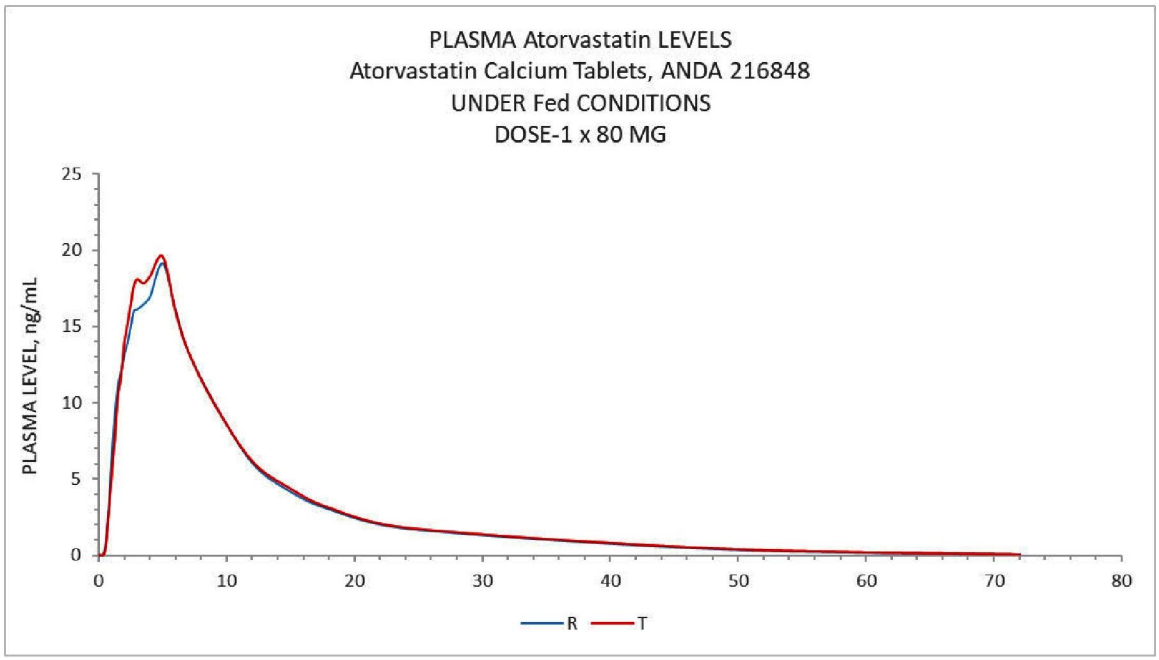
Was the Fed bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

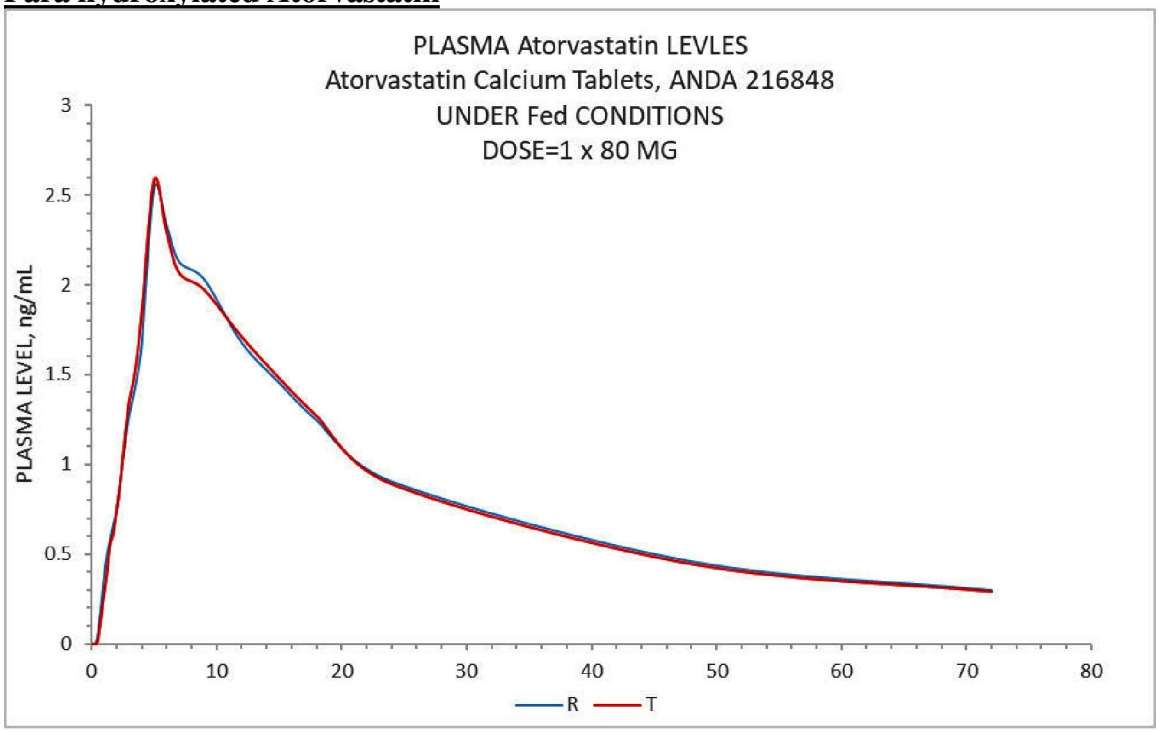
Atorvastatin



Ortho hydroxylated Atorvastatin



Para hydroxylated Atorvastatin



4.2 Formulation Data

4.2.1 Test Formulation

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet			
	10mg	20mg	40mg	80mg	10mg	20mg	40mg	80mg
Atorvastatin Calcium								
Calcium Carbonate								
Microcrystalline Cellulose								
Croscarmellose Sodium (b) (4)								
Polysorbate 80								
Hydroxypropyl Cellulose								
Magnesium Stearate								

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Opadry White YS-1-7040-CN	(b) (4)				
	(b) (4)				
Total	**156.00**	**312.00**	**624.00**	**1248.00**	**/**

RS Formulation (NOT FOR RELEASE UNDER FOIA)[10]

(b) (4)

1 Page has been withheld in full as b4 (CCI/ TS) immediately following this page

4.2.2 Inactive Ingredients (IIG Table) [11,12]

Adults
The recommended starting dose of atorvastatin calcium tablets are 10 mg or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets are 10 mg to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food.

Ingredient	Quantity/ Tablet				Maximum amount (mg) based on MDD (80 mg)	IIG limit (mg) (Oral Route)	Above or below IIG
	10mg	20mg	40mg	80mg			
Calcium Carbonate, USP	[redacted]						(b) (4)
Microcrystalline Cellulose, NF							
Lactose, Monohydrate, NF							
Croscarmellose Sodium, NF							
Polysorbate 80, NF							
Hydroxypropyl Cellulose, NF							
Magnesium Stearate, NF							
Hydroxypropyl Methylcellulose							

[11] IIG-MDD master spreadsheet
[12] FDA internal IIG database

Polyethylene Glycol (b) (4)	(b) (4)
Titanium Dioxide	
Talc	

Pediatric Patients
For children, 10-17 years of age, the recommended starting dose of atorvastatin calcium tablets are 10 mg/day; the usual dose range is 10 mg to 20 mg orally once daily

Ingredient	Quantity/ Tablet				Maximum amount (mg) based on MDD (20 mg)	IIG limit (mg) (Oral Route)	Above or below IIG
	10mg	20mg	40mg	80mg			
Calcium Carbonate, USP	(b) (4)						
Microcrystalline Cellulose, NF							
Lactose, Monohydrate, NF							
Croscarmellose Sodium, NF							
Polysorbate 80, NF							
Hydroxypropyl Cellulose, NF							
Magnesium Stearate, NF							

Hydroxypropyl Methylcellulose	(b) (4)
Polyethylene Glycol (b) (4)	
Titanium Dioxide	
Talc	

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☒ Yes ☐ No ☐ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:

- Test product formulations of 10 mg, 20 mg, 40 mg base are proportionally similar to the 80 mg of the test product.

4.3 Dissolution Testing

4.3.1 Dissolution Data

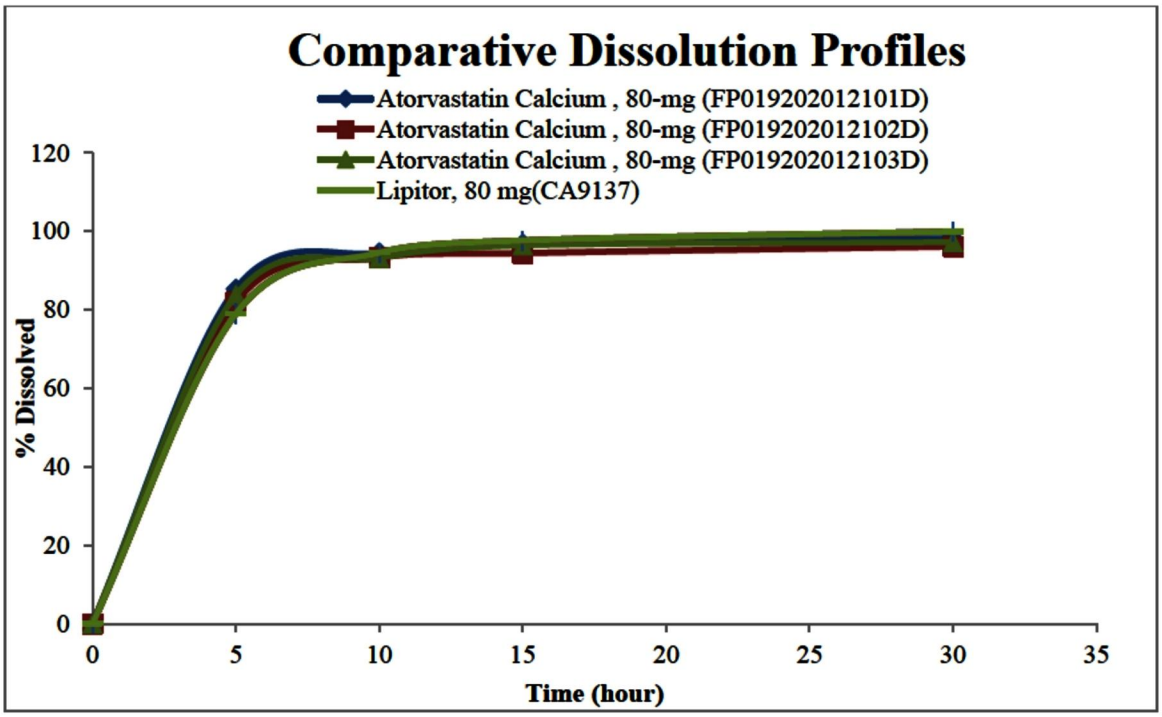
Dissolution Conditions					**Apparatus:**	[redacted] (b) (4)				
					Speed of Rotation:					
					Medium:					
					Volume:					
					Temperature:					
Firm's Proposed Specifications			10mg, 20mg, 40mg, 80mg							
Dissolution Testing Site (Name, Address)			Lepu Pharmaceutical Technology Co., Ltd. No.27 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province, China							
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times(min)**				**Study Report Location**
						5	10	15	30	
Study Report #: RD-PDR-LP006P-001B	04/16/2020	Lipitor/CA9137 (02/28/2022)	80mg Tablet	12	Mean	79.0%	94.5%	97.6%	99.9%	Section 2.7
					Range	[redacted] (b) (4)				
					%CV	10.3	1.5	1.4	1.6	
	01/22/2021	Atorvastatin Calcium Tablets/FP019202012101D (12/25/2020)	80mg Tablet	12	Mean	85.3%	94.5%	96.8%	98.2%	
					Range	[redacted] (b) (4)				
					%CV	2.8	2.3	1.5	1.1	
	01/22/2021	Atorvastatin Calcium Tablets/FP019202012102D (12/26/2020)	80mg Tablet	12	Mean	81.9%	93.2%	94.4%	96.1%	
					Range	[redacted] (b) (4)				
					%CV	2.9	1.7	1.2	0.9	

	01/22/2021	Atorvastatin Calcium Tablets/FP019202012103D (12/29/2020)	80mg Tablet	12	Mean	83.7%	93.2%	96.4%	97.2%
					Range	(b) (4)			
					%CV	3.3	1.0	1.0	0.9
	06/01/2020	Lipitor/AM9624 (07/31/2021)	40mg Tablet	12	Mean	85.7%	93.6%	94.9%	96.4%
					Range	(b) (4)			
					%CV	4.7	2.3	2.9	1.7
	04/19/2021	Atorvastatin Calcium Tablets/FP018202103201D (03/17/2021)	40mg Tablet	12	Mean	90.6%	97.1%	98.2%	98.6%
					Range	(b) (4)			
					%CV	2.7	1.7	1.3	1.0
	04/20/2021	Atorvastatin Calcium Tablets/FP018202103202D (03/20/2021)	40mg Tablet	12	Mean	90.5%	95.3%	96.4%	97.2%
					Range	(b) (4)			
					%CV	1.6	1.4	1.4	1.3
	04/20/2021	Atorvastatin Calcium Tablets/FP018202103203D (03/23/2021)	40mg Tablet	12	Mean	88.9%	95.0%	97.5%	98.1%
					Range	(b) (4)			
					%CV	3.0	2.7	1.8	1.5
	05/30/2020	Lipitor/AP8066 (12/31/2021)	20mg Tablet	12	Mean	87.5%	96.0%	97.3%	99.1%
					Range	(b) (4)			
					%CV	2.3	1.5	1.1	0.8
	04/18/2021	Atorvastatin Calcium Tablets/FP017202103301D (03/17/2021)	20mg Tablet	12	Mean	88.4%	93.2%	95.1%	95.7%
					Range	(b) (4)			
					%CV	2.4	2.2	1.6	1.3
	04/18/2021	Atorvastatin Calcium Tablets/FP017202103302D (03/20/2021)	20mg Tablet	12	Mean	89.4%	94.4%	96.6%	97.2%
					Range	(b) (4)			
					%CV	2.6	2.3	1.8	1.6
	04/19/2021	Atorvastatin Calcium Tablets/FP017202103303D (03/23/2021)	20mg Tablet	12	Mean	90.9%	96.2%	98.2%	98.9%
					Range	(b) (4)			
					%CV	1.8	2.0	1.8	1.7

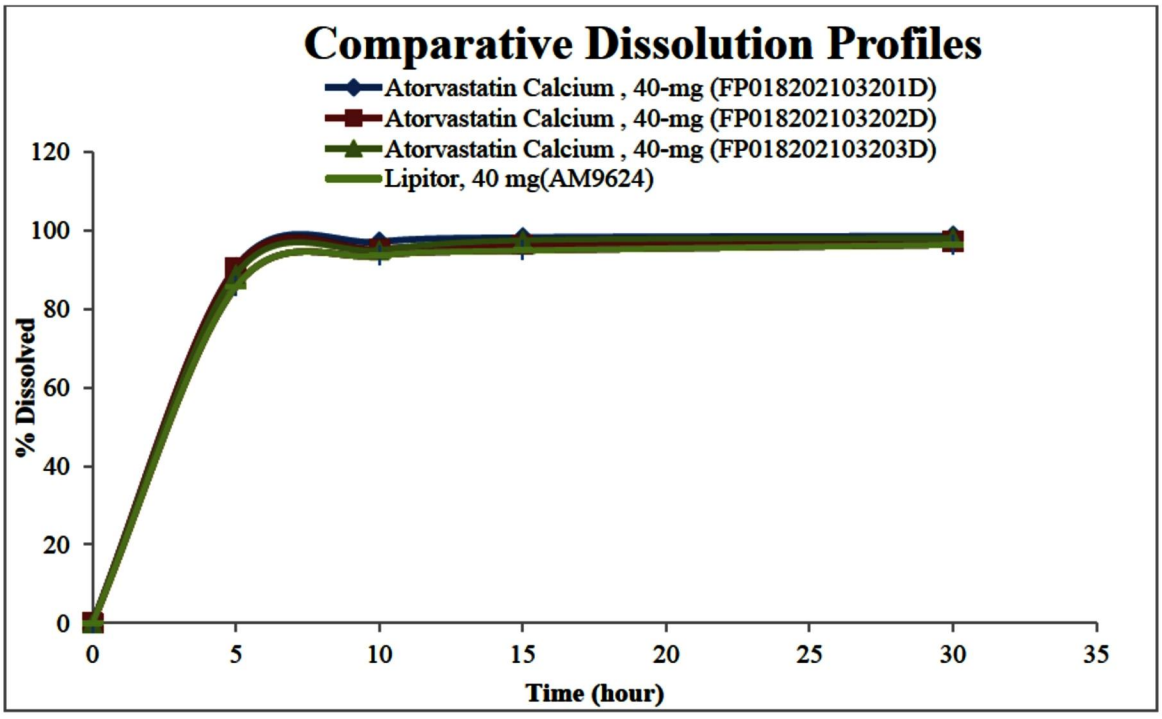
	05/29/2020	Lipitor/AP8067 (06/30/2021)	10mg Tablet	12	Mean	92.1%	97.1%	98.5%	99.3%
					Range	[redacted]			
					%CV	2.4	1.5	1.1	1.1
	04/15/2021	Atorvastatin Calcium Tablets/FP016202103401D (03/17/2021)	10mg Tablet	12	Mean	91.3%	95.3%	96.7%	97.0%
					Range	[redacted]			
					%CV	2.8	1.9	1.9	1.9
	04/16/2021	Atorvastatin Calcium Tablets/FP016202103402D (03/20/2021)	10mg Tablet	12	Mean	90.6%	96.2%	96.9%	97.3%
					Range	[redacted]			
					%CV	1.8	1.7	1.5	1.8
	04/16/2021	Atorvastatin Calcium Tablets/FP016202103403D (03/23/2021)	10mg Tablet	12	Mean	91.8%	95.6%	96.3%	97.0%
					Range	[redacted]			
					%CV	2.1	1.5	1.3	1.3

4.3.2 Dissolution Profiles

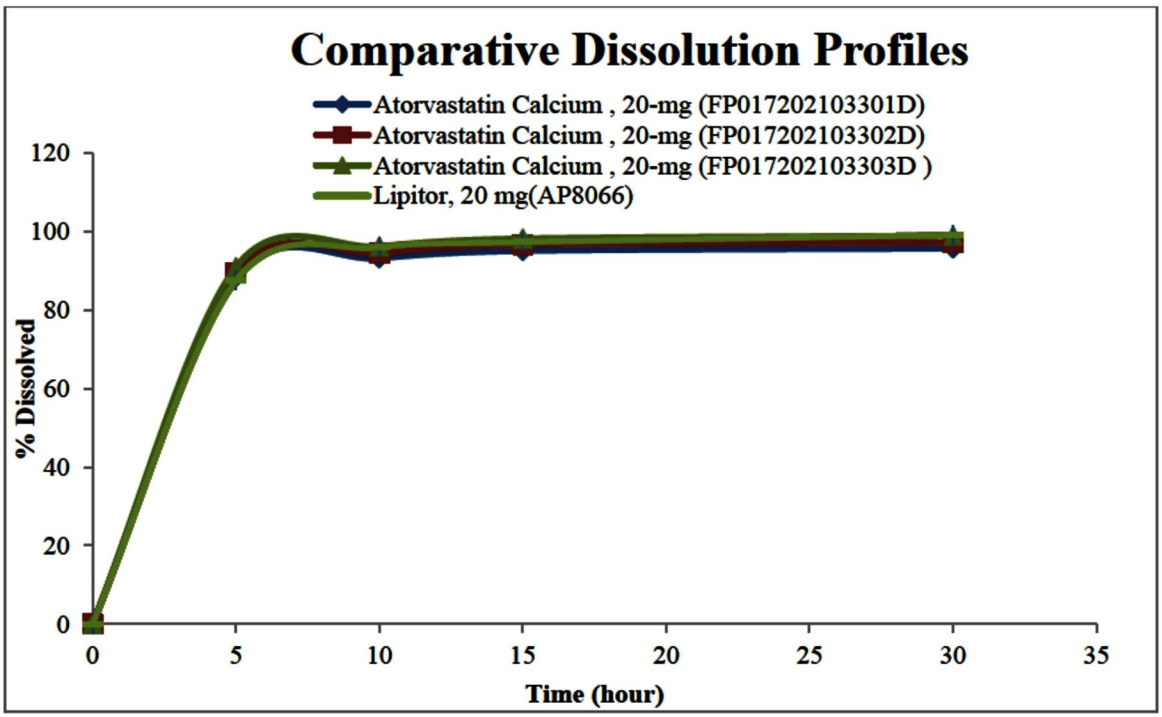
Atorvastatin Calcium Tablets 80 mg:



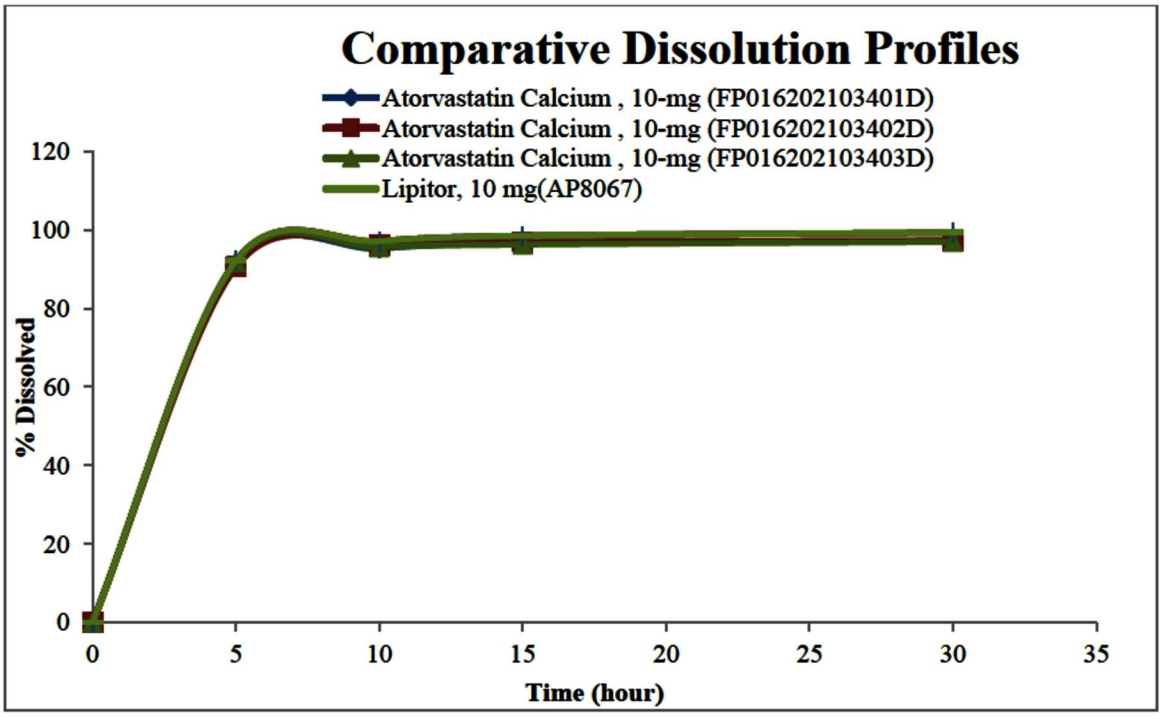
Atorvastatin Calcium Tablets 40 mg:



Atorvastatin Calcium Tablets 20 mg:



Atorvastatin Calcium Tablets 10 mg:



4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	The f2 values are not calculated because the test product showed rapidly dissolving profiles (greater than 90% drug release is observed in 10 minutes for atorvastatin) for test product.

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	CFR 320.22(d)(2)

Overall Comments: Adequate

The applicant conducted the dissolution testing using FDA recommended dissolution method[13] (shown below).

USP apparatus	USP apparatus II (Paddles)
Volume	900 mL
Medium	0.05 M Phosphate buffer pH 6.8
Rotation Speed	(b) (4)
Temperature	37°C ± 0.05°C
Sampling times (hours)	5, 10, 15 and 30 mins
Applicant's proposed Specifications	Not less than (b) (4) % (Q) of the labelled amount of Atorvastatin

- The dissolution testing in QC release media is reviewed separately by the Office of Pharmaceutical Quality (OPQ) and is currently pending applicant's response to drug product review deficiencies[14]. The applicant was asked to revise the acceptance criteria of dissolution for release and stability specifications for all strengths by including the time limit for dissolution.

- Based on the dissolution data, the test product of 80 mg strength showed comparable drug release to the lower strengths (10 mg, 20 mg and 40 mg) of test product and to the respective strength of the reference product. From a bioequivalence standpoint, the dissolution data is adequate in supporting the waiver request for the lower strengths.

Overall, from a BE perspective the dissolution testing data is adequate with respect to supporting waiver requests for the lower immediate release strength(s) of the test product.

[13] FDA Dissolution Methods database. Search Atorvastatin Calcium. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm
[14] GDRP. ANDA 216848. https://panorama.fda.gov/task/view?ID=61d4a198008c65b90f7b14518c04719e

4.4 Attachments

4.4.1 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	Atorvastatin2-fasting include 46.xlsx O-hydroxy fastingEXCLUDE.xlsx P-hydroxy fasting exclude.xlsx	Highly Variable Reference Scaled 3-F	216848-ANALYSIS.doc O 216848-ANALYSIS.do 216848-ANALYSIS.doc	Highly Variable Reference Scaled 3-I Highly Variable Reference Scaled 3-I Highly Variable Reference Scaled 3-I
Fed	Fed ALL EXCLUDE.xlsx O-hydroxy fed 1.xlsx P-hydroxyfed.xlsx	Fed Highly Variable Reference Scaled 3-I	216848-ANALYSIS.doc o-hydroxy 216848-ANALYSIS.do P-hydroxy 216848-ANALYSIS.do	Fed Highly Variable Reference Scaled 3-I Fed Highly Variable Reference Scaled 3-I Fed Highly Variable Reference Scaled 3-I

BIOEQUIVALENCE C

ANDA: 216848

APPLICANT: Lepu

DRUG PRODUCT:

The Division of Bioequ
at this time.

The bioequivalence co
issuance. However, the

5 OUTCOME

Completed Assignment for 216848 ID: 48307

Reviewer: Smith, Taylor **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Atorvastatin Calcium Tablets USP, EQ 10 mg, EQ 20 mg, EQ 40 mg and EQ 80 mg

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*S re*	*Sub ta l*		
48307	01/04/2022	BIO	ANDA Original [1]	1	1	Edit	Delete
48307	01/04/2022	Parallel	Fasting Study [1]	1	1	Edit	Delete
48307	01/04/2022	Parallel	Fed Study [1]	1	1	Edit	Delete
48307	01/04/2022	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.5]	0.5	0.5	Edit	Delete
4830	01/04/2022	Parallel	Pre-Screening [0.25]	0 5	0.2	Edit	Delete
				Total	4		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208336

OTHER REVIEW(s)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date: July 25, 2023

Reviewer: Heather Le, Pharm.D., BCPS, Safety Evaluator
Division of Pharmacovigilance I (DPV-I)

Team Leader: Daniel Woronow, MD, FACC
Medical Officer, DPV-I

Division Directors: Jamie Ridley Klucken, PharmD, MBA, BCPS, BCACP
Acting Associate Director, DPV-I

Product Names, Application Type/Number, Applicant:

Drug Name	Active Ingredient(s)	NDA	Applicant
Lipitor	Atorvastatin calcium	020702	Upjohn
Liptruzet	Atorvastatin calcium, Ezetimibe	200153*	Organon
Caduet	Amlodipine besylate, Atorvastatin calcium	021540	Pharmacia
Baycol	Cerivastatin sodium	020740*	Bayer Pharms
Lescol	Fluvastatin sodium	020261*	Novartis
Lescol XL	Fluvastatin sodium	021192	Novartis
Altoprev	Lovastatin	021316	Covis Pharma BV
Mevacor	Lovastatin	019643*	Merck
Livalo	Pitavastatin calcium	022363	Kowa Co
Nikita	Pitavastatin sodium	209875*	Lupin Ltd
Zypitamag	Pitavastatin magnesium	208379	Medicure
Pravachol	Pravastatin sodium	019898*	Bristol Myers Squibb
Pravigard PAC (copackaged)	Aspirin, Pravastatin sodium	021387*	Bristol Myers Squibb
Crestor	Rosuvastatin calcium	021366	IPR
Ezallor Sprinkle	Rosuvastatin calcium	208647	Sun Pharma Global
Rosuvastatin zinc	Rosuvastatin zinc	202172	Watson Labs Inc (Tentative approval)
Roszet	Ezetimibe, Rosuvastatin calcium	213072*	Althera Pharms
Zocor	Simvastatin	019766	Organon
Flolipid	Simvastatin	206679	TCG Fluent Pharma

(b) (4)			
Vytorin	Ezetimibe, Simvastatin	021687	Organon
Juvisync	Simvastatin, Sitagliptin	202343*	Merck Sharp Dohme
* Discontinued			

Subject: Myasthenia Gravis and Ocular Myasthenia

TTT Record ID: (b) (4)

SS ID #:

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of myasthenia gravis and ocular myasthenia associated with β-hydroxy β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (commonly called statins) reported in case reports from the FDA Adverse Event Reporting System (FAERS) and medical literature. Information and recommendations in this review will aid DDLO in their evaluation of the current labeling for statins and determination of whether any regulatory action is warranted.

DDLO requested this review to determine if class labeling changes are needed (b) (4)

DPV-I identified 23 cases from FAERS (n=22) and from the published medical literature (n=1) of myasthenia gravis and ocular myasthenia associated with statin use. These cases provide information to support a causal association of newly diagnosed myasthenia gravis or ocular myasthenia following the initiation of statin therapy, including a temporal relationship, positive dechallenge (n=16), and positive rechallenge (n=4). We also identified cases that described recurrence of myasthenia gravis or ocular myasthenia with different statins. The identification of cases across the statin class, recurrence of myasthenia gravis or ocular myasthenia with different statins, with biologic plausibility, supports a class effect.

In conclusion, we find an association between statin use and myasthenia gravis, including ocular myasthenia.

Based on this review DPV-I recommends the following:

- Update ADVERSE REACTIONS *Postmarketing Experience* to reflect the potential risk of myasthenia gravis, including ocular myasthenia, with all single-ingredient statins and multi-ingredient products containing statins.

1 INTRODUCTION

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of myasthenia gravis and ocular myasthenia associated with β-hydroxy β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (commonly called statins) reported in case reports from the FDA Adverse Event Reporting System (FAERS) and medical literature. Information and recommendations in this review will aid DDLO in their evaluation of the current labeling for statins and determination of whether any regulatory action is warranted.

1.1 BACKGROUND

Myasthenia Gravis and Ocular Myasthenia

Myasthenia gravis is the most common neuromuscular transmission disorder. It is an autoimmune neuromuscular disorder characterized by fluctuating motor weakness involving ocular, bulbar, limb, and/or respiratory muscles. The weakness is due to an antibody-mediated, immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors or receptor-associated proteins). Although myasthenia gravis is the most common neuromuscular transmission disorder, it is a relatively uncommon disorder with an annual incidence of approximately 7 to 23 new cases per million. The prevalence is approximately 70 to 320 per million. The prevalence of the disease has been increasing since the mid-20th century, likely due to better recognition of the condition, aging of the population, and the longer life span of affected patients.[1]

Myasthenia gravis is characterized by skeletal muscle weakness that fluctuates over the course of a day. Muscle weakness may occur with any muscle but most frequently affects ocular and other bulbar muscle function more than other muscle groups. Ocular symptoms may include ptosis due to weakness of levator palpebrae muscles and diplopia due to weakness of extraocular muscles. Symptoms are frequently asymmetric and pupillary function is expected to be normal (assuming no concomitant neuro-ophthalmological diseases).[1]

When the clinical manifestations of myasthenia gravis are isolated to the levator palpebrae superioris, orbicularis oculi, and extraocular muscles affecting eye movement, it is referred to as ocular myasthenia. Over one-half of patients with myasthenia gravis initially present with isolated ptosis, diplopia, or both, and no signs or symptoms of weakness elsewhere. The disease stays localized to the extraocular muscles in 15 percent of cases.[2]

Specific examination techniques may be used to help diagnose myasthenia gravis or ocular myasthenia and localize motor weakness to the neuromuscular junction. One example is the ice pack test, which can be used as part of the neurologic examination for patients with ptosis. In patients with myasthenia gravis, ptosis can be overcome temporarily by direct cooling of the eyelid muscles. Although sensitivity appears to be approximately 80% in those with prominent ptosis due to myasthenia gravis, the test lacks specificity and is therefore not a confirmatory test. For most patients with clinical features of myasthenia gravis, the diagnosis may be confirmed by the presence of autoantibodies against acetylcholine receptor (AChR) or against other muscle receptor proteins (e.g., muscle-specific tyrosine kinase (MuSK), or low-density lipoprotein

receptor-related protein (LRP4)). For symptomatic patients who do not have autoantibodies (seronegative), electrodiagnostic testing that shows evidence of impaired signal transmission at the neuromuscular junction is used to confirm the diagnosis of myasthenia gravis.[3]

Initial therapy for most patients with mild to moderate myasthenia gravis is an oral acetylcholinesterase inhibitor, usually pyridostigmine. If symptoms do not resolve, immunotherapy (initially with glucocorticoids then nonsteroidal immunotherapies such as azathioprine or mycophenolate for maintenance) is indicated. For acute exacerbations and myasthenic crisis, therapeutic plasma exchange (plasmapheresis) and intravenous immune globulin (IVIG) are considered rapid therapies but benefits are only short term (weeks).

Certain drugs, such as aminoglycosides and neuromuscular blocking agents, have established pharmacologic adverse effects on neuromuscular transmission. Many other drugs have been associated with myasthenic exacerbation in case reports: fluoroquinolones, telithromycin, intravenous local anesthetics (e.g., lidocaine and procaine), magnesium sulfate, penicillamine, immune checkpoint inhibitors (e.g., nivolumab and pembrolizumab), beta blockers, procainamide, and statins.[4]

Summary of Events Leading to this Review

Through the periodic safety update report (PSUR) for NDA 022363 Livalo (pitavastatin)[5], dated August 31, 2022, DDLO learned that the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) sent the statin marketing authorization holders a signal assessment report for statins and myasthenia gravis and ocular myasthenia. The report noted positive disproportionality (VigiBase, EudraVigilance) between statins and myasthenia gravis and ocular myasthenia, included 21 cases reported in the literature, and provided some pathophysiological hypotheses supporting a class effect. (b) (4)

DDLO consulted DPV on January 11, 2023, to review FAERS and the medical literature for cases of myasthenia gravis and ocular myasthenia with statins and to provide an assessment of the cases and any causal relationship.

(b) (4)

1.2 REGULATORY HISTORY

There are seven single-ingredient statins approved by the FDA and currently marketed for the treatment of hyperlipidemia and the prevention of cardiovascular disease. The first statin product, Mevacor (lovastatin), was approved on August 31, 1987, but has been discontinued from marketing.[7]

Liptruzet (atorvastatin, ezetimibe), Lescol (fluvastatin), Nikita (pitavastatin), Pravachol (pravastatin), Pravigard PAC (aspirin, pravastatin), (b) (4) and Juvisync (simvastatin, sitagliptin) have also been withdrawn from the market. None of these products were withdrawn for safety or effectiveness issues and are currently marketed under multiple ANDAs.[8,9,10,11,12,13,14,15]

Roszet (ezetimibe, rosuvastatin) was withdrawn from the market after misbranding issues.[16]

Baycol (cerivastatin) was withdrawn from the market because of 52 deaths attributed to drug-related rhabdomyolysis that led to kidney failure.[17]

Table 1 lists all the FDA-approved statins, including single-ingredient products and fixed dose combinations in the U.S.

Table 1. FDA-Approved Statins

Drug Name	Active Ingredient(s)	NDA	Applicant	Approval Date
Lipitor	Atorvastatin calcium	020702	Upjohn	12/17/1996
Liptruzet	Atorvastatin calcium, Ezetimibe	200153*	Organon	5/3/2013
Caduet	Amlodipine besylate, Atorvastatin calcium	021540	Pharmacia	1/30/2004

Baycol	Cerivastatin sodium	020740*	Bayer Pharms	6/26/1997
Lescol	Fluvastatin sodium	020261*	Novartis	12/31/1993
Lescol XL	Fluvastatin sodium	021192	Novartis	10/6/2000
Altoprev	Lovastatin	021316	Covis Pharma BV	6/26/2002
Mevacor	Lovastatin	019643*	Merck	8/31/1987
Livalo	Pitavastatin calcium	022363	Kowa Co	8/3/2009
Nikita	Pitavastatin sodium	209875*	Lupin Ltd	8/4/2017
Zypitamag	Pitavastatin magnesium	208379	Medicure	7/14/2017
Pravachol	Pravastatin sodium	019898*	Bristol Myers Squibb	10/31/1991
Pravigard PAC (copackaged)	Aspirin, Pravastatin sodium	021387*	Bristol Myers Squibb	6/24/2003
Crestor	Rosuvastatin calcium	021366	IPR	8/12/2003
Ezallor Sprinkle	Rosuvastatin calcium	208647	Sun Pharma Global	12/18/2018
Rosuvastatin zinc	Rosuvastatin zinc	202172	Watson Labs Inc (Tentative approval)	2/12/2016
Roszet	Ezetimibe, Rosuvastatin calcium	213072*	Althera Pharms	3/23/2021
Zocor	Simvastatin	019766	Organon	12/23/1991
Flolipid	Simvastatin	206679	TCG Fluent Pharma	4/21/2016
[redacted]				(b) (4)
Vytorin	Ezetimibe, Simvastatin	021687	Organon	7/23/2004
Juvisync	Simvastatin, Sitagliptin	202343*	Merck Sharp Dohme	10/7/2011
* Discontinued Source: Drugs@FDA				

1.3 RELEVANT PRODUCT LABELING

FDA-approved labeling for currently marketed single-ingredient statins were reviewed. The labeling for Pravachol (pravastatin) was also reviewed despite withdrawal from the market since it is currently marketed under multiple ANDAs. None of the single-ingredient statin USPIs contain language specifically addressing myasthenia gravis or ocular myasthenia.[18,19,20,21,22,23,24,25,26] The USPIs for Lescol XL (fluvastatin), Pravachol (pravastatin), and Altoprev (lovastatin) mention "*Neurological*: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis)…" in ADVERSE REACTIONS *Postmarketing Experience*.[19,20,22]

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

The following case definition[27] was used to develop the case series for myasthenia gravis and ocular myasthenia. A tiered case definition for inclusion was used based on the level of diagnostic certainty.

Tier I:

1. Clinical diagnosis of myasthenia gravis or ocular myasthenia by a healthcare provider (i.e., neurologist or ophthalmologist; patient reports of a diagnosis by a healthcare provider are accepted)[a]
   OR
2. One of the following, in association with fatigable muscle weakness (including isolated ptosis and/or diplopia):
   a. Autoantibodies against AChR, MuSK, or LRP4
   b. Electrodiagnostic testing that shows evidence of impaired signal transmission at the neuromuscular junction
      i. Nerve conduction studies with repetitive nerve stimulation
      ii. Electromyography (EMG)
   c. Positive ice pack test

Tier II:

1. Diagnosis or documentation consistent with myasthenia gravis or ocular myasthenia. Cases in this category have not been confirmed by a healthcare provider and may not provide serologic or electrodiagnostic testing

2.2 Causality Criteria

Causality was assessed using the World Health Organization-Uppsala Monitoring Center (WHO-UMC) system for standardized case causality assessment (Table 2).[28] A conservative approach to assessing causality was used in this review.

Table 2. Causality Categories and Criteria Adapted from the WHO-UMC System

Category	Criteria
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that make a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations (e.g., past medical history of myasthenia gravis or ocular myasthenia)
Unassessable	• Cases cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

[a] Experienced clinicians may be able to diagnose myasthenia gravis based on symptoms and testing to exclude alternative diagnoses in certain situations as some patients are seronegative, however, positive autoantibody tests, positive electrodiagnostic testing, and clinical descriptions of symptoms consistent with myasthenia gravis further increase the diagnostic certainty of myasthenia gravis or ocular myasthenia in these cases.

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of search	January 20, 2023†
Time period of search	Through January 19, 2023
Search type	*RxLogix PV Reports Quick Query*
Product terms	HMG-CoA Reductase Inhibitor [EPC] (Therapeutic Drug Class)
MedDRA search terms (Version 25.1)	Myasthenia gravis (PT), Ocular myasthenia (PT)
* See Appendix A for a description of the FAERS database. †Another FAERS search was run from January 20, 2023 through June 28, 2023 and retrieved 19 cases. After deduplication, there were three unique cases. Two were duplicates from the previous FAERS search and the one remaining case did not contain enough information to assess. Abbreviations: EPC=established product class, HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

2.4 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in Table 4 and Table 5.

Table 4. Literature Search Strategy	
Date of search	February 27, 2023
Database	PubMed@FDA

Table 4. Literature Search Strategy	
Search terms	("atorvastatin"[MeSH Terms] OR "atorvastatin"[All Fields] OR "atorvastatine"[All Fields] OR "atorvastatin s"[All Fields] OR ("fluvastatin"[MeSH Terms] OR "fluvastatin"[All Fields]) OR ("lovastatin"[MeSH Terms] OR "lovastatin"[All Fields] OR "lovastatine"[All Fields] OR "lovastatin s"[All Fields]) OR ("pitavastatin"[Supplementary Concept] OR "pitavastatin"[All Fields]) OR ("pravastatin"[MeSH Terms] OR "pravastatin"[All Fields] OR "pravastatin s"[All Fields]) OR ("rosuvastatin calcium"[MeSH Terms] OR ("rosuvastatin"[All Fields] AND "calcium"[All Fields]) OR "rosuvastatin calcium"[All Fields] OR "rosuvastatin"[All Fields]) OR ("simvastatin"[MeSH Terms] OR "simvastatin"[All Fields] OR "simvastatin s"[All Fields] OR "simvastatins"[All Fields]) OR ("hydroxymethylglutaryl coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl coa reductase inhibitors"[All Fields] OR "statin"[All Fields] OR "statins"[All Fields] OR "statin s"[All Fields] OR "statine"[Supplementary Concept] OR "statine"[All Fields] OR "statines"[All Fields])) AND ("myasthenia gravis"[MeSH Terms] OR ("myasthenia"[All Fields] AND "gravis"[All Fields]) OR "myasthenia gravis"[All Fields] OR ("myasthenia gravis"[MeSH Terms] OR ("myasthenia"[All Fields] AND "gravis"[All Fields]) OR "myasthenia gravis"[All Fields] OR ("ocular"[All Fields] AND "myasthenia"[All Fields]) OR "ocular myasthenia"[All Fields]) OR ("myasthenia"[All Fields] OR "myasthenias"[All Fields]))
Years included in search	All

Table 5. Literature Search Strategy	
Date of search	February 27, 2023
Database	Embase
Search terms	('atorvastatin'/exp OR atorvastatin OR 'fluvastatin'/exp OR fluvastatin OR 'lovastatin'/exp OR lovastatin OR 'pitavastatin'/exp OR pitavastatin OR 'pravastatin'/exp OR pravastatin OR 'rosuvastatin'/exp OR rosuvastatin OR 'simvastatin'/exp OR simvastatin OR 'statin'/exp OR statin) AND ('myasthenia gravis'/exp OR 'myasthenia gravis' OR (('myasthenia'/exp OR myasthenia) AND gravis) OR 'ocular myasthenia'/exp OR 'ocular myasthenia' OR (ocular AND ('myasthenia'/exp OR myasthenia)) OR 'myasthenia'/exp OR myasthenia)
Years included in search	All

2.5 PERIODIC SAFETY REPORTS

DPV screened the following recent periodic safety reports for currently marketed single-ingredient statins for Applicants' assessment of myasthenia gravis or ocular myasthenia with statin use:

- Lipitor (atorvastatin calcium) (NDA 020702) Periodic Adverse Experience Report (PAER). Reporting period: November 1, 2021, to October 31, 2022.[29]
- Lescol/Lescol XL (fluvastatin) (NDA 021192) PSUR. Reporting Period: September 1, 2017, to August 31, 2022.[30]
- Altoprev (lovastatin) (NDA 021316) Extended-Release Tablets PAER. Reporting period: June 26, 2021, to June 25, 2022.[31]
- [redacted] (b) (4) (NDA 022363) Periodic Benefit-Risk Evaluation Report (PBRER)/ PSUR. Reporting Period: July 17, 2019, to July 16, 2022.[5]
- Zypitamag (pitavastatin) (NDA 208379) Periodic Adverse Drug Experience Report (PADER). Reporting period: July 14, 2021, to July 13, 2022.[32]
- Crestor (rosuvastatin calcium) (NDA 021366) PBRER. Reporting Period: November 7, 2021, to November 6, 2022.[33]
- Ezallor Sprinkle (rosuvastatin) (NDA 208647) Capsules PADER. Reporting period: December 18, 2021, to December 17, 2022.[34]
- Flolipid (simvastatin oral suspension) (NDA 206679) Annual Report. Reporting Period: April 21, 2020, to April 20, 2021.[35,b]
- Zocor (simvastatin) (NDA 019766) PADER. Reporting Period: December 24, 2021, to December 23, 2022.[36]

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 302 reports. After applying the case definition in Section 2.1, the causality criteria in Section 2.2, and accounting for duplicate reports, 22 FAERS cases were included in the case series of myasthenia gravis or ocular myasthenia reported with statin use. One additional case was identified from the published medical literature for inclusion in the case series, for a total of 23 cases in the case series (see Figure 1).

[b] Annual report for the reporting period April 21, 2021, to April 20, 2022, has not been received by FDA. Correspondence requesting overdue Annual Report was sent to the Applicant on January 10, 2023.

Figure 1. Case Selection

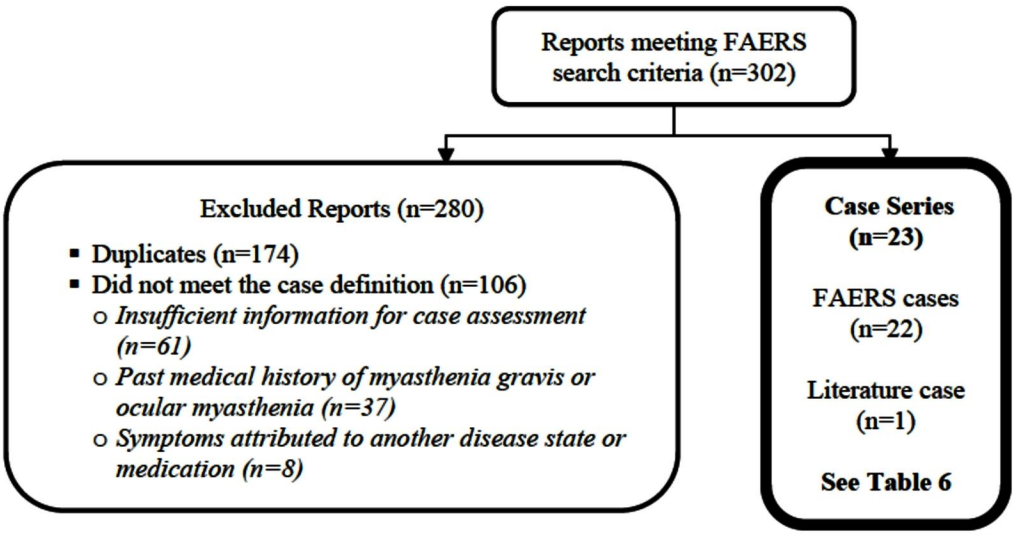


Table 6 summarizes the 23 cases from FAERS (n=22) and the medical literature (n=1) of myasthenia gravis or ocular myasthenia reported with statin use for this case series.

Appendix B contains a line listing of the 22 FAERS cases in this case series.

Table 6. Descriptive Characteristics of Myasthenia Gravis or Ocular Myasthenia With Statins in This FAERS and Medical Literature Case Series, Received by FDA or Published Through January 19, 2023 (n=23)

Case source*	
FAERS	22
Literature	1†
Initial FDA received date or publication date	
≤ 1999	1
2000 – 2005	2
2006 – 2010	9
2011 – 2015	4
2016 – 2020	7
Age (years) (n=22)	
Mean	62.3
Median	64.5
Range	43 – 83
FAERS Serious Outcome‡ (n=21)	
Hospitalization	8
Life-threatening	1
Disability	5
Other serious	16

Sex	
Male	13
Female	10
Country	
U.S.	12
Foreign	11
FAERS Case Type (n=22)	
Expedited	21
Direct	1
Statin[§, ‖]	
Atorvastatin	14
Rosuvastatin	5
Simvastatin	5
Fluvastatin	2
Pravastatin	2
Lovastatin	1
Time to onset	
<1 month	8
1-6 months	9
≥ 6 months – <1 year	0
1-2 years	4
3+ years	1
Not reported	1
Autoantibodies (AChR, MuSK, LRP4)	
Positive	11
Negative	6
Not reported	6
Electrodiagnostic findings (EMG or RNS)	
Positive	7
Not reported	16
Icepack test	
Positive	2
Not reported	21
Diagnosis	
By a neurologist or ophthalmologist	9
Not reported/specified	14
Manifestations[¶]	
Ptosis	17
Diplopia/extraocular motor defect	13
Respiratory dysfunction	1
Muscle involvement other than above	17
Action taken with statin	
Discontinued	23
Treatment[**]	
No treatment/only statin discontinuation	10

Required treatment for a limited time††	5
Required continued treatment	8
Outcome	
Symptom resolution	13
Partial symptom resolution	3
No symptom resolution	6
Not reported	1
Rechallenge	
Positive‡‡	4
Not reported	19
Concomitant drugs associated with myasthenia gravis	
Yes§§	3
No	8
Not reported	12
Case Definition Tier	
I	20
II	3
Causality	
Probable	3
Possible	20

* FAERS - Includes any case identified in either FAERS alone or in both FAERS and the literature
Literature - Includes cases only identified in the literature

† Purvin V, Kawasaki A, Smith KH, Kesler A. Statin-associated myasthenia gravis. Medicine. 2006; 85: 82-5. This literature article described four patient cases. Two cases were identified in FAERS and included in the case series (FAERS case #6049864 and 15660805), one was deemed unlikely because the patient had a past medical history of myasthenia gravis, and the last case was included in the case series as a literature-only case.

‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

§ A case may report more than one statin. (n=4) (statins were tried sequentially)

‖ The case series did not include any cases of myasthenia gravis or ocular myasthenia associated with pitavastatin use. In 2021, pitavastatin only accounted for 0.3% of total statin prescriptions dispensed from U.S. outpatient retail pharmacies.[37]

¶ A case may report more than one manifestation.

** Types of treatment included cholinesterase inhibitors, immunosuppressants, corticosteroids, and intravenous immune globulin.

†† Treatment for a limited time is defined as any myasthenia gravis treatment that is not noted to be ongoing.

‡‡ A positive rechallenge refers to the adverse event recurring after restarting with the same statin or switching to a different statin. A case is only counted once regardless of how many instances of rechallenge occurred with the same patient.

§§ metoprolol (n=2), bisoprolol (n=1)

Abbreviations: AChR=Acetylcholine receptor, MuSK=Muscle-specific kinase, LRP4=Low density lipoprotein receptor-related protein 4, EMG=Electromyography, RNS=Repetitive nerve stimulation

Reviewer's comments: There were 20 cases (19 FAERS cases and 1 from the medical literature) assessed by DPV-I as fulfilling WHO-UMC criteria for a possible causal association between statins and myasthenia gravis or ocular myasthenia. Nine of these cases[c] were especially noteworthy for a time to onset within three months following statin initiation, no other possible

[c] FAERS Case #s: 12517096, 15429473, 6206794, 12791606, 10096604, 17886479, 10109733, 6049864, and the medical literature case from Purvin et al.

cause was noted, and clinical improvement occurred with or without myasthenia gravis related treatment, after discontinuation of the statin.

There were 11 FAERS cases that were considered less robust but still contained enough information to be included in the case series. Three[d] of these cases were classified as Tier II and did not have confirmatory diagnostic testing or diagnosis by a neurologist or ophthalmologist but still described patients developing symptoms consistent with myasthenia gravis or ocular myasthenia with onset after statin initiation. In five cases[e], statin therapy was discontinued but symptoms persisted. In FAERS Case #7289226, a neurologist made the diagnosis of myasthenia gravis but confirmatory diagnostic tests were negative; although the patient was switched to different statins, seemingly without a statin free period in between, there was resolution of symptoms two weeks after discontinuation of all statins. In FAERS Case #14616419, time to onset was not reported, but it was stated that myasthenia gravis was diagnosed after initiation of simvastatin with positive AChR antibodies. In the last case, the time to onset was long (8 years) but the patient experienced respiratory distress requiring intubation and MuSK antibody was positive. Despite statin discontinuation and treatment with plasmapheresis, IVIG, pyridostigmine bromide, prednisone, and mycophenolate mofetil, the patient remains symptomatic (FAERS Case #9649419).

We cannot exclude the possibility that statins unmasked or exacerbated preexisting myasthenia gravis[4] in combination with other factors in the six cases mentioned above where discontinuation of statins did not lead to symptom resolution. FAERS Case #18332521, 6818913, and 6206794 discussed below also had features supporting this concept.

The four cases reporting positive rechallenge (probable causality (n=3) and possible causality (n=1)) are discussed below.

3.1.1 Best Representative Cases

Three cases reported positive rechallenges with various statins. They are summarized below:

> **FAERS Case #15660805, 2018, United States, Expedited, Serious Outcome: Other, Manufacturer Control #US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-109216:**
> This is a published case report[38] of a 71-year-old man with a past medical history of hypertension. Two weeks after starting simvastatin, he developed bilateral ptosis and hoarseness. His symptoms improved each morning upon awakening and worsened later in the day. One year later his bilateral ptosis was worse on the left with a positive Cogan lid twitch sign and bilateral orbicularis weakness. Single fiber EMG showed increased jitter, AChR antibodies were negative, and creatine kinase levels were normal. He noted improvement in symptoms within two weeks of stopping simvastatin and reported that he was almost completely asymptomatic within two months. A subsequent rechallenge with

[d] FAERS Case #s: 6231174, 6328988, 6051684
[e] Patient were treated (FAERS Case #s: 3790170, 8745325, 6688182) or not treated (FAERS Case #s: 3200687 and 5920762).

pravastatin led to a recurrence of his myasthenic symptoms, although no subsequent dechallenge is reported.

Reviewer's comment: This Tier I case of myasthenia gravis was assessed as probable due to the positive dechallenge and subsequent positive rechallenge with a different statin, and temporal relationship with statin administration. Tier I is based on abnormal electrodiagnostic testing that included single fiber EMG demonstrating "increased jitter."[39] "Increased jitter" can also be seen in motor neuron disease, polyneuropathies, polymyositis, and facioscapulohumeral dystrophy. Concomitant medications were not mentioned and therefore could not be assessed. Although not stated in the publication, we assume the past medical history included an indication for statin use, in addition to reported hypertension.

FAERS Case #18332521, 2020, Great Britain, Expedited, Serious Outcome: Disability, Manufacturer Control #GB-009507513-0209GBR00001:

This is a published case report[40] of a 67-year-old woman with a past medical history of hyperthyroidism, myocardial infarction, and hypercholesterolemia. She had a past surgical history of thyroidectomy. She was started on atorvastatin and within three months she began to experience ocular and systemic weakness. Atorvastatin was discontinued and after six weeks her muscle weakness resolved. Because her lipid levels were elevated, she was started sequentially on fluvastatin, simvastatin, then "benzafibrate". With each medication, the muscle weakness recurred after 2 to 3 months of treatment. She was finally restarted on atorvastatin because it had "the least side-effects". At presentation to the Ophthalmology Department, she had a 2-year history of progressive bilateral blepharoptosis, intermittent diplopia, and symmetrical proximal muscle weakness, which began within 3 months of starting atorvastatin 2 years prior. On examination she showed a "strikingly fatigable myogenic ptosis and variable incomitant horizontal and vertical strabismus consistent with a diagnosis of ocular myasthenia." She was euthyroid and AChR and striated-muscle antibodies were not detected. Discontinuation of the atorvastatin led to quick clinical improvement and 2 months later she had residual mild aponeurotic ptosis with no fatiguability and slight weakness of the shoulder girdle.

Reviewer's comment: This case was assessed as probable due to the multiple positive dechallenge and positive rechallenge instances with various statin medications, although some residual mild ptosis and shoulder weakness persisted after statin discontinuation. There is a temporal relationship of the patient's symptoms to statin administration. This is a Tier I case as the patient was diagnosed with ocular myasthenia by an ophthalmologist. Despite the strength of the causal association demonstrated in this case, we cannot exclude the possibility that the myasthenic findings may have had multiple contributing etiologies, as mild symptoms persisted after statin discontinuation.

FAERS Case #6818913, 2008, Norway, Expedited, Serious Outcome: Hospitalization, Other, Manufacturer Control #NO-PFIZER INC-2008097042:

This is a published case report[41] of a 43-year-old male who presented to the hospital with a myocardial infarction. On examination, he was diagnosed with diabetes mellitus and

hyperlipidemia. He was started on atorvastatin 10mg daily. "He soon experienced a diffuse myalgia which worsened with 20mg atorvastatin daily." He also developed bilateral ptosis. One year later he suffered another myocardial infarction and atorvastatin was increased to 40mg daily. After 2-3 weeks, his ptosis worsened and he noticed double vision. The patient then went to see a neurologist and myasthenia gravis was suspected. Ptosis, but not diplopia, was improved by intravenous edrophonium chloride. AChR antibody was elevated (10.8 nmol/L, normal <0.4nmol/L). Single fiber EMG showed increased jitter and blocking in 24/30 pairs that were studied. Treatment with pyridostigmine, azathioprine, IV immunoglobulin, and plasma exchange provided no benefit. Atorvastatin was then discontinued and within a few days the patient's ptosis was completely resolved. The diplopia remained unchanged. Six months after statin discontinuation, AChR antibody level was normal but was found to be slightly elevated on follow-up. The patient suffered another myocardial infarction one year after atorvastatin was discontinued and was started on pravastatin. His ptosis recurred very quickly and again improved immediately after discontinuation of pravastatin. Pravastatin was tried yet again with the same results and discontinued. The patient was then treated with ezetimibe and he did not experience a recurrence of muscular complaints and his blepharoptosis resolved. His diplopia remained "remarkably stable" and was surgically treated after two years.

Reviewer's comment: This case was assessed as probable due to the multiple positive dechallenge and positive rechallenge instances, and temporal relationship of the patient's symptoms and statin administration. This case fulfills our Tier I criteria, including diagnosis of myasthenia gravis by a neurologist. Despite the strength of the causal association demonstrated in this case, we cannot exclude the possibility that the myasthenic findings may have had multiple contributing etiologies, as diplopia persisted after statin discontinuation.

One FAERS cases reported a positive rechallenge with the same statin, simvastatin. The case is summarized below:

FAERS Case #6206794, 2006, Canada, Expedited, Serious Outcome: Other, Manufacturer Control #2006RR-04710:

This is a published case report of a 54-year-old man with a past medical history of type 2 diabetes, hypertension, hypercholesterolemia, and recent four-vessel coronary artery bypass grafting. He developed proximal myalgias approximately 2 months after starting simvastatin 20mg daily. He reported "painful rolling wave-like muscle contractions that would migrate throughout his upper and lower arms. Similar phenomena was subsequently experienced in his quadriceps. He noted that sudden limb extension or tapping would provoke these abnormal muscle movements and that repetition would mitigate their intensity." Simvastatin was discontinued and his symptoms improved but did not resolve completely. His cardiologist then restarted him on simvastatin 40mg daily to achieve target cholesterol levels for secondary prevention. This caused his myalgias and rolling muscular contractions to return. His symptoms were most severe upon standing up in the morning. The simvastatin was discontinued again and although his

symptoms improved again, he experienced persistent attenuated myalgias and abnormal involuntary muscle movements. Approximately 1 year later he developed mild, bilateral, activity-dependent ptosis and dysarthria with no ophthalmoparesis, diplopia, dysphagia, or limb-girdle weakness. These symptoms lasted approximately 5 months before gradually remitting. Due to ongoing symptoms, he was referred for neuromuscular consultation 3 years after symptom onset. Several tests and labs were done including single-fiber electromyography. Findings were interpreted as evidence of mild instability of neuromuscular transmission consistent with myasthenia gravis. The patient's anti-acetylcholine receptor antibody titer was positive at 2.49 nmol/L (normal, <0.40 nmol/L). Although after 2 years his anti-acetylcholine receptor antibody titer remained elevated (1.66 nmol/L), there have not been any further myasthenic episodes.[42]

Reviewer's comment: This case was assessed as possible due to the positive dechallenge and positive rechallenge. This case also meets our Tier I criteria, although the patient also had symptoms atypical for myasthenia gravis, such as myalgias and abnormal involuntary muscle movement. Additionally, in this case the patient experienced symptom recurrence after statin discontinuation which could suggest that myasthenia gravis may have been present subclinically prior to treatment with simvastatin and was exacerbated by exposure to the drug.[43]Despite the strength of the causal association demonstrated in this case, we cannot exclude the possibility that the myasthenic findings may have had multiple contributing etiologies, as mild symptoms persisted, and recurred, after statin discontinuation.

3.2 LITERATURE CASES

Using the search strategy listed in Table 4 and Table 5, DPV-I retrieved 202 unique citations from the published medical literature. The titles and abstracts of these articles were reviewed to identify articles specific to statin-associated myasthenia gravis or ocular myasthenia. Of the 202 articles, one case report[38] was incorporated into our case series. The remaining 201 were excluded from further review for the following reasons:

Table 7. Literature Articles Excluded (n=201)

Exclusion Reason	PubMed@FDA (n=45)	Embase (n=156)*
Unrelated to the topic of statin-associated myasthenia gravis or ocular myasthenia	18	136
Review article	6	4
General article	4	9
Commentary	4	0
Past medical history of myasthenia gravis or ocular myasthenia	4	4
Already identified in the FAERS search	9	3

* The Embase search retrieved 35 duplicate excluded articles from the PubMed@FDA search. These articles are included in the PubMed@FDA column and not in the Embase column.

3.3 PERIODIC SAFETY REPORTS

The most recent Crestor PBRER[33] assessed the risk of myasthenia gravis and ocular myasthenia in response to PRAC's signal assessment report. A review of the Applicant's global safety database retrieved 164 case reports of rosuvastatin for myasthenia gravis related PTs. In 126 case reports, the Applicant determined that there was insufficient information to assess for causality. In 31 case reports, the Applicant determined causality was confounded by concomitant medications and underlying disease. "The remaining six case reports[f] were identified as note-worthy due to plausible temporal relationship, compatibility with myasthenia gravis (clinically and diagnostically), positive dechallenge, and a lack of potential confounders and/or alternative explanations for the reported myasthenia gravis and related events." [It is unclear why the Applicant's assessment does not add up to 164 total case reports]. The Applicant's search of Eudravigilance database retrieved 106 case reports of myasthenia gravis and related PTs with rosuvastatin. Of these cases, 58 were identified as duplicates and 6 were already captured in the Applicant's global safety database. Of the remaining 42 case reports, the Applicant determined that 32 had insufficient information to assess causality and the remaining 10 cases were confounded by concomitant medications and patients' underlying disease conditions. The Applicant's literature review retrieved 25 articles. Of those, 18 did not identify any new safety information, 2 were excluded from further discussion, and the remaining 5 case reports were included in the 6 note-worthy case reports mentioned above. Based on review of all available information (the Applicant's global safety database, Eudravigilance database, and literature review), the Applicant considered that there is a reasonable possibility of a causal relationship between rosuvastatin and myasthenia gravis including ocular myasthenia. Consequently, it was recommended to include myasthenia gravis and ocular myasthenia in sections 4.4 (Special warnings & special precautions for use) and 4.8 (Undesirable effects) of the Crestor CDS. The CDS was updated after the data lock point on November 10, 2022. Specific verbiage for section 4.4 (Special warnings & special precautions for use) is noted below:

> "Statins may in rare instances induce or aggravate myasthenia gravis or ocular myasthenia (see section 4.8 Undesirable effects) including reports of recurrence when the same or a different statin was administered. Crestor should be used with caution in patients with these conditions and should be discontinued if they are induced or aggravated". [33]

The most recent Lescol XL(fluvastatin) PSUR provided a response to PRAC's request on myasthenia gravis. The Applicant retrieved three cases concerning myasthenia gravis or ocular myasthenia in their search. They concluded that a review of the cases did not identify any noteworthy case. The three cases lacked information about time to onset, medical history, family history and other medications used precluding causality assessment. There were only three cases reported cumulatively and no cases reported over the last decade of use. The Applicant opined

[f] Of the six case reports, five were literature case reports and one was from the Applicant's safety database. The case from their safety database details a patient who has a past medical history of myasthenia gravis that they think was worsened by rosuvastatin. Because of the past medical history of myasthenia gravis, this case would have been excluded from our case series. Of the five literature reports, two were from Purvin et al. and one was from Khalid et al. which were identified in our FAERS and literature searches and included in our case series. The remaining two case reports were from Oh et al. which were also identified in our FAERS and literature searches but excluded from the case series because the patients had a past medical history of myasthenia gravis.

that the evidence with fluvastatin is insufficient to establish a casual association and hence no label change is warranted.[30]

The most recent Livalo (pitavastatin) PBRER/PSUR provided comment on the statin and myasthenia gravis safety signal presented by PRAC. The Applicant states that the WHO VigiBase contains no reports of myasthenia gravis with pitavastatin and a search of their safety database retrieved no cases. The Applicant noted the background rate for the incidence of myasthenia gravis might suggest that there would be at least 60 cases in patients exposed to pitavastatin, and therefore the signal was considered refuted.[5]

The most recent Lipitor (atorvastatin) and Zocor (simvastatin) PADERs listed eight cases coded with the PT *Myasthenia gravis* (n=6, four cases for atorvastatin and two cases for simvastatin) and the PT *Myasthenic syndrome* (n=2, one case for atorvastatin and one case for simvastatin). The Applicant for Lipitor provided comments for three of the five cases and said a possible contributory role of atorvastatin cannot be excluded in two cases and myasthenia gravis was more likely a concurrent disease and unmasked in one case because of short latency. The Applicant for Zocor did not provide a specific analysis of these cases.[g] They both concluded that there were no actions due to safety issues during the reporting period needed.[29,36]

Myasthenia gravis and ocular myasthenia were not assessed by the Applicants in the most recent Altoprev (lovastatin extended-release), Zypitamag (pitavastatin magnesium), or Ezallor Sprinkle (rosuvastatin) PADERs or the Flolipid (simvastatin oral suspension) Annual Report screened by DPV-I. [31,32,34,35]

4 DISCUSSION

DPV-I identified 23 cases from FAERS (n=22) and from the published medical literature (n=1) of myasthenia gravis and ocular myasthenia associated with statin use. DPV-I assessed these cases as probable (n=3) or possible (n=20) causality. Most (n=20) of these cases were classified as Tier 1, with a diagnosis of myasthenia gravis or ocular myasthenia supported by confirmatory autoantibody tests (n=11), electrodiagnostic testing (n=7), and/or diagnosis by a neurologist or ophthalmologist (n=9); the remaining 3 cases were classified as Tier 2 (i.e., diagnosis or documentation consistent with myasthenia gravis or ocular myasthenia but did not include confirmatory tests or diagnosis by an expert clinician). These cases provide information to support a causal association of newly diagnosed myasthenia gravis or ocular myasthenia following the initiation of statin therapy, including a temporal relationship, positive dechallenge (n=16), and positive rechallenge (n=4). We identified cases of interest with all statins, except for pitavastatin. In 2021, pitavastatin only accounted for 0.3% of total statin prescriptions dispensed from U.S. outpatient retail pharmacies. Pitavastatin's market share in the U.S. was fairly consistent from 2017 to 2021.[37] We also identified cases that described recurrence of myasthenia gravis or ocular myasthenia with different statins. There are two pathophysiological hypotheses that have been proposed to explain the role of statins in the occurrence of myasthenia gravis.

[g] All of the six cases coded with the PT *Myasthenia gravis* were identified in FAERS and were not included in the case series. The Applicant for Lipitor included the narrative for the one case with the PT *Myasthenic syndrome* and there was not enough information to assess causality and the syndrome was thought to be attributed to pantoprazole and ramipril. The Applicant for Zocor did not provide any case narratives.

1. Mitochondrial dysfunction induced by statins via depletion of coenzyme Q10 (ubiquinone), leading to dysfunction of the pre- and post-synaptic terminal motor interfaces (with high level of mitochondria) which could alter the transmission in the neuromuscular junction.[44]
2. Antibodies against the neuromuscular junction that could be induced by statins. These drugs are known for their immunomodulatory properties, including their ability to induce the production of cytokines Th2 that play a role in the development of myasthenia gravis.[45]

The identification of cases across the statin class, recurrence of myasthenia gravis or ocular myasthenia with different statins, with biologic plausibility, supports a class effect.

Considerations for Labeling

Decisions about whether to include an adverse event in labeling are typically based on reasonable evidence indicating a causal relationship between occurrence of an adverse event and the use of a drug (§ 201.57(c)(7)), including factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) evidence of a dose-response relationship, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the temporal association between drug administration and the event, (6) existence of dechallenge and rechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.[46,47] The cases in our case series fulfill the above criteria based on the number of cases of positive dechallenge and rechallenge (including those with other statins) and the number of cases with a temporal association.

In consideration of the limited number of cases in the context of millions of statin prescriptions dispensed each year for decades, the team recommends updating the ADVERSE REACTIONS section of the labeling at this time. Additionally, although we presented cases to support adding myasthenia gravis, including ocular myasthenia, to statin labeling, it is difficult to establish confirmed causality due to the nature of the disease. Patients being prescribed statins do not undergo myasthenia gravis related antibody testing prior to drug initiation, therefore we cannot determine whether or not myasthenia gravis was present subclinically prior to statin initiation.

DPV-I and DDLO met on June 2, 2023, to discuss this safety signal. DDLO concluded there is an association between statin use and myasthenia gravis and ocular myasthenia. (b) (4)

[redacted]

Limitations of this Review

We cannot exclude the possibility that statins unmasked or exacerbated preexisting myasthenia gravis[4] in combination with other factors. There is not much data from statin-induced myasthenia gravis specifically, but it is thought that in drug-induced myasthenia gravis, discontinuation of the offending agent usually leads to complete resolution of myasthenia gravis symptoms in 2 to 6

months in the majority of patients. By one year symptoms have completely resolved in about 70% of patients with penicillamine-induced myasthenia gravis. The fact that some patients remain symptomatic long after stopping the offending drug suggests that in some cases, myasthenia gravis may have been present subclinically prior to treatment with the offending drug and exacerbated by exposure to the drug.[43]

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, we find an association between statin use and myasthenia gravis, including ocular mya

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS LINE LISTING OF STATINS AND MYASTHENIA GRAVIS AND OCULAR MYASTHENIA CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	13-DEC-2006	6206794	1	2006RR-04710	Expedited (15-Day)	53	Male	CAN	OT
2	25-MAY-2006	6051684	4	2006UW09657	Expedited (15-Day)	82	Male	CAN	OT,HO
3	11-JUN-2020	17886479	3	NVSC2020FR159721	Expedited (15-Day)	56	Male	FRA	OT
3†	28-JUN-2018	15080280	3	FR-SUN PHARMACEUTICAL INDUSTRIES LTD-2018RR-176810	Expedited (15-Day)	56	Male	FRA	DS
3†	06-JUL-2018	15116593	3	FR-PFIZER INC-2018267702	Expedited (15-Day)	56	Male	FRA	DS
3†	10-JUL-2018	15123822	5	FR-TEVA-2018-FR-923572	Expedited (15-Day)	56	Male	FRA	DS
3†	03-AUG-2018	15237349	5	PHHY2018FR059883	Expedited (15-Day)	56	Male	FRA	DS,OT
3†	06-NOV-2018	15592858	5	FR-MYLANLABS-2018M1082441	Expedited (15-Day)	56	Male	FRA	DS,OT
3†	04-JUN-2020	17860203	1	FR-PFIZER INC-2020216303	Expedited (15-Day)	56	Male	FRA	LT,OT
3†	15-JUN-2020	17894969	1	FR-TEVA-2020-FR-1788770	Expedited (15-Day)	56	Male	FRA	OT
3†	15-JUN-2020	17895686	1	FR-TEVA-2020-FR-1788796	Expedited (15-Day)	56	Male	FRA	OT
3†	17-JUN-2020	17902646	3	FR-AUROBINDO-AUR-APL-2020-029119	Expedited (15-Day)	56	Male	FRA	OT
3†	18-JUN-2020	17911896	2	FR-SUN PHARMACEUTICAL INDUSTRIES LTD-2020RR-250351	Expedited (15-Day)	56	Male	FRA	OT
3†	18-JUN-2020	17911956	1	FR-TEVA-2020-FR-1790723	Expedited (15-Day)	56	Male	FRA	OT
3†	19-JUN-2020	17917192	1	FR-MICRO LABS LIMITED-ML2020-01796	Expedited (15-Day)	56	Male	FRA	OT
3†	23-JUN-2020	17929824	2	FR-ACCORD-186316	Expedited (15-Day)	56	Male	FRA	OT

4	09-MAR-2018	14616419	2	FR-009507513-1803FRA001350	Expedited (15-Day)	83	Male	FRA	OT
5	30-SEP-2020	18332521	1	GB-009507513-0209GBR00001	Expedited (15-Day)	67	Female	GBR	DS
5†	14-SEP-2020	18264168	1	GB-TEVA-2002B-00949	Expedited (15-Day)	67	Female	GBR	OT
5†	05-OCT-2020	18344792	1	GB-MYLANLABS-MK-6001778	Expedited (15-Day)	67	Female	GBR	OT
5†	09-SEP-2002	3835655	3	WAES 0209GBR00001	Expedited (15-Day)	67	Female	GBR	DS
5†	01-OCT-2002	3847628	1	PHBS2002GB11123	Expedited (15-Day)	67	Female	GBR	OT
5†	16-JAN-2003	3891530	1	2003000930	Expedited (15-Day)	67	Female	GBR	OT
5†	31-JAN-2003	3902840	1	PHFR2003GB00477	Expedited (15-Day)	67	Female	GBR	OT
5†	03-JAN-2005	5714768	1	2002056073	Expedited (15-Day)	67	Female	GBR	OT
5†	15-FEB-2012	8406309	2	US-RANBAXY-2012US-52635	Expedited (15-Day)	67	Female	GBR	OT
5†	31-JAN-2014	9859344	3	GB-PFIZER INC-2014024807	Expedited (15-Day)	67	Female	GBR	OT
6	26-SEP-2018	15429473	2	PHHY2018GB108466	Expedited (15-Day)	72	Female	GBR	OT,HO,DS
6†	04-OCT-2018	15465020	2	GB-PFIZER INC-2018394249	Expedited (15-Day)	72	Female	GBR	OT,HO,DS
6†	05-OCT-2018	15466842	2	GB-TEVA-2018-GB-960989	Expedited (15-Day)	72	Female	GBR	OT,HO,DS
6†	09-OCT-2018	15475854	2	GB-SUN PHARMACEUTICAL INDUSTRIES LTD-2018RR-186322	Expedited (15-Day)	72	Female	GBR	OT,HO,DS
6†	05-MAR-2019	16032990	2	GB-ACCORD-110258	Expedited (15-Day)	72	Female	GBR	OT,HO,DS
6†	01-APR-2019	16141230	1	GB-MYLANLABS-2019M1028541	Expedited (15-Day)	72	Female	GBR	OT,HO,DS
7	06-FEB-2007	6231174	2	JP-PFIZER INC-2006154549	Expedited (15-Day)	50	Female	JPN	OT,HO
8	22-FEB-2010	7289226	1	KR-PFIZER INC-2010017934	Expedited (15-Day)	51	Male	KOR	OT,HO

9	21-NOV-2008	6818913	5	NO-PFIZER INC-2008097042	Expedited (15-Day)	43	Male	NOR	OT,HO
9†	17-NOV-2008	6813016	1	NO-RANBAXY-2008RR-19175	Expedited (15-Day)	43	Male	NOR	OT
9†	17-NOV-2008	6822856	1	GXKR2008NO10649	Expedited (15-Day)	43	Male	NOR	OT
9†	03-DEC-2008	6830846	3	NO-BRISTOL-MYERS SQUIBB COMPANY-14422927	Expedited (15-Day)	43	Male	NOR	OT,HO
9†	20-JUL-2009	7069262	1	ADR6672009 (ARROW LOG NO: 2009AG0190)	Expedited (15-Day)	43	Male	NOR	OT
9†	28-JAN-2013	9316630	1	2008AP003127	Expedited (15-Day)	43	Male	NOR	OT
10	22-APR-2014	10096604	1	NZ-MYLANLABS-2014S1008286	Expedited (15-Day)	48	Male	NZL	OT
10†	21-APR-2014	10088071	1	PHHY2014NZ043116	Expedited (15-Day)	48	Male	NZL	OT
10†	30-APR-2014	10142690	2	NZ-RANBAXY-2014RR-80488	Expedited (15-Day)	48	Male	NZL	OT
10†	31-JAN-2014	9859351	1	NZ-PFIZER INC-2014024802	Expedited (15-Day)	48	Male	NZL	OT
10†	22-APR-2014	10101606	1	2014AP002641	Expedited (15-Day)	48	Male	USA	OT
11	23-APR-2014	10109733	1	2014AP002640	Expedited (15-Day)	69	Female	NZL	
11†	21-APR-2014	10088069	1	PHHY2014NZ043640	Expedited (15-Day)	69	Female	NZL	HO
11†	22-APR-2014	10096642	1	NZ-MYLANLABS-2014S1008287	Expedited (15-Day)	69	Female	NZL	OT
11†	30-APR-2014	10142696	2	NZ-RANBAXY-2014RR-80490	Expedited (15-Day)	69	Female	NZL	OT
11†	31-JAN-2014	9859354	1	NZ-PFIZER INC-2014024806	Expedited (15-Day)	69	Female	NZL	OT
11†	19-FEB-2014	9916555	1	IPC201402-000081	Expedited (15-Day)	69	Female	NZL	OT
12	29-SEP-2016	12791606	2	US-AUROBINDO-AUR-APL-2016-11901	Expedited (15-Day)	46	Female	USA	OT
12†	05-OCT-2016	12818353	1	US-MYLANLABS-2016M1042534	Expedited (15-Day)	46	Female	USA	OT

12†	07-SEP-2016	12720834	1	US-ASTRAZENECA-2016SE92705	Expedited (15-Day)	46	Female	USA	OT
12†	22-SEP-2016	12770786	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-124324	Expedited (15-Day)	46	Female	USA	OT
12†	06-OCT-2016	12826906	1	PHHY2016US134242	Expedited (15-Day)	46	Female	USA	OT
12†	19-OCT-2016	12862671	1	US-TEVA-702826USA	Expedited (15-Day)	46	Female	USA	OT
13	28-OCT-2013	9649419	4	US-PFIZER INC-2006071654	Expedited (15-Day)	47	Female	USA	OT,HO
14	30-JUN-2016	12517096	2	US-PFIZER INC-2016321179	Expedited (15-Day)	55	Female	USA	OT
14†	24-JUN-2016	12497353	1	US-MYLANLABS-2016M1026184	Expedited (15-Day)	55	Female	USA	OT
14†	27-JUN-2016	12502215	1	PHHY2016US085395	Expedited (15-Day)	55	Female	USA	OT
14†	30-JUN-2016	12516950	1	US-APOTEX-2016AP009413	Expedited (15-Day)	55	Female	USA	OT
14†	01-JUL-2016	12521024	2	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2016US-117993	Expedited (15-Day)	55	Female	USA	OT
14†	08-JUL-2016	12538833	1	US-DRREDDYS-USA/USA/16/0081201	Expedited (15-Day)	55	Female	USA	OT
14†	09-JUL-2016	12542707	1	US-SCIEGEN PHARMACEUTICALS INC-2016SCILIT00288	Expedited (15-Day)	55	Female	USA	OT
14†	08-SEP-2016	12726452	1	US-PFIZER INC-2016416105	Expedited (15-Day)	55	Female	USA	OT
15	08-SEP-2011	8745325	1	US-FDA-7736829	Direct	63	Female	USA	DS
16	30-APR-2002	3790170	1	001-0981-M0202192	Expedited (15-Day)	66	Male	USA	OT
17	29-JAN-1999	3200687	3	001-0981-990191	Expedited (15-Day)	70	Female	USA	OT
18	22-MAY-2006	6049864	1	2006AC00919	Expedited (15-Day)	70	Male	USA	DS,OT
19	27-NOV-2018	15660805	1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-109216	Expedited (15-Day)	71	Male	USA	OT
19†	31-MAY-2007	6331423	1	2007RR-07670	Expedited (15-Day)	71	Male	USA	OT

19†	15-FEB-2012	8406049	1	US-RANBAXY-2007RR-07670	Expedited (15-Day)	71	Male	USA	OT
20	07-JUN-2007	6328988	2	US-MERCK-0706USA00071	Expedited (15-Day)	76	Female	USA	HO,LT
21	31-OCT-2005	5920762	1	2005134361	Expedited (15-Day)	77	Male	USA	DS
22	01-JUL-2008	6688182	1	US-MERCK-0607USA04119	Expedited (15-Day)		Male	USA	HO

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.

† Duplicate case

Abbreviations: HO=hospitalization, LT= life-threatening, DS= disability, OT=other medically significant, CAN=Canada, FRA=France, GBR=Great Britain, JPN=Japan, KOR=Korea, NOR=Norway, NZL=New Zealand, USA=United States

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HEATHER D LE
07/25/2023 09:42:05 AM

DANIEL I WORONOW
07/25/2023 09:57:54 AM

JAMIE L KLUCKEN
07/25/2023 10:22:55 AM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HEATHER D LE
07/25/2023 03:22:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216848

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 216848

INFORMATION REQUEST

Saxon International Associates
U.S. Agent for Lepu Pharmaceutical Technology Co., Ltd.
10 Debary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Peter Saxon:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 4, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Biopharmaceutics

1. We have reviewed your response dated 8/05/2022. Your proposed rotation [redacted] (b) (4) is not acceptable because [redacted] (b) (4) Therefore, based on the totality of the information provided, we recommend that you implement the following dissolution method and acceptance criterion for your proposed Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 and 80 mg

   Dissolution method: 900 mL of 0.05 M phosphate buffer, pH 6.8 using USP Apparatus 2 (paddle) at 60 rpm

   Acceptance criterion: Q=[redacted] (b) (4) % in 30 minutes

   Note that the dissolution acceptance criterion is set based on the mean value. Therefore, some batches may require Stage 2 and occasionally Stage 3 testing. Update your drug product batch release and stability specifications accordingly. In addition, be advised, that all proposed exhibit batches are expected to meet the revised dissolution specifications in your stability program through your

proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

We request a prompt written response, no later than September 28, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact DeWayne R. Johnson, PharmD, Regulatory Business Process Manager, at dewayne.johnson@fda.hhs.gov or (301) 796 - 2343.

Sincerely,

{See appended electronic signature page}

DeWayne R. Johnson, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ANDA 216848

DISCIPLINE REVIEW LETTER
QUALITY

Saxon International Associates
U.S. Agent for Lepu Pharmaceutical Technology Co., Ltd.
10 DeBary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Peter Saxon:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 4, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

1. (b) (4)

2. (b) (4)

B. Drug Product

3. [redacted] (b) (4)

4. [redacted] (b) (4)

5. [redacted] (b) (4)

6. [redacted] (b) (4)

7. [redacted] (b) (4)

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

12. (b) (4)

C. Manufacturing

a. Process

1. (b) (4)

2. (b) (4)

3. (b) (4)

(b) (4)

4. (b) (4)

5. (b) (4)

b. Facility

(b) (4)

Please see the FDA's "Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/148197/download). Please also see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-

response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

D. Biopharmaceutics

1. We noticed that you have submitted very limited data/information (section 3.2.P.2) to support the suitability of your proposed [redacted] (b) (4) To demonstrate the suitability of your proposed dissolution method for the proposed drug product, submit additional information listed below, including complete dissolution profiles for the proposed drug product, Atorvastatin Calcium Tablets, USP, 10 mg, 20 mg, 40 mg and 80 mg:

1. Provide dissolution data for all strengths of the proposed drug product, [redacted] (b) (4) .

2. [redacted] (b) (4) provide data demonstrating the discriminating ability of the optimized method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations (e.g., ± 10 to 20% change to the specified limit values or ranges for these variables) affecting bioavailability and dissolution. Submit the dissolution profile data and similarity testing results obtained with an appropriate statistical test (e.g., f2 values) comparing the target and variant drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product:

    a. It is noted that various variables like the change in the levels of the Particle Size Distribution and Polymorphism may significantly impact dissolution of your proposed drug product. Demonstrate the discriminating ability of the dissolution method with regards to these formulation variables, as per the above recommendations.
    b. Provide a) the manufacturing date, storage conditions and the age of the batches used in the above studies, b) the number of dosage units used to generate the dissolution data, c) table number and separate table heading for each table, and d) graphic presentation for the mean dissolution data for each table.

3. The adequacy of the proposed dissolution acceptance criterion will be determined after assessing the above requested information and upon acceptability of the proposed dissolution method.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than August 7, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an

appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact DeWayne R. Johnson, PharmD, Regulatory Business Process Manager, at dewayne.johnson@fda.hhs.gov or (301) 796 - 2343.

Sincerely,

{See appended electronic signature page}

DeWayne R. Johnson, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

ANDA 216848

DISCIPLINE REVIEW LETTER

Saxon International Associates
U.S. Agent for Lepu Pharmaceutical Technology Co., Ltd.
10 DeBary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 4, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have concluded the Labeling review of this ANDA and have identified the following initial deficiencies:

Labeling deficiencies based on your submission received January 04, 2022:

1. CONTAINER LABEL
   a. Add the "USP" descriptor to the end of the established name on all container labels (i.e. Atorvastatin Calcium Tablets, USP).

   b. Increase the prominence of the middle digits of the NDC numbers by increasing their size in comparison to the remaining digits or putting them in bold type to help minimize the risk for medication error (e.g., XXXX-**XXXX**-XX). Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

   c. Product strength: Use a method to better distinguish the 40 mg and 80 mg strengths of the drug product (e.g., boxing, contrasting colors, and/or some other means) as currently presented the proposed colors appear similar. Refer to the Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to

Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

d. Include a statement of the place of business per 21 CFR 201.1(i).

e. Bar code: Revise the bar code to a vertical orientation to ensure accurate scanning to minimize medication error. Refer to Guidance for Industry - Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

2. PRESCRIBING INFORMATION
   a. GENERAL
      i. (b) (4) DESCRIPTION, HOW SUPPLIED).
      ii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the Prescribing Information.
      iii. Ensure there is adequate space between text, symbols and numerals throughout the Prescribing Information. For example, in subsection 1.2, revise "≥190 mg/dL" to "≥ 190 mg/dL" and in the subsection 2.2 heading, revise “to17 Years” to “to 17 Years”.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION
      i. (b) (4)
      ii. Revise the Limitation statement and Title (as shown below) to be in accordance with the Guidance for Industry – Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements:

      These highlights do not include all the information needed to use ATORVASTATIN CALCIUM TABLETS safely and effectively. See full prescribing information for ATORVASTATIN CALCIUM TABLETS.

      ATORVASTATIN CALCIUM tablets, for oral use
      Initial U.S. Approval: 1996
      iii. ADVERSE REACTIONS: Revise the contact phone number (e.g. 86-0576-88812311) to a U.S. phone number.

iv. [redacted] (b) (4)

v. DRUG INTERACTIONS table, 2nd column, 4th row: Add a space between the numerical dose and unit of measure (i.e. change "40mg" to "40 mg").

vi. Revision date: Include a revision date at the end of the HIGHLIGHTS section per 21 CFR 201.57(a)(15).

c. [redacted] (b) (4)

d. DRUG INTERACTIONS, section 7.2 Drug Interactions that may Decrease Exposure to Atorvastatin Calcium Tablets, Table 4, last sentence in Clinical Impact section: Revise "atorvastation" to "atorvastatin".

e. [redacted] (b) (4)

f. [redacted] (b) (4)

g. CLINICAL STUDIES

i. section 14.1 Prevention of Cardiovascular Disease, Figure 3: Revise [redacted] (b) (4) to "Atorvastatin 80 mg" and "Atorvastatin 10 mg" in accordance with the RLD.

ii. section 14.1 Prevention of Cardiovascular Disease, Table 8, column 1, last row: Add a space between "othertraumatic" (i.e. other traumatic).

iii. section 14.1 Prevention of Cardiovascular Disease, Table 8, footnotes section: Add the statement "Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons" to a new line below "CABG: coronary artery bypass graft" in accordance with the RLD.

h. [redacted] (b) (4)

i. HOW SUPPLIED/ STORAGE AND HANDLING: Add the product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).

j. Manufacturer/Distributor/Packager: Add manufacturer information (e.g., name and location of business) per 21 CFR 201.1 and 21 CFR 201.100(e) after the PATIENT COUNSELING INFORMATION section.

3. PATIENT INFORMATION LEAFLET

a. Section entitled "What is Cholesterol?", 4th sentence: Revise [redacted] (b) (4) to "…or if heart disease starts early in your family." in accordance with the RLD.

b. Section entitled "How Should I Take Atorvastatin Calcium Tablets?",
   i. Add a bullet to the first paragraph in accordance with the RLD.
   ii. [redacted] (b) (4)
   iii. Create a line break before the sentence "Don't break Atorvastatin Calcium Tablets before taking." in accordance with the RLD.

c. section entitled "How do I store Atorvastatin Calcium Tablets?", 3rd bullet: Bold the statement "**Keep Atorvastatin Calcium Tablets and all medicines out of the reach of children**." in accordance with the RLD.

d. [redacted] (b) (4)

e. section entitled "What are the Ingredients in Atorvastatin Calcium Tablets?", Inactive Ingredients section: Revise [redacted] (b) (4) to lactose monohydrate in the list of inactive ingredients to be consistent with the information provided in your Quality submission.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than June 14, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi
Project Manager
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

ANDA 216848

INFORMATION REQUEST

Saxon International Associates
U.S. Agent for Lepu Pharmaceutical Technology Co., Ltd.
10 Debary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Peter Saxon:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 4, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg and 80 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Biopharmaceutics

We note that the dissolution method for your proposed product Atorvastatin Calcium Tablets differs from the USP. Please **initiate a revision to an official monograph** for Atorvastatin Calcium Tablets to the USP under the USP Pending Monograph Process. Until your product is in alignment with the dissolution test specifications (dissolution method) in the USP monograph, include the following statement in the description section on Labeling: "FDA approved dissolution test specifications differ from the USP."

We request a prompt written response, no later than September 30, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact DeWayne R. Johnson, PharmD, Regulatory Business Process Manager, at dewayne.johnson@fda.hhs.gov or (301) 796 - 2343.

Sincerely,

{See appended electronic signature page}

DeWayne R. Johnson, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ANDA 216848

ACKNOWLEDGEMENT
ANDA RECEIPT

Saxon International Associates
U.S. Agent for Lepu Pharmaceutical Technology Co., Ltd.
10 DeBary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Peter Saxon:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Atorvastatin Calcium Tablets USP, 10 mg, 20 mg, 40 mg, and 80 mg

DATE OF APPLICATION: January 4, 2022

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: January 4, 2022

Reference is made to the information requests dated February 14, 2022 and February 22, 2022, and to any amendments thereafter.

This original ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). The GDUFA goal date for review of this standard original ANDA is November 3, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current thinking on topics through guidances for industry,

including the Agency's recommendations reflected in relevant product specific guidances.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

Prior to the action date of your ANDA or supplement to your application, we recommend you:

- Review the regulations that describe the requirements for National Drug Code(s) (NDC(s)) including the requirements for obtaining new NDC(s) and restrictions regarding the use of NDC(s) [see 21 CFR 207.33 and 21 CFR 207.35, respectively].
- Ensure that NDC(s) that appear on prescription drug labeling (e.g., Prescribing Information, outer packaging, carton labeling, container labeling) are assigned correctly per the above. CDER does not typically review the accuracy of NDC(s) on prescription drug labeling prior to approval.
- Optionally, reserve new NDC(s) by referring to the Drug Registration and Listing website or contacting eDRLS@fda.hhs.gov. Include the required additional data elements when converting the NDC reservation submission to a drug registration and listing submission when a drug is approved.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Devon Lee, Regulatory Project Manager, at devon.lee@fda.hhs.gov[1] or (301) 837 - 7615. We also recommend that you sign up for

Generic Drug e-mail updates,[2] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Annie Phung, Pharm.D.
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

---

[1] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

[2] See FDA's Subscription Management Center at https://www.fda.gov/about-fda/contact-fda/get-email-updates

ANDA 216848

Saxon International Asso
U.S. Agent for Lepu Phar
10 DeBary Place
Summit, NJ 07901
Attention: Peter Saxon

Dear Peter Saxon: