CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022363Orig1s008, s009

Trade Name: LIVALO

Generic Name: Pitavastatin

Sponsor: Kowa Pharmaceuticals America, Inc.

Approval Date: 02/28/2012

Indications:

LIVALO is a HMG-CoA reductase inhibitor indicated for: Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022363Orig1s008, 009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202513Orig1s008, 009

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22363/S-008 and S-009

SUPPLEMENT APPROVAL

Kowa Pharmaceuticals America, Inc.
US Agent for Kowa Company Limited
Attention: John M. Ostrander, Ph.D.
Senior Director, Regulatory Affairs
530 Industrial Park Blvd
Montgomery, AL 36117

Dear Dr. Ostrander:

Please refer to your Supplemental New Drug Application (sNDA) dated September 23, 2011, received September 23, 2011 (S-008); and dated December 23, 2011, received December 27, 2011 (S-009), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Livalo (pitavastatin) Tablets, 1 mg, 2 mg, and 4 mg.

We acknowledge receipt of your amendments dated November 21, and December 28, 2011, and February 10, 2012, to S-008 and dated February 10, 2012, to S-009.

We also refer to our letter dated August 11, 2011, requesting that sponsors of HMG-CoA reductase inhibitor (statin) drugs, modify their labeling based on our comprehensive review of clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin coadministration. Additional reference is made to our August 31, 2011, prior approval supplement request letter.

Supplement-008 provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **CLINICAL PHARMACOLOGY,** and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Livalo (pitavastatin) package insert.

Supplement-009 provides changes to the **CLINICAL PHARMACOLOGY**, **Pharmacokinetics** subsection of the Livalo package insert to add information on protease inhibitors and Diltiazem LA.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must 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 http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

AMY G EGAN
02/28/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022363Orig1s008, 009

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIVALO® safely and effectively. See full prescribing information for LIVALO.

LIVALO (pitavastatin) Tablet, Film Coated for Oral use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Dosage and Administration
Dosage in Patients with Renal Impairment (2.2) 8/2011

----------INDICATIONS AND USAGE----------
LIVALO is a HMG-CoA reductase inhibitor indicated for:
- Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) (1.1)

Limitations of Use (1.2):
- Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.
- The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.
- LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------
- LIVALO can be taken with or without food, at any time of day (2.1) Dose Range: 1 mg to 4 mg once daily (2.1)
- **Primary hyperlipidemia and mixed dyslipidemia:** Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day. (2.1)
- **Moderate and severe renal impairment (glomerular filtration rate 30 – 59 and 15 - 29 mL/min/1.73 m^2, respectively) as well as end-stage renal disease on hemodialysis:** Starting dose of 1 mg once daily and maximum dose of 2 mg once daily (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 1 mg, 2 mg, and 4 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)
- Co-administration with cyclosporine (4, 7.1, 12.3)

----------WARNINGS AND PRECAUTIONS----------
- **Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):** Risks increase in a dose-dependent manner, with advanced age (>65), renal impairment, and inadequately treated hypothyroidism. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness, and discontinue LIVALO if signs or symptoms appear (5.1)
- **Liver enzyme abnormalities:** Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2)

----------ADVERSE REACTIONS----------
The most frequent adverse reactions (rate ≥2.0% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Kowa Pharmaceuticals America, Inc. at 1-877-334-3464 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- **Erythromycin:** Combination increases pitavastatin exposure. Limit LIVALO to 1 mg once daily (2.3, 7.2)
- **Rifampin:** Combination increases pitavastatin exposure. Limit LIVALO to 2 mg once daily (2.4, 7.3)
- **Concomitant lipid-lowering therapies**: Use with fibrates or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with LIVALO. (5.1, 7.4, 7.5)

----------USE IN SPECIFIC POPULATIONS----------
- **Pediatric use:** Safety and effectiveness have not been established. (8.4)
- **Renal impairment:** Limitation of a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily for patients with moderate and severe renal impairment as well as patients receiving hemodialysis (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION
Revised: (2/2012)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Drug therapy should be one component of multiple-risk-factor intervention in individuals who require modifications of their lipid profile. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate.

1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

LIVALO® is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

1.2 Limitations of Use

Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.

The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.

LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for LIVALO is 1 to 4 mg orally once daily at any time of the day with or without food. The recommended starting dose is 2 mg and the maximum dose is 4 mg. The starting dose and maintenance doses of LIVALO should be individualized according to patient characteristics, such as goal of therapy and response.

After initiation or upon titration of LIVALO, lipid levels should be analyzed after 4 weeks and the dosage adjusted accordingly.

2.2 Dosage in Patients with Renal Impairment

Patients with moderate and severe renal impairment (glomerular filtration rate 30 – 59 mL/min/1.73 m^2 and 15 – 29 mL/min/1.73 m^2 not receiving hemodialysis, respectively) as well as end-stage renal disease receiving hemodialysis should receive a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily.

2.3 Use with Erythromycin

In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[see Drug Interactions (7.2)]*.

2.4 Use with Rifampin

In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Drug Interactions (7.3)]*.

3 DOSAGE FORMS AND STRENGTHS

1 mg: Round white film-coated tablet. Debossed “KC” on one side and “1” on the other side of the tablet.
2 mg: Round white film-coated tablet. Debossed “KC” on one side and “2” on the other side of the tablet.
4 mg: Round white film-coated tablet. Debossed “KC” on one side and “4” on the other side of the tablet.

4 CONTRAINDICATIONS

The use of LIVALO is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO *[see Adverse Reactions (6.1)]*.
- Patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, LIVALO may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.2)]*.

- Nursing mothers. Animal studies have shown that LIVALO passes into breast milk. Since HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, LIVALO, like other HMG-CoA reductase inhibitors, is contraindicated in pregnant or nursing mothers *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.
- Co-administration with cyclosporine *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO. These risks can occur at any dose level, but increase in a dose-dependent manner.

LIVALO should be prescribed with caution in patients with predisposing factors for myopathy. These factors include advanced age (>65 years), renal impairment, and inadequately treated hypothyroidism. The risk of myopathy may also be increased with concurrent administration of fibrates or lipid-modifying doses of niacin. LIVALO should be administered with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin *[see Drug Interactions (7.6), Use in Specific Populations (8.5, 8.6) and Clinical Pharmacology (12.3)]*.

LIVALO therapy should be discontinued if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. LIVALO therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities

Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including LIVALO. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

In placebo-controlled Phase 2 studies, ALT >3 times the upper limit of normal was not observed in the placebo, LIVALO 1 mg, or LIVALO 2 mg groups. One out of 202 patients (0.5%) administered LIVALO 4 mg had ALT >3 times the upper limit of normal.

It is recommended that liver enzyme tests be performed before the initiation of LIVALO and if signs or symptoms of liver injury occur.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LIVALO, promptly interrupt therapy. If an alternate etiology is not found do not restart LIVALO.

As with other HMG-CoA reductase inhibitors, LIVALO should be used with caution in patients who consume substantial quantities of alcohol. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of LIVALO *[see Contraindications (4)]*.

5.3 Endocrine Function

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

6 ADVERSE REACTIONS

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

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) *[see Warnings and Precautions (5.1)]*.
- Liver Enzyme Abnormalities *[see Warning and Precautions (5.2)]*.

Of 4,798 patients enrolled in 10 controlled clinical studies and 4 subsequent open-label extension studies, 3,291 patients were administered pitavastatin 1 mg to 4 mg daily. The mean continuous exposure of pitavastatin (1 mg to 4 mg) was 36.7 weeks (median 51.1 weeks). The mean age of the patients was 60.9 years (range; 18 years – 89 years) and the gender distribution was 48% males and 52% females. Approximately 93% of the patients were Caucasian, 7% were Asian/Indian, 0.2% were African American and 0.3% were Hispanic and other.

6.1 Clinical Studies Experience

Because clinical studies on LIVALO are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of LIVALO cannot be directly compared with that in the clinical studies of other HMG-CoA reductase inhibitors and may not reflect the frequency of adverse reactions observed in clinical practice.

Adverse reactions reported in ≥ 2% of patients in controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had treatment duration of up to 12 weeks.

Table 1. Adverse Reactions* Reported by ≥2.0% of Patients Treated with LIVALO and > Placebo in Short-Term Controlled Studies

Adverse Reactions*	Placebo N= 208	LIVALO 1 mg N=309	LIVALO 2 mg N=951	LIVALO 4 mg N=1540
Back Pain	2.9%	3.9%	1.8%	1.4%
Constipation	1.9%	3.6%	1.5%	2.2%
Diarrhea	1.9%	2.6%	1.5%	1.9%
Myalgia	1.4%	1.9%	2.8%	3.1%
Pain in extremity	1.9%	2.3%	0.6%	0.9%

* Adverse reactions by MedDRA preferred term.

Other adverse reactions reported from clinical studies were arthralgia, headache, influenza, and nasopharyngitis.

The following laboratory abnormalities have also been reported: elevated creatine phosphokinase, transaminases, alkaline phosphatase, bilirubin, and glucose.

In controlled clinical studies and their open-label extensions, 3.9% (1 mg), 3.3% (2 mg), and 3.7% (4 mg) of pitavastatin-treated patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: elevated creatine phosphokinase (0.6% on 4 mg) and myalgia (0.5% on 4 mg).

Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO.

6.2 Postmarketing Experience:

The following adverse reactions have been identified during postapproval use of LIVALO. 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 LIVALO therapy reported since market introduction, regardless of causality assessment, include the following: abdominal discomfort, abdominal pain, dyspepsia, nausea, asthenia, fatigue, malaise, hepatitis, jaundice, fatal and non-fatal hepatic failure, dizziness, hypoesthesia, insomnia, depression, interstitial lung disease, erectile dysfunction and muscle spasms.

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 Cyclosporine

Cyclosporine significantly increased pitavastatin exposure. Co-administration of cyclosporine with LIVALO is contraindicated [*see Contraindications (4), and Clinical Pharmacology (12.3)]*.

7.2 Erythromycin

Erythromycin significantly increased pitavastatin exposure. In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.3 Rifampin

Rifampin significantly increased pitavastatin exposure. In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

7.4 Gemfibrozil
Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of LIVALO with gemfibrozil should be avoided.

7.5 Other Fibrates
Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, LIVALO should be administered with caution when used concomitantly with other fibrates *[see Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

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

7.7 Warfarin
LIVALO had no significant pharmacokinetic interaction with R- and S- warfarin. LIVALO had no significant effect on prothrombin time (PT) and international normalized ratio (INR) when administered to patients receiving chronic warfarin treatment *[see Clinical Pharmacology (12.3)]*. However, patients receiving warfarin should have their PT and INR monitored when pitavastatin is added to their therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic effects: Pregnancy Category X
LIVALO is contraindicated in women who are or may become pregnant. Serum cholesterol and TG increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy *[see Contraindications (4)]*.

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

Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation.

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3, 10, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.

Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1, 0.3, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

In perinatal/postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 0.1, 0.3, 1, 3, 10, 30 mg/kg/day from organogenesis through weaning, maternal toxicity consisting of mortality at ≥0.3 mg/kg/day and impaired lactation at all doses contributed to the decreased survival of neonates in all dose groups (0.1 mg/kg/day represents approximately 1 time human systemic exposure at 4 mg/day dose based on AUC).

LIVALO may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking LIVALO, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers
It is not known whether pitavastatin is excreted in human milk, however, it has been shown that a small amount of another drug in this class passes into human milk. Rat studies have shown that pitavastatin is excreted into breast milk. Because another drug in this class passes into human milk and HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require LIVALO treatment should be advised not to nurse their infants or to discontinue LIVALO *[see Contraindications (4)]*.

8.4 Pediatric Use
Safety and effectiveness of LIVALO in pediatric patients have not been established.

8.5 Geriatric Use
Of the 2,800 patients randomized to LIVALO 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were 65 years and older. No significant differences in efficacy or safety were observed between elderly patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
Patients with moderate and severe renal impairment (glomerular filtration rate 30 – 59 mL/min/1.73 m^2 and 15 – 29 mL/min/1.73 m^2 not receiving hemodialysis, respectively) as well as end-stage renal disease receiving hemodialysis should receive a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
LIVALO is contraindicated in patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels.

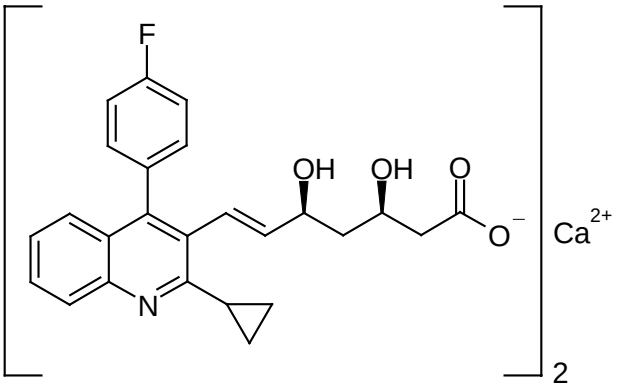
10 OVERDOSAGE

There is no known specific treatment in the event of overdose of pitavastatin. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis is unlikely to be of benefit due to high protein binding ratio of pitavastatin.

11 DESCRIPTION

LIVALO (pitavastatin) is an inhibitor of HMG-CoA reductase. It is a synthetic lipid-lowering agent for oral administration.

The chemical name for pitavastatin is (+)monocalcium *bis*{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}. The structural formula is:



The empirical formula for pitavastatin is $C_{50}H_{46}CaF_2N_2O_8$ and the molecular weight is 880.98. Pitavastatin is odorless and occurs as white to pale-yellow powder. It is freely soluble in pyridine, chloroform, dilute hydrochloric acid, and tetrahydrofuran, soluble in ethylene glycol, sparingly soluble in octanol, slightly soluble in methanol, very slightly soluble in water or ethanol, and practically insoluble in acetonitrile or diethyl ether. Pitavastatin is hygroscopic and slightly unstable in light.

Each film-coated tablet of LIVALO contains 1.045 mg, 2.09 mg, or 4.18 mg of pitavastatin calcium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base and the following inactive ingredients: lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose, magnesium aluminometasilicate, magnesium stearate, and film coating containing the following inactive ingredients: hypromellose, titanium dioxide, triethyl citrate, and colloidal anhydrous silica.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins.

12.2 Pharmacodynamics

In a randomized, double-blind, placebo-controlled, 4-way parallel, active-comparator study with moxifloxacin in 174 healthy participants, LIVALO was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 16 mg (4 times the recommended maximum daily dose).

12.3 Pharmacokinetics

Absorption: Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both C_{max} and $AUC_{0\text{-}inf}$ increased in an approximately dose-proportional manner for single LIVALO doses from 1 to 24 mg once daily. The absolute bioavailability of pitavastatin oral solution is 51%. Administration of LIVALO with a high fat meal (50% fat content) decreases pitavastatin C_{max} by 43% but does not significantly reduce pitavastatin AUC. The C_{max} and AUC of pitavastatin did not differ following evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the percent change from baseline for LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the small intestine but very little in the colon.

Distribution: Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells is minimal.

Metabolism: Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite in human plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uridine 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion: A mean of 15% of radioactivity of orally administered, single 32 mg ^{14}C-labeled pitavastatin dose was excreted in urine, whereas a mean of 79% of the dose was excreted in feces within 7 days. The mean plasma elimination half-life is approximately 12 hours.

Race: In pharmacokinetic studies pitavastatin C_{max} and AUC were 21 and 5% lower, respectively in Black or African American healthy volunteers compared with those of Caucasian healthy volunteers. In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in C_{max} and AUC.

Gender: In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C_{max} and AUC were 60 and 54% higher, respectively in females. This had no effect on the efficacy or safety of LIVALO in women in clinical studies.

Geriatric: In a pharmacokinetic study which compared healthy young and elderly (≥65 years) volunteers, pitavastatin C_{max} and AUC were 10 and 30% higher, respectively, in the elderly. This had no effect on the efficacy or safety of LIVALO in elderly subjects in clinical studies.

Renal Impairment: In patients with moderate renal impairment (glomerular filtration rate of 30 – 59 mL/min/1.73 m^2) and end stage renal disease receiving hemodialysis, pitavastatin $AUC_{0\text{-}inf}$ is 102 and 86% higher than those of healthy volunteers, respectively, while pitavastatin C_{max} is 60 and 40% higher than those of healthy volunteers, respectively. Patients received hemodialysis immediately before pitavastatin dosing and did not undergo hemodialysis during the pharmacokinetic study. Hemodialysis patients have 33 and 36% increases in the mean unbound fraction of pitavastatin as compared to healthy volunteers and patients with moderate renal impairment, respectively.

In another pharmacokinetic study, patients with severe renal impairment (glomerular filtration rate 15 – 29 mL/min/1.73 m^2) not receiving hemodialysis were administered a single dose of LIVALO 4 mg. The $AUC_{0\text{-}inf}$ and the C_{max} were 36 and 18% higher, respectively, compared with those of healthy volunteers. For both patients with severe renal impairment and healthy volunteers, the mean percentage of protein-unbound pitavastatin was approximately 0.6%.

The effect of mild renal impairment on pitavastatin exposure has not been studied.

Hepatic Impairment: The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. The ratio of pitavastatin C_{max} between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers was 2.7. The ratio of pitavastatin AUC_{inf} between patients with moderate hepatic impairment and healthy volunteers was 3.8. The ratio of pitavastatin C_{max} between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteers was 1.3. The ratio of pitavastatin AUC_{inf} between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean pitavastatin $t_{½}$ for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively.

Drug-Drug Interactions: The principal route of pitavastatin metabolism is glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system.

Warfarin: The steady-state pharmacodynamics (international normalized ratio [INR] and prothrombin time [PT]) and pharmacokinetics of warfarin in healthy volunteers were unaffected by the co-administration of LIVALO 4 mg daily. However, patients receiving warfarin should have their PT time or INR monitored when pitavastatin is added to their therapy.

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max*}
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Darunavir/Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16	↓ 26%	↓ 4%
Lopinavir/Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24	↓ 20%	↓4 %
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15	↑10%	↑15%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days	↑ 15%	↓ 12%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

*Data presented as x-fold change represent the ratio between co-administration and pitavastatin alone (i.e., 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).
† Considered clinically significant *[see Dosage and Administration (2) and Drug Interactions (7)]*
BID = twice daily; QD = once daily; LA = Long Acting

Table 3. Effect of Pitavastatin Co-Administration on Systemic Exposure to Other Drugs

Co-administered drug	Dose regimen		Change in AUC*	Change in C_{max}*
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Darunavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 3%	↑ 6%
Lopinavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 9%	↓ 7%
Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 11%	↓ 11%
Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 8%	↑ 2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	Enalapril	↑ 12%	↑ 12%
		Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 - 7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑ 7%	↑ 3%
		S-warfarin	↑ 6%	↑ 3%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days		↑ 9%	↑ 2%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days		↓ 3%	↓ 4%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15		↓ 2%	↓ 7%
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days		↓ 15%	↓ 18%

Data presented as % change represent % difference relative to the investigated drug alone (i.e., 0% = no change).
BID = twice daily; QD = once daily; LA = Long Acting

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 92-week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors.

In a 92-week carcinogenicity study in rats given pitavastatin at 1, 5, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.

In a 26-week transgenic mouse (Tg rasH2) carcinogenicity study where animals were given pitavastatin at 30, 75, and 150 mg/kg/day by oral gavage, no clinically significant tumors were observed.

Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rats, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test, clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity.

Pitavastatin had no adverse effects on male and female rat fertility at oral doses of 10 and 30 mg/kg/day, respectively, at systemic exposures 56- and 354-times clinical exposure at 4 mg/day based on AUC.

Pitavastatin treatment in rabbits resulted in mortality in males and females given 1 mg/kg/day (30-times clinical systemic exposure at 4 mg/day based on AUC) and higher during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened) indicative of possible ischemia. Lower doses (15-times human systemic exposure) did not show significant toxicity in adult males and females. However, decreased implantations, increased resorptions, and decreased viability of fetuses were observed.

13.2 Animal Toxicology and/or Pharmacology

Central Nervous System Toxicity
CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Wallerian degeneration has not been observed with pitavastatin. Cataracts and lens opacities were seen in dogs treated for 52 weeks at a dose level of 1 mg/kg/day (9 times clinical exposure at the maximum human dose of 4 mg/day based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia or Mixed Dyslipidemia

Dose-ranging study: A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study was performed to evaluate the efficacy of LIVALO compared with placebo in 251 patients with primary hyperlipidemia (Table 4). LIVALO given as a single daily dose for 12 weeks significantly reduced plasma LDL-C, TC, TG, and Apo-B compared to placebo and was associated with variable increases in HDL-C across the dose range.

Table 4. Dose-Response in Patients with Primary Hypercholesterolemia (Adjusted Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C
Placebo	53	-3	-2	-2	1	0
LIVALO 1mg	52	-32	-25	-23	-15	8
LIVALO 2mg	49	-36	-30	-26	-19	7
LIVALO 4mg	51[#]	-43	-35	-31	-18	5

The number of subjects for Apo-B was 49

Active-controlled study with atorvastatin (NK-104-301): LIVALO was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 817 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomized to a 12-week treatment with either LIVALO or atorvastatin (Table 5). Non-inferiority of pitavastatin to a given dose of atorvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 5. For the percent change from baseline to endpoint in LDL-C, LIVALO was non-inferior to atorvastatin for the two pairwise comparisons: LIVALO 2 mg vs. atorvastatin 10 mg and LIVALO 4 mg vs. atorvastatin 20 mg. Mean treatment differences (95% CI) were 0% (-3%, 3%) and 1% (-2%, 4%), respectively.

Table 5. Response by Dose of LIVALO and Atorvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 2 mg daily	315	-38	-30	-28	-14	4	-35
LIVALO 4 mg daily	298	-45	-35	-32	-19	5	-41
Atorvastatin 10 mg daily	102	-38	-29	-28	-18	3	-35
Atorvastatin 20 mg daily	102	-44	-36	-33	-22	2	-41
Atorvastatin 40 mg daily	----------Not Studied----------						
Atorvastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with simvastatin (NK-104-302): LIVALO was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 843 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomized to a 12 week treatment with either LIVALO or simvastatin (Table 6). Non-inferiority of pitavastatin to a given dose of simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 6. For the percent change from baseline to endpoint in LDL-C, LIVALO was non-inferior to simvastatin for the two pairwise comparisons: LIVALO 2 mg vs. simvastatin 20 mg and LIVALO 4 mg vs. simvastatin 40 mg. Mean treatment differences (95% CI) were 4% (1%, 7%) and 1% (-2%, 4%), respectively.

Table 6. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 2 mg daily	307	-39	-30	-28	-16	6	-36
LIVALO 4 mg daily	319	-44	-35	-32	-17	6	-41
Simvastatin 20 mg daily	107	-35	-27	-25	-16	6	-32
Simvastatin 40 mg daily	110	-43	-34	-31	-16	7	-39
Simvastatin 80 mg	----------Not Studied----------						

Active-controlled study with pravastatin in elderly (NK-104-306): LIVALO was compared with the HMG-CoA reductase inhibitor pravastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled non-inferiority Phase 3 study of 942 elderly patients (≥65 years) with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period, and then were randomized to a once daily dose of LIVALO or pravastatin for 12 weeks (Table 7). Non-inferiority of LIVALO to a given dose of pravastatin was assumed if the lower bound of the 95% CI for the treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 7. LIVALO significantly reduced LDL-C compared to pravastatin as demonstrated by the following pairwise dose comparisons: LIVALO 1 mg vs. pravastatin 10 mg, LIVALO 2 mg vs. pravastatin 20 mg and LIVALO 4 mg vs. pravastatin 40 mg. Mean treatment differences (95% CI) were 9% (6%, 12%), 10% (7%, 13%) and 10% (7%, 13%), respectively.

Table 7. Response by Dose of LIVALO and Pravastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 1 mg daily	207	-31	-25	-22	-13	1	-29
LIVALO 2 mg daily	224	-39	-31	-27	-15	2	-36
LIVALO 4 mg daily	210	-44	-37	-31	-22	4	-41
Pravastatin 10 mg daily	103	-22	-17	-15	-5	0	-20
Pravastatin 20 mg daily	96	-29	-22	-21	-11	-1	-27
Pravastatin 40 mg daily	102	-34	-28	-24	-15	1	-32
Pravastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with simvastatin in patients with ≥ 2 risk factors for coronary heart disease (NK-104-304): LIVALO was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 351 patients with primary hyperlipidemia or mixed dyslipidemia with ≥2 risk factors for coronary heart disease. After a 6- to 8-week wash-out/dietary lead-in period, patients were randomized to a 12-week treatment with either LIVALO or simvastatin (Table 8). Non-inferiority of LIVALO to simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 8. LIVALO 4 mg was non-inferior to simvastatin 40 mg for percent change from baseline to endpoint in LDL-C. The mean treatment difference (95% CI) was 0% (-2%, 3%).

Table 8. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia with ≥2 Risk Factors for Coronary Heart Disease (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 4 mg daily	233	-44	-34	-31	-20	7	-40
Simvastatin 40 mg daily	118	-44	-34	-31	-15	5	-39
Simvastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with atorvastatin in patients with type II diabetes mellitus (NK-104-305): LIVALO was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, non-inferiority Phase 3 study of 410 subjects with type II diabetes mellitus and combined dyslipidemia. Patients entered a 6- to 8-week washout/dietary lead-in period and were randomized to a once daily dose of LIVALO or atorvastatin for 12 weeks. Non-inferiority of LIVALO was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

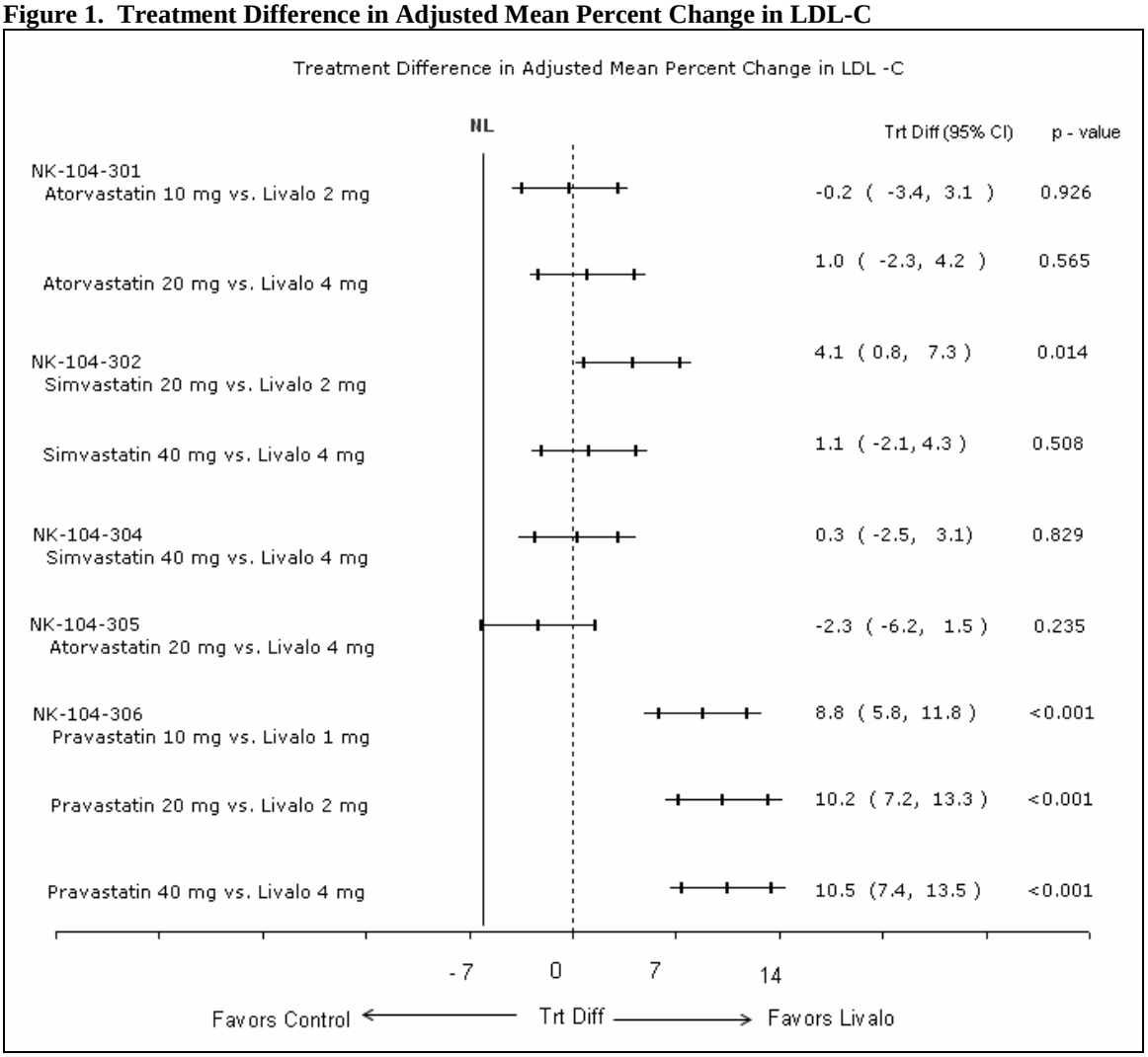
Lipid results are shown in Table 9. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit so that the non-inferiority objective was not achieved.

Table 9. Response by Dose of LIVALO and Atorvastatin in Patients with Type II Diabetes Mellitus and Combined Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 4 mg daily	274	-41	-32	-28	-20	7	-36
Atorvastatin 20 mg daily	136	-43	-34	-32	-27	8	-40
Atorvastatin 40 mg daily	----------Not Studied----------						
Atorvastatin 80 mg daily	----------Not Studied----------						

The treatment differences in efficacy in LDL-C change from baseline between LIVALO and active controls in the Phase 3 studies are summarized in Figure 1.

Figure 1. Treatment Difference in Adjusted Mean Percent Change in LDL-C



NL=non-inferiority limit.

16 HOW SUPPLIED/STORAGE AND HANDLING

LIVALO tablets for oral administration are provided as white, film-coated tablets that contain 1 mg, 2 mg, or 4 mg of pitavastatin. Each tablet has “KC” debossed on one side and a code number specific to the tablet strength on the other.

Packaging
LIVALO (pitavastatin) Tablets are supplied as;

- NDC 0002-4770-90 : 1 mg. Round white film-coated tablet debossed “KC” on one face and “1” on the reverse; HDPE bottles of 90 tablets
- NDC 0002-4771-90 : 2 mg. Round white film-coated tablet debossed “KC” on one face and “2” on the reverse; HDPE bottles of 90 tablets
- NDC 0002-4772-90 : 4 mg. Round white film-coated tablet debossed “KC” on one face and “4” on the reverse; HDPE bottles of 90 tablets

Storage
Store at room temperature between 15°C and 30°C (59° to 86° F) [see USP]. Protect from light.

17 PATIENT COUNSELING INFORMATION

The patient should be informed of the following:

17.1 Dosing Time
LIVALO can be taken at any time of the day with or without food.

17.2 Muscle Pain
Patients should be advised to promptly notify their physician of any unexplained muscle pain, tenderness, or weakness. They should discuss all medication, both prescription and over the counter, with their physician.

17.3 Pregnancy
Women of childbearing age should use an effective method of birth control to prevent pregnancy while using LIVALO. Discuss future pregnancy plans with your healthcare professional, and discuss when to stop LIVALO if you are trying to conceive. If you are pregnant, stop taking LIVALO and call your healthcare professional.

17.4 Breastfeeding
Women who are breastfeeding should not use LIVALO. If you have a lipid disorder and are breastfeeding, stop taking LIVALO and consult with your healthcare professional.

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

Manufactured under license from: Kowa Company, Limited Tokyo 103-8433 Japan
Product of Japan
Manufactured into tablets by: Patheon, Inc. Cincinnati, OH 45237 USA or by Kowa Company, LTD Nagoya, 462-0024 Japan
Marketed by: Kowa Pharmaceuticals America, Inc. Montgomery, AL 36117 USA
and Lilly USA, LLC. Indianapolis, IN 46285 USA
To request additional information or if you have questions concerning LIVALO please phone Kowa Pharmaceuticals America, Inc. at 877-8-LIVALO (877-854-8256) or fax your inquiry to 800-689-0244

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022363Orig1s008, 009

Tracked Changes Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIVALO® safely and effectively. See full prescribing information for LIVALO.

LIVALO (pitavastatin) Tablet, Film Coated for Oral use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Dosage and Administration
Dosage in Patients with Renal Impairment (2.2) 8/2011

----------INDICATIONS AND USAGE----------
LIVALO is a HMG-CoA reductase inhibitor indicated for:
- Patients with primary hyperlipidemia or ~~and~~ mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) (1.1)

Limitations of Use (1.2):
- Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.
- The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.
- LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------
- LIVALO can be taken with or without food, at any time of day (2.1)
  Dose Range: 1 mg to 4 mg once daily (2.1)
- **Primary hyperlipidemia and mixed dyslipidemia:** Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day. (2.1)
- **Moderate and severe renal impairment (glomerular filtration rate 30 – 59 and 15 - 29 mL/min/1.73 m^2, respectively) as well as end-stage renal disease on hemodialysis:** Starting dose of 1 mg once daily and maximum dose of 2 mg once daily (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 1 mg, 2 mg, and 4 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)
- Co-administration with cyclosporine (4, 7.1, 12.3)

----------WARNINGS AND PRECAUTIONS----------
- **Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):** Risks increase in a dose-dependent manner, with advanced age (>65), renal impairment, and inadequately treated hypothyroidism~~, and combination use with fibrates.~~ Advise patients to promptly report unexplained muscle pain, tenderness, or weakness, and discontinue LIVALO if signs or symptoms appear (5.1)
- **Liver enzyme~~s~~ abnormalities ~~and monitoring~~:** Persistent elevations in hepatic transaminases can occur. ~~Monitor~~ Check liver enzyme~~s~~ tests before initiating therapy and as clinically indicated thereafter ~~during treatment~~ (5.2)

----------ADVERSE REACTIONS----------
The most frequent adverse reactions (rate ≥2.0% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Kowa Pharmaceuticals America, Inc. at 1-877-334-3464 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- **Erythromycin:** Combination increases pitavastatin exposure. Limit LIVALO to 1 mg once daily (2.3, 7.2)
- **Rifampin:** Combination increases pitavastatin exposure. Limit LIVALO to 2 mg once daily (2.4, 7.3)
- **Concomitant lipid-lowering therapies ~~Fibrates~~**: Use with fibrates or lipid-modifying doses (≥1 g/day) of niacin ~~products may~~ increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with LIVALO. (5.1, 7.4, 7.5)

----------USE IN SPECIFIC POPULATIONS----------
- **Pediatric use:** Safety and effectiveness have not been established. (8.4)
- **Renal impairment:** Limitation of a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily for patients with moderate and severe renal impairment as well as patients receiving hemodialysis (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION
Revised: ~~8/2011~~ (2/2012)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Drug therapy should be one component of multiple-risk-factor intervention in individuals who require modifications of their lipid profile. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate.

1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

LIVALO® is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

1.2 Limitations of Use

Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.

The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.

LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for LIVALO is 1 to 4 mg orally once daily at any time of the day with or without food. The recommended starting dose is 2 mg and the maximum dose is 4 mg. The starting dose and maintenance doses of LIVALO should be individualized according to patient characteristics, such as goal of therapy and response.

After initiation or upon titration of LIVALO, lipid levels should be analyzed after 4 weeks and the dosage adjusted accordingly.

2.2 Dosage in Patients with Renal Impairment

Patients with moderate and severe renal impairment (glomerular filtration rate 30 – 59 mL/min/1.73 m^2 and 15 – 29 mL/min/1.73 m^2 not receiving hemodialysis, respectively) as well as end-stage renal disease receiving hemodialysis should receive a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily.

2.3 Use with Erythromycin

In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[see Drug Interactions (7.2)]*.

2.4 Use with Rifampin

In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Drug Interactions (7.3)]*.

3 DOSAGE FORMS AND STRENGTHS

1 mg: Round white film-coated tablet. Debossed “KC” on one side and “1” on the other side of the tablet.
2 mg: Round white film-coated tablet. Debossed “KC” on one side and “2” on the other side of the tablet.
4 mg: Round white film-coated tablet. Debossed “KC” on one side and “4” on the other side of the tablet.

4 CONTRAINDICATIONS

The use of LIVALO is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO *[see Adverse Reactions (6.1)]*.
- Patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, LIVALO may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.2)]*.

- Nursing mothers. Animal studies have shown that LIVALO passes into breast milk. Since HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, LIVALO, like other HMG-CoA reductase inhibitors, is contraindicated in pregnant or nursing mothers *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.
- Co-administration with cyclosporine *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO. These risks can occur at any dose level, but increase in a dose-dependent manner.

LIVALO should be prescribed with caution in patients with predisposing factors for myopathy. These factors include advanced age (>65 years), renal impairment, and inadequately treated hypothyroidism. The risk of myopathy may also be increased with concurrent administration of fibrates or lipid-modifying doses of niacin. LIVALO should be administered with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin *[see Drug Interactions (7.6), Use in Specific Populations (8.5, 8.6) and Clinical Pharmacology (12.3)]*.

LIVALO therapy should be discontinued if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. LIVALO therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities ~~and Monitoring~~

Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including LIVALO. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

In placebo-controlled Phase 2 studies, ALT >3 times the upper limit of normal was not observed in the placebo, LIVALO 1 mg, or LIVALO 2 mg groups. One out of 202 patients (0.5%) administered LIVALO 4 mg had ALT >3 times the upper limit of normal.

It is recommended that liver enzyme tests be performed before ~~and at 12 weeks following both~~ the initiation of ~~therapy~~ LIVALO and if signs or symptoms of liver injury occur.

~~Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times upper limit of normal persist, reduction of dose or withdrawal of LIVALO is recommended.~~
There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LIVALO, promptly interrupt therapy. If an alternate etiology is not found do not restart LIVALO.

As with other HMG-CoA reductase inhibitors, LIVALO should be used with caution in patients who consume substantial quantities of alcohol. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of LIVALO *[see Contraindications (4)]*.

5.3 Endocrine Function

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

6 ADVERSE REACTIONS

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

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) *[see Warnings and Precautions (5.1)]*.
- Liver Enzyme Abnormalities *[see Warning and Precautions (5.2)]*.

Of 4,798 patients enrolled in 10 controlled clinical studies and 4 subsequent open-label extension studies, 3,291 patients were administered pitavastatin 1 mg to 4 mg daily. The mean continuous exposure of pitavastatin (1 mg to 4 mg) was 36.7 weeks (median 51.1 weeks). The mean age of the patients was 60.9 years (range; 18 years – 89 years) and the gender distribution was 48% males and 52% females. Approximately 93% of the patients were Caucasian, 7% were Asian/Indian, 0.2% were African American and 0.3% were Hispanic and other.

6.1 Clinical Studies Experience

Because clinical studies on LIVALO are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of LIVALO cannot be directly compared with that in the clinical studies of other HMG-CoA reductase inhibitors and may not reflect the frequency of adverse reactions observed in clinical practice.

Adverse reactions reported in ≥ 2% of patients in controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had treatment duration of up to 12 weeks.

Table 1. Adverse Reactions* Reported by ≥2.0% of Patients Treated with LIVALO and > Placebo in Short-Term Controlled Studies

Adverse Reactions*	Placebo N= 208	LIVALO 1 mg N=309	LIVALO 2 mg N=951	LIVALO 4 mg N=1540
Back Pain	2.9%	3.9%	1.8%	1.4%
Constipation	1.9%	3.6%	1.5%	2.2%
Diarrhea	1.9%	2.6%	1.5%	1.9%
Myalgia	1.4%	1.9%	2.8%	3.1%
Pain in extremity	1.9%	2.3%	0.6%	0.9%

* Adverse reactions by MedDRA preferred term.

Other adverse reactions reported from clinical studies were arthralgia, headache, influenza, and nasopharyngitis.

The following laboratory abnormalities have also been reported: elevated creatine phosphokinase, transaminases, alkaline phosphatase, bilirubin, and glucose.

In controlled clinical studies and their open-label extensions, 3.9% (1 mg), 3.3% (2 mg), and 3.7% (4 mg) of pitavastatin-treated patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: elevated creatine phosphokinase (0.6% on 4 mg) and myalgia (0.5% on 4 mg).

Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO.

6.2 Postmarketing Experience:

The following adverse reactions have been identified during postapproval use of LIVALO. 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 LIVALO therapy reported since market introduction, regardless of causality assessment, include the following: abdominal discomfort, abdominal pain, dyspepsia, nausea, asthenia, fatigue, malaise, hepatitis, jaundice, fatal and non-fatal hepatic failure, dizziness, hypoesthesia, insomnia, depression, interstitial lung disease, erectile dysfunction and muscle spasms.

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 Cyclosporine

Cyclosporine significantly increased pitavastatin exposure. Co-administration of cyclosporine with LIVALO is contraindicated [*see Contraindications (4), and Clinical Pharmacology (12.3)]*.

7.2 Erythromycin

Erythromycin significantly increased pitavastatin exposure. In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.3 Rifampin

Rifampin significantly increased pitavastatin exposure. In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of LIVALO with gemfibrozil should be avoided.

7.5 Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors ~~may be~~ is increased with concurrent administration of other fibrates, LIVALO should be administered with caution when used concomitantly with ~~gemfibrozil or~~ other fibrates *[see Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

7.6 ~~5~~ Niacin

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

7.7 ~~6~~ Warfarin

LIVALO had no significant pharmacokinetic interaction with R- and S- warfarin. LIVALO had no significant effect on prothrombin time (PT) and international normalized ratio (INR) when administered to patients receiving chronic warfarin treatment *[see Clinical Pharmacology (12.3)]*. However, patients receiving warfarin should have their PT and INR monitored when pitavastatin is added to their therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category X

LIVALO is contraindicated in women who are or may become pregnant. Serum cholesterol and TG increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy *[see Contraindications (4)]*.

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

Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation.

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3, 10, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.

Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1, 0.3, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

In perinatal/postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 0.1, 0.3, 1, 3, 10, 30 mg/kg/day from organogenesis through weaning, maternal toxicity consisting of mortality at ≥0.3 mg/kg/day and impaired lactation at all doses contributed to the decreased survival of neonates in all dose groups (0.1 mg/kg/day represents approximately 1 time human systemic exposure at 4 mg/day dose based on AUC).

LIVALO may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking LIVALO, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether pitavastatin is excreted in human milk, however, it has been shown that a small amount of another drug in this class passes into human milk. Rat studies have shown that pitavastatin is excreted into breast milk. Because another drug in this class passes into human milk and HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants,

women who require LIVALO treatment should be advised not to nurse their infants or to discontinue LIVALO *[see Contraindications (4)]*.

8.4 Pediatric Use
Safety and effectiveness of LIVALO in pediatric patients have not been established.

8.5 Geriatric Use
Of the 2,800 patients randomized to LIVALO 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were 65 years and older. No significant differences in efficacy or safety were observed between elderly patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
Patients with moderate and severe renal impairment (glomerular filtration rate 30 – 59 mL/min/1.73 m^2 and 15 – 29 mL/min/1.73 m^2 not receiving hemodialysis, respectively) as well as end-stage renal disease receiving hemodialysis should receive a starting dose of LIVALO 1 mg once daily and a maximum dose of LIVALO 2 mg once daily *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
LIVALO is contraindicated in patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels.

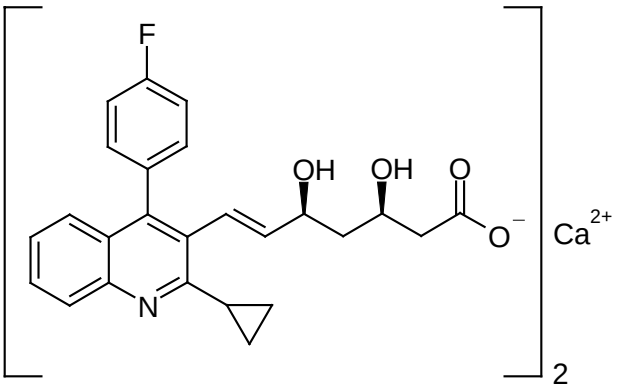
10 OVERDOSAGE

There is no known specific treatment in the event of overdose of pitavastatin. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis is unlikely to be of benefit due to high protein binding ratio of pitavastatin.

11 DESCRIPTION

LIVALO (pitavastatin) is an inhibitor of HMG-CoA reductase. It is a synthetic lipid-lowering agent for oral administration.

The chemical name for pitavastatin is (+)monocalcium *bis*{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}. The structural formula is:



The empirical formula for pitavastatin is $C_{50}H_{46}CaF_2N_2O_8$ and the molecular weight is 880.98. Pitavastatin is odorless and occurs as white to pale-yellow powder. It is freely soluble in pyridine, chloroform, dilute hydrochloric acid, and tetrahydrofuran, soluble in ethylene glycol, sparingly soluble in octanol, slightly soluble in methanol, very slightly soluble in water or ethanol, and practically insoluble in acetonitrile or diethyl ether. Pitavastatin is hygroscopic and slightly unstable in light.

Each film-coated tablet of LIVALO contains 1.045 mg, 2.09 mg, or 4.18 mg of pitavastatin calcium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base and the following inactive ingredients: lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose, magnesium aluminometasilicate, magnesium stearate, and film coating containing the following inactive ingredients: hypromellose, titanium dioxide, triethyl citrate, and colloidal anhydrous silica.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins.

12.2 Pharmacodynamics

In a randomized, double-blind, placebo-controlled, 4-way parallel, active-comparator study with moxifloxacin in 174 healthy participants, LIVALO was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 16 mg (4 times the recommended maximum daily dose).

12.3 Pharmacokinetics

Absorption: Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both C_{max} and $AUC_{0\text{-}inf}$ increased in an approximately dose-proportional manner for single LIVALO doses from 1 to 24 mg once daily. The absolute bioavailability of pitavastatin oral solution is 51%. Administration of LIVALO with a high fat meal (50% fat content) decreases pitavastatin C_{max} by 43% but does not significantly reduce pitavastatin AUC. The C_{max} and AUC of pitavastatin did not differ following evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the percent change from baseline for LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the small intestine but very little in the colon.

Distribution: Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells is minimal.

Metabolism: Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite in human plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uridine 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion: A mean of 15% of radioactivity of orally administered, single 32 mg ^{14}C-labeled pitavastatin dose was excreted in urine, whereas a mean of 79% of the dose was excreted in feces within 7 days. The mean plasma elimination half-life is approximately 12 hours.

Race: In pharmacokinetic studies pitavastatin C_{max} and AUC were 21 and 5% lower, respectively in Black or African American healthy volunteers compared with those of Caucasian healthy volunteers. In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in C_{max} and AUC.

Gender: In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C_{max} and AUC were 60 and 54% higher, respectively in females. This had no effect on the efficacy or safety of LIVALO in women in clinical studies.

Geriatric: In a pharmacokinetic study which compared healthy young and elderly (≥65 years) volunteers, pitavastatin C_{max} and AUC were 10 and 30% higher, respectively, in the elderly. This had no effect on the efficacy or safety of LIVALO in elderly subjects in clinical studies.

Renal Impairment: In patients with moderate renal impairment (glomerular filtration rate of 30 – 59 mL/min/1.73 m^2) and end stage renal disease receiving hemodialysis, pitavastatin $AUC_{0\text{-}inf}$ is 102 and 86% higher than those of healthy volunteers, respectively, while pitavastatin C_{max} is 60 and 40% higher than those of healthy volunteers, respectively. Patients received hemodialysis immediately before pitavastatin dosing and did not undergo hemodialysis during the pharmacokinetic study. Hemodialysis patients have 33 and 36% increases in the mean unbound fraction of pitavastatin as compared to healthy volunteers and patients with moderate renal impairment, respectively.

In another pharmacokinetic study, patients with severe renal impairment (glomerular filtration rate 15 – 29 mL/min/1.73 m^2) not receiving hemodialysis were administered a single dose of LIVALO 4 mg. The $AUC_{0\text{-}inf}$ and the C_{max} were 36 and 18% higher, respectively, compared with those of healthy volunteers. For both patients with severe renal impairment and healthy volunteers, the mean percentage of protein-unbound pitavastatin was approximately 0.6%.

The effect of mild renal impairment on pitavastatin exposure has not been studied.

Hepatic Impairment: The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. The ratio of pitavastatin C_{max} between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers was 2.7. The ratio of pitavastatin AUC_{inf} between patients with moderate hepatic impairment and healthy volunteers was 3.8. The ratio of pitavastatin C_{max} between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteers was 1.3. The ratio of pitavastatin AUC_{inf} between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean pitavastatin $t_{½}$ for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively.

Drug-Drug Interactions: The principal route of pitavastatin metabolism is glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system.

Warfarin: The steady-state pharmacodynamics (international normalized ratio [INR] and prothrombin time [PT]) and pharmacokinetics of warfarin in healthy volunteers were unaffected by the co-administration of LIVALO 4 mg daily. However, patients receiving warfarin should have their PT time or INR monitored when pitavastatin is added to their therapy.

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max*}
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Darunavir/Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16	↓ 26%	↓ 4%
Lopinavir/Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24	↓ 20%	↓4 %
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15	↑10%	↑15%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days	↑ 15%	↓ 12%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

*Data presented as x-fold change represent the ratio between co-administration and pitavastatin alone (i.e., 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).
† Considered clinically significant *[see Dosage and Administration (2) and Drug Interactions (7)]*
BID = twice daily; QD = once daily; LA = Long Acting

Table 3. Effect of Pitavastatin Co-Administration on Systemic Exposure to Other Drugs

Co-administered drug	Dose regimen		Change in AUC*	Change in C_{max}*
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Darunavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 3%	↑ 6%
Lopinavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 9%	↓ 7%
Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 11%	↓ 11%
Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 8%	↑ 2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	Enalapril	↑ 12%	↑ 12%
		Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 - 7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑ 7%	↑ 3%
		S-warfarin	↑ 6%	↑ 3%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days		↑ 9%	↑ 2%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days		↓ 3%	↓ 4%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15		↓ 2%	↓ 7%
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days		↓ 15%	↓ 18%

Data presented as % change represent % difference relative to the investigated drug alone (i.e., 0% = no change).
BID = twice daily; QD = once daily; LA = Long Acting

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 92-week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors.

In a 92-week carcinogenicity study in rats given pitavastatin at 1, 5, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.

In a 26-week transgenic mouse (Tg rasH2) carcinogenicity study where animals were given pitavastatin at 30, 75, and 150 mg/kg/day by oral gavage, no clinically significant tumors were observed.

Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rats, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test, clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity.

Pitavastatin had no adverse effects on male and female rat fertility at oral doses of 10 and 30 mg/kg/day, respectively, at systemic exposures 56- and 354-times clinical exposure at 4 mg/day based on AUC.

Pitavastatin treatment in rabbits resulted in mortality in males and females given 1 mg/kg/day (30-times clinical systemic exposure at 4 mg/day based on AUC) and higher during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened) indicative of possible ischemia. Lower doses (15-times human systemic exposure) did not show significant toxicity in adult males and females. However, decreased implantations, increased resorptions, and decreased viability of fetuses were observed.

13.2 Animal Toxicology and/or Pharmacology

Central Nervous System Toxicity
CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Wallerian degeneration has not been observed with pitavastatin. Cataracts and lens opacities were seen in dogs treated for 52 weeks at a dose level of 1 mg/kg/day (9 times clinical exposure at the maximum human dose of 4 mg/day based on AUC comparisons.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia or Mixed Dyslipidemia
Dose-ranging study: A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study was performed to evaluate the efficacy of LIVALO compared with placebo in 251 patients with primary hyperlipidemia (Table 4). LIVALO given as a single daily dose for 12 weeks significantly reduced plasma LDL-C, TC, TG, and Apo-B compared to placebo and was associated with variable increases in HDL-C across the dose range.

Table 4. Dose-Response in Patients with Primary Hypercholesterolemia (Adjusted Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C
Placebo	53	-3	-2	-2	1	0
LIVALO 1mg	52	-32	-25	-23	-15	8
LIVALO 2mg	49	-36	-30	-26	-19	7
LIVALO 4mg	51[#]	-43	-35	-31	-18	5

The number of subjects for Apo-B was 49

Active-controlled study with atorvastatin (NK-104-301): LIVALO was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 817 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomized to a 12-week treatment with either LIVALO or atorvastatin (Table 5). Non-inferiority of pitavastatin to a given dose of atorvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 5. For the percent change from baseline to endpoint in LDL-C, LIVALO was non-inferior to atorvastatin for the two pairwise comparisons: LIVALO 2 mg vs. atorvastatin 10 mg and LIVALO 4 mg vs. atorvastatin 20 mg. Mean treatment differences (95% CI) were 0% (-3%, 3%) and 1% (-2%, 4%), respectively.

Table 5. Response by Dose of LIVALO and Atorvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 2 mg daily	315	-38	-30	-28	-14	4	-35
LIVALO 4 mg daily	298	-45	-35	-32	-19	5	-41
Atorvastatin 10 mg daily	102	-38	-29	-28	-18	3	-35
Atorvastatin 20 mg daily	102	-44	-36	-33	-22	2	-41
Atorvastatin 40 mg daily	----------Not Studied----------						
Atorvastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with simvastatin (NK-104-302): LIVALO was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 843 patients with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomized to a 12 week treatment with either LIVALO or simvastatin (Table 6). Non-inferiority of pitavastatin to a given dose of simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 6. For the percent change from baseline to endpoint in LDL-C, LIVALO was non-inferior to simvastatin for the two pairwise comparisons: LIVALO 2 mg vs. simvastatin 20 mg and LIVALO 4 mg vs. simvastatin 40 mg. Mean treatment differences (95% CI) were 4% (1%, 7%) and 1% (-2%, 4%), respectively.

Table 6. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 2 mg daily	307	-39	-30	-28	-16	6	-36
LIVALO 4 mg daily	319	-44	-35	-32	-17	6	-41
Simvastatin 20 mg daily	107	-35	-27	-25	-16	6	-32
Simvastatin 40 mg daily	110	-43	-34	-31	-16	7	-39
Simvastatin 80 mg	----------Not Studied----------						

Active-controlled study with pravastatin in elderly (NK-104-306): LIVALO was compared with the HMG-CoA reductase inhibitor pravastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled non-inferiority Phase 3 study of 942 elderly patients (≥65 years) with primary hyperlipidemia or mixed dyslipidemia. Patients entered a 6- to 8-week wash-out/dietary lead-in period, and then were randomized to a once daily dose of LIVALO or pravastatin for 12 weeks (Table 7). Non-inferiority of LIVALO to a given dose of pravastatin was assumed if the lower bound of the 95% CI for the treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 7. LIVALO significantly reduced LDL-C compared to pravastatin as demonstrated by the following pairwise dose comparisons: LIVALO 1 mg vs. pravastatin 10 mg, LIVALO 2 mg vs. pravastatin 20 mg and LIVALO 4 mg vs. pravastatin 40 mg. Mean treatment differences (95% CI) were 9% (6%, 12%), 10% (7%, 13%) and 10% (7%, 13%), respectively.

Table 7. Response by Dose of LIVALO and Pravastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 1 mg daily	207	-31	-25	-22	-13	1	-29
LIVALO 2 mg daily	224	-39	-31	-27	-15	2	-36
LIVALO 4 mg daily	210	-44	-37	-31	-22	4	-41
Pravastatin 10 mg daily	103	-22	-17	-15	-5	0	-20
Pravastatin 20 mg daily	96	-29	-22	-21	-11	-1	-27
Pravastatin 40 mg daily	102	-34	-28	-24	-15	1	-32
Pravastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with simvastatin in patients with ≥ 2 risk factors for coronary heart disease (NK-104-304): LIVALO was compared with the HMG-CoA reductase inhibitor simvastatin in a randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 351 patients with primary hyperlipidemia or mixed dyslipidemia with ≥2 risk factors for coronary heart disease. After a 6- to 8-week wash-out/dietary lead-in period, patients were randomized to a 12-week treatment with either LIVALO or simvastatin (Table 8). Non-inferiority of LIVALO to simvastatin was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

Lipid results are shown in Table 8. LIVALO 4 mg was non-inferior to simvastatin 40 mg for percent change from baseline to endpoint in LDL-C. The mean treatment difference (95% CI) was 0% (-2%, 3%).

Table 8. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hyperlipidemia or Mixed Dyslipidemia with ≥2 Risk Factors for Coronary Heart Disease (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 4 mg daily	233	-44	-34	-31	-20	7	-40
Simvastatin 40 mg daily	118	-44	-34	-31	-15	5	-39
Simvastatin 80 mg daily	----------Not Studied----------						

Active-controlled study with atorvastatin in patients with type II diabetes mellitus (NK-104-305): LIVALO was compared with the HMG-CoA reductase inhibitor atorvastatin in a randomized, multicenter, double-blind, double-dummy, parallel group, active-controlled, non-inferiority Phase 3 study of 410 subjects with type II diabetes mellitus and combined dyslipidemia. Patients entered a 6- to 8-week washout/dietary lead-in period and were randomized to a once daily dose of LIVALO or atorvastatin for 12 weeks. Non-inferiority of LIVALO was considered to be demonstrated if the lower bound of the 95% CI for the mean treatment difference was greater than -6% for the mean percent change in LDL-C.

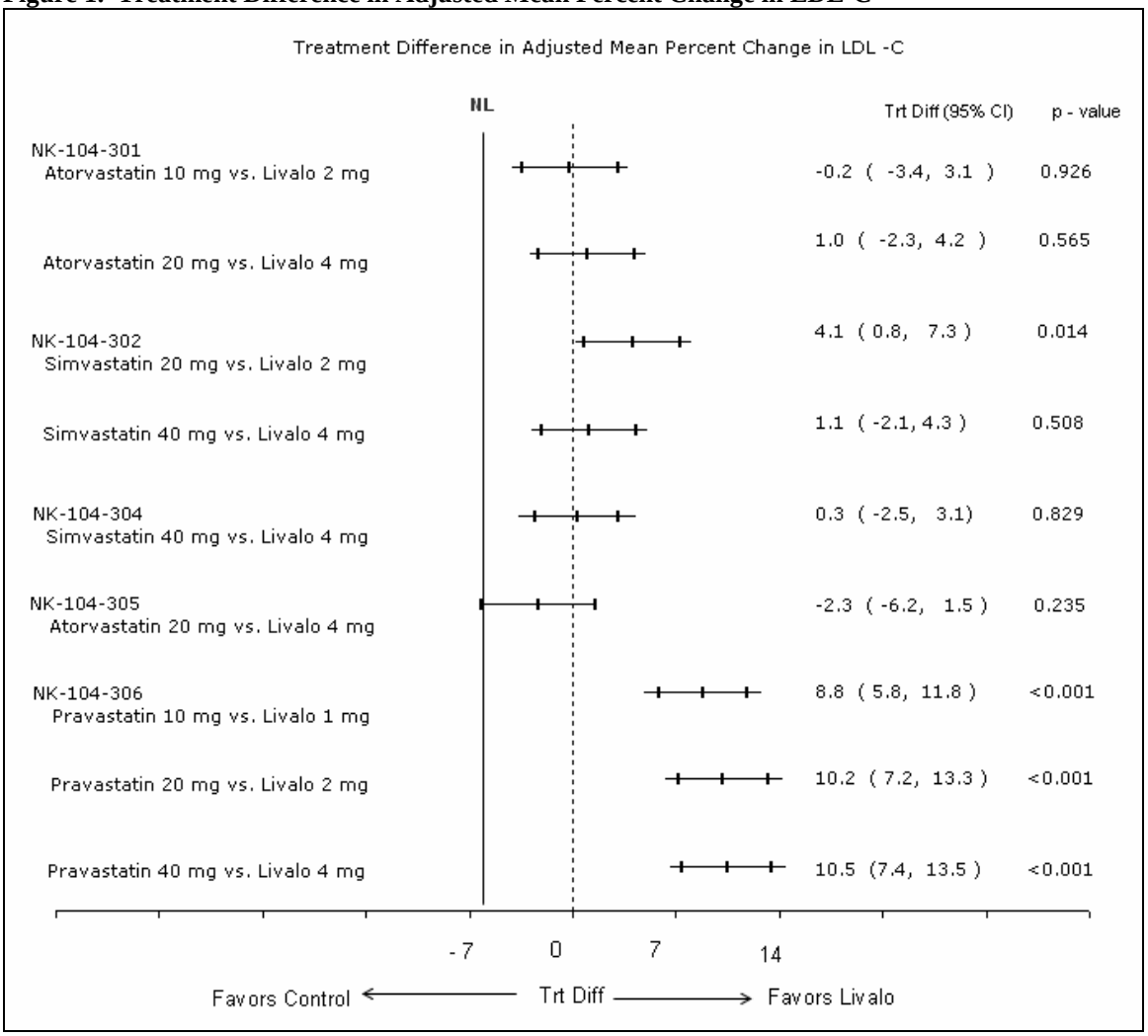
Lipid results are shown in Table 9. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit so that the non-inferiority objective was not achieved.

Table 9. Response by Dose of LIVALO and Atorvastatin in Patients with Type II Diabetes Mellitus and Combined Dyslipidemia (Mean % Change from Baseline at Week 12)

Treatment	N	LDL-C	Apo-B	TC	TG	HDL-C	non-HDL-C
LIVALO 4 mg daily	274	-41	-32	-28	-20	7	-36
Atorvastatin 20 mg daily	136	-43	-34	-32	-27	8	-40
Atorvastatin 40 mg daily	----------Not Studied----------						
Atorvastatin 80 mg daily	----------Not Studied----------						

The treatment differences in efficacy in LDL-C change from baseline between LIVALO and active controls in the Phase 3 studies are summarized in Figure 1.

Figure 1. Treatment Difference in Adjusted Mean Percent Change in LDL-C



NL=non-inferiority limit.

16 HOW SUPPLIED/STORAGE AND HANDLING

LIVALO tablets for oral administration are provided as white, film-coated tablets that contain 1 mg, 2 mg, or 4 mg of pitavastatin. Each tablet has “KC” debossed on one side and a code number specific to the tablet strength on the other.

Packaging
LIVALO (pitavastatin) Tablets are supplied as;

- NDC 0002-4770-90 : 1 mg. Round white film-coated tablet debossed “KC” on one face and “1” on the reverse; HDPE bottles of 90 tablets
- NDC 0002-4771-90 : 2 mg. Round white film-coated tablet debossed “KC” on one face and “2” on the reverse; HDPE bottles of 90 tablets
- NDC 0002-4772-90 : 4 mg. Round white film-coated tablet debossed “KC” on one face and “4” on the reverse; HDPE bottles of 90 tablets

Storage
Store at room temperature between 15°C and 30°C (59° to 86° F) [see USP]. Protect from light.

17 PATIENT COUNSELING INFORMATION

The patient should be informed of the following:

17.1 Dosing Time
LIVALO can be taken at any time of the day with or without food.

17.2 Muscle Pain
Patients should be advised to promptly notify their physician of any unexplained muscle pain, tenderness, or weakness. They should discuss all medication, both prescription and over the counter, with their physician.

17.3 Pregnancy
Women of childbearing age should use an effective method of birth control to prevent pregnancy while using LIVALO. Discuss future pregnancy plans with your healthcare professional, and discuss when to stop LIVALO if you are trying to conceive. If you are pregnant, stop taking LIVALO and call your healthcare professional.

17.4 Breastfeeding
Women who are breastfeeding should not use LIVALO. If you have a lipid disorder and are breastfeeding, stop taking LIVALO and consult with your healthcare professional.

17.5 Liver Enzymes
It is recommended that liver enzyme ~~s~~ tests be checked before ~~and at 12 weeks following both~~ the initiation of LIVALO ~~therapy and any elevation of dose,~~ and if signs or symptoms of liver injury occur. ~~periodically (e.g., semiannually) thereafter.~~ All patients treated with LIVALO should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

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and Lilly USA, LLC. Indianapolis, IN 46285 USA
To request additional information or if you have questions concerning LIVALO please phone Kowa Pharmaceuticals America, Inc. at 877-8-LIVALO (877-854-8256) or fax your inquiry to 800-689-0244

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022363Orig1s008, 009

MEDICAL REVIEW(S)

Clinical Review for Statin Class Labeling Changes

February 15, 2012
Amy G. Egan, M.D., M.P.H.

On August 11, 2011 the Division of Metabolism and Endocrinology Products (DMEP) issued supplement request letters to the sponsors of all HMG-CoA reductase inhibitor (statin) drugs requesting changes to the labeling so as to furnish adequate information for the safe and effective use of their statin. These labeling changes were based on FDA's comprehensive review of the statin class of drugs, including clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration. This review will serve to summarize the safety issues and the sources and reviews of the data.

1. Liver enzyme abnormalities – TSI #57

On March 19, 2007 DMEP opened Tracked Safety Issue (TSI) #57 to evaluate hepatotoxicity associated with the statin class of drugs. This was based on articles in the published literature which suggested that FDA should re-evaluate current recommendations in statin labeling for routine periodic monitoring of liver enzyme tests.

In March 2008, DMEP issued Information Request letters to the statin sponsors requesting the following:

a. Does <<APPLICANT>> have an opinion or recommendation regarding the utility of baseline and/or periodic monitoring of serum aminotransferase activity prior to and/or during treatment with <<STATIN>>? Please address this question for subjects with normal liver function and for those with asymptomatic liver disease (e.g., NAFLD, hepatitis C).
b. Upon what clinical evidence or other consideration are these opinions or recommendations based?
c. Please provide the number of phase 2 and 3 trials conducted with <<STATIN>> for which you have access to the raw data.

The table below summarizes the sponsors' responses to the first question:

Table 10. Overview of Industry responses to FDA questions on hepatotoxicity of statins			
Sponsor	Product	Text suggests interest in withdrawal of monitoring	caveats
Andrx	Lovastatin ER	No	none
AstraZeneca	rosuvastatin	Yes	none
Bristol-Myers Squibb	pravastatin	N/A	No text to delete
Merck	lovastatin	No	None
Merck	simvastatin	No	None
Novartis	fluvastatin	No	None
Pfizer	atorvastatin	Yes	10 mg dose only

In general, most sponsors agreed that liver enzyme testing prior to initiation of statin therapy was appropriate, but acknowledged that there appeared to be limited utility to routine liver biochemistry monitoring during treatment. One sponsor commented on the recommendations of the Liver Expert Panel convened by the National Lipid Association which stated that "because there is no evidence that a relation exists between elevated serum aminotransferase levels and significant liver injury, or that routine monitoring of liver biochemistries will identify individuals likely to develop rare cases of idiosyncratic liver failure, the requirement for routine liver biochemistry monitoring in patients receiving any of the currently marketed statin therapies should be re examined." Another sponsor noted that "nearly 50% of hyperlipidemic patients have coexisting non-alcoholic fatty liver disease (NAFLD) and it is well known that LFT levels fluctuate in NAFLD."

In conjunction with the request to statin sponsors, DMEP requested that the Office of Surveillance and Epidemiology (OSE) conduct a review to characterize the risk of clinically serious hepatotoxicity in association with statins and assist in a determination if the statin class labeling for liver enzyme monitoring should be retained, revised, or removed. OSE had conducted 5 postmarket reviews of statins and hepatotoxicity between 2000 and 2009. Those reviews had consistently noted that reporting of statin-associated serious liver injury to AERS was extremely low (reporting rate of ≤2 per one million patient-years).

The OSE review of AERS was completed May 13, 2011. The review focused on cases of severe liver injury, defined as a 4 (severe liver injury) or a 5 (death or liver transplant) using the Drug Induced Liver Injury Network (DILIN) liver injury severity scale. Cases meeting those criteria were further assessed for causality. Seventy-five cases (27 with a severity score of 4 and 48 with a severity score of 5 [37 deaths and 11 liver transplants]) were assessed for causality, 30 of which (14 deaths, 7 liver transplantations, and 9 severe liver injury) were assessed as possibly (25-49% likelihood) or probably (50-74% likelihood) associated with

statin therapy. No cases were assessed as highly likely (75-95% likelihood) or definitely (>95% likelihood) associated with statin therapy. OSE noted that "despite rising use of statins as a class since the late 1990s, there has not been a detectable uptick in the annual rates of fatal (deaths or liver transplant) or severe liver injury possibly or probably causally associated cases." The cases are summarized in the table below:

Table 6. Characteristics of U.S. AERS Cases With A Liver Injury Severity Score of 4 (Severe) or 5 (Death or Transplant) and Causally Associated* With Statin Therapy. Source: AERS, marketing through January 1, 2009)

Liver Injury Severity Score	**5 (Death)**	**5 (Transplant)**	**4 (Severe)**
# of Cases	14	7	9
Median Age in Years (range)	66 (51-89)	48 (40-71)	58 (47-71)
Percent Female	79% (11/14)	71% (5/7)	67% (6/9)
Statin at the Time of Event Median Daily Dose in mg (range [n])			
Atorvastatin	4 -- (10, 10 [n=2])	3 10 (10-20 [n=3])	4 10 (10-20 [n=3])
Cerivastatin	--	--	--
Fluvastatin	--	--	1 – (20 [n=1])
Lovastatin	1 -- (20 [n=1])	1 -- (-- [n=0])	--
Pravastatin	3 -- (20, 40 [n=2])	--	1 – (10 [n=1])
Rosuvastatin	--	--	--
Simvastatin	6 20 (10-40 [n=5])	3 20 (20-40 [n=3])	3 – (40 [n=1])
Time to Onset in Months,** Median (range)	2.5 (3 wk – 12 mo)	1.5 (2.4 wk - 6 mo)	2 (5 wk – 8 mo)
Peak Serum Total Bilirubin Level in mg/dL, Median (range [n])	23 (2.9-51 [n=12])	27 (22-32 [n=4])	10 (1.2-25 [n=9])
Peak Serum ALT Level in units/L, Median (range[n]) reference range: 6-41 units/L	1,127 (148-4,300 [n=10])	2,912 (2,037-13,531[n=4])	1,319 (538-3,000 [n=9])
Peak Serum AST Level in units/L, Median (range[n]) reference range: 9-34 units/L	1,497 (81-7,200 [n=11])	2,294 (1,755-6,815 [n=4])	1,260 (853-3,000 [n=9])
Peak Serum ALP Level in units/L, Median (range[n]) reference range: 37-116 units/L	206 (155-623 [n=9])	-- (290, 602 [n=2])	307 (131-800 [n=4])

*Defined as probably associated (supported by the evidence as implicating the drug but not definite or highly likely) or possibly associated (causality is not supported by the preponderance of evidence, but one cannot definitively exclude the possibility)

**Time to onset defined as the interval between exposure time or time after dose increased to reported liver injury event

OSE also looked at cases from the DILIN and Acute Liver Failure Study Group (ALFSG), organizations which have been systematically submitting reports to FDA of drug associated liver injury referred to their respective liver injury outcome studies. For statin associated liver injury, DILIN has submitted 25 reports to FDA as of January 1, 2011, twelve of which resulted in an outcome of hospitalization. In the ALFSG database, there were 9 reports of drug-induced liver injury (DILI) associated with statin therapy. OSE cited a 2010 article from

ALFSG that included 133 prospectively identified cases of idiopathic DILI resulting in acute liver failure. Fifteen patients were taking statins and in 6 of these 15 individuals a statin was identified as the only potential DILI agent. The authors noted that statin hepatotoxicity is "generally benign" and the identification of these 6 cases represents a "provocative observation".

Using the AERS and drug utilization databases, reporting rates were calculated for U.S. statin cases associated with liver injury and an outcome of death or liver transplant, from the time of initial marketing approval through January 1, 2009. It should be noted that reporting rates are subject to secular reporting trends which normally preclude generation of reporting rates between products with initial marketing dates greater than 2-4 years apart. Despite the limitations of the analysis, it appears that reporting levels for serious liver injury in association with currently marketed statins are generally similar.

Table 9. Number of U.S. Statin Cases Associated with Liver Injury and an Outcome of Death or Liver Transplant (Severity Score 5). Initial Marketing Approval Through January 1, 2009

Generic Name (Brand)	Number of cases	Total Number of Prescriptions (TRxs) Dispensed by U.S. Retail Pharmacies, 1991-2008‡ (in millions)	Observed reporting rate as cases per (b) (4)
Lovastatin (Mevacor, Advicor, Altocor)	23		(b) (4)
Pravastatin (Pravachol)	11		
Simvastatin (Zocor, Vytorin, Simcor)	51		
Fluvastatin (Lescol)	4		
Atorvastatin (Lipitor)	64		
Rosuvastatin (Crestor)	3		
Total	**156**		

OSE also reviewed current monitoring guidelines including the National Lipid Association's Liver Expert Panel, which state:

> *The Liver Expert Panel does not believe that the available scientific evidence supports the routine monitoring of liver biochemistries in asymptomatic patients receiving statins. The Panel makes this recommendation because (1) irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature, and (2) no data exist to show that routine monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. In the view of the Panel, routine monitoring will instead identify patients with isolated*

increased aminotransferase levels, which could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events.

OSE further noted that the NLA's Statin Safety Task Force had a slightly divergent opinion and made the following recommendation:

Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, (b) (4) *However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.*

The OSE review concluded:

Serious, hepatocellular DILI can be caused by statins. Although the routine monitoring of serum ALT and other markers for liver injury is vital for drug development, it does not appear to be useful in a post marketing, non study, ambulatory setting to routinely detect and prevent serious liver injury in association with statins. In place of current recommendations for serum enzyme monitoring, labeling for statins should focus on an alert to identify serious liver injury and clinical symptoms of liver injury, interruption of therapy, physician interactions, and emphasize the importance of appropriate diagnostic work up.

OSE further recommended:

It is justified that the recommendation to (b) (4) *be removed.*

Based on these recommendations, DMEP requested the following changes to statin labeling:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, under **WARNINGS AND PRECAUTIONS**:

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

Under **5 WARNINGS AND PRECAUTIONS, Liver Dysfunction:**

It is recommended that liver enzyme tests be performed before the initiation of <<STATIN>> (b) (4) (b) (4)

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including <<STATIN>>. If serious liver injury with clinical symptoms and/or

hyperbilirubinemia or jaundice occurs during treatment with <<STATIN>>, promptly interrupt therapy. If an alternate etiology is not found do not restart <<STATIN>>.

Under **6 ADVERSE REACTIONS, Post-Marketing Experience:**

(b) (4)

Under **17 PATIENT COUNSELING INFORMATION, Liver Enzymes:**

It is recommended that liver enzyme tests be (b) (4) before the initiation of <<STATIN>> and if signs or symptoms of liver injury occur. All patients treated with <<STATIN>> should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

To the Patient Package Insert, under **"What are the possible side effects of <<STATIN>>? Liver problems":**

Your doctor should do blood tests to check your liver before you start taking <<STATIN>> and if you have symptoms of liver problems while you take <<STATIN>>. 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 colored urine
- yellowing of your skin or the whites of your eyes

2. Cognitive effects – TSI #772

On September 2, 2009 DMEP opened TSI #772 to evaluate the effect of statins on cognition. This was based on a complaint received from Joe Graedon of the People's Pharmacy, and an unpublished study by Duane Graveline, M.D., M.P.H. and Jay S. Cohen, M.D. entitled "Lipitor-associated memory loss: analysis of 662 cases of cognitive damage", as well as other articles from the published literature.

In attempting to assess this risk, DMEP looked initially at pre-clinical data. Several of the statin drug sponsors had performed pre-clinical cognition studies; however, those studies only address the issue of dementia syndromes, and are less helpful in addressing the issue of acute confusional states or memory impairment. Therefore, it was determined that there was no value added to re-assessing the pre-clinical data.

DMEP sent information request letters to those statin sponsors who had conducted clinical trials in which some form of neurocognitive assessment had been conducted as part of the study protocol. Those trials included: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Heart Protection Study (HPS), and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

The findings were as follows:

- **PROSPER:** Subjects were screened with a Mini Mental Status Exam (MMSE) and excluded if their score was <24. Cognitive function was assessed in all 5,804 participants at six different time points during the study.

Four neuropsychological tests were performed, two of which tested executive function (attention and speed) and two of which tested memory (immediate and delayed). All tests showed a significant decline over time (3-year follow-up); however, there was no difference between treatment groups, pravastatin 40 mg versus placebo.

- **HPS:** A modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants during their final follow-up, either face-to-face in the clinic or over the telephone. Data were available on 8086/10269 (79%) of simvastatin-allocated subjects and 7834/10267 (76%) of placebo-allocated subjects. No significant differences were observed between the treatment groups in the percentages of participants classified as cognitively impaired (defined as a TICS-m score below 22 out of 39), either overall (23.7% simvastatin 40 mg-allocated vs. 24.2% placebo-allocated) or in subgroups defined with respect to their age at study entry (<65 years: 17.1% vs. 17.8%; 65-69 years: 25.8% vs. 25.4%; 70-80 years: 34.6% vs. 36.2%) or their previous history of cerebrovascular disease (no prior stroke: 22.8% vs. 23.3%; prior stroke: 31.9% vs. 33.3%). Nor was there any significant difference between the groups in mean TICS-m score (24.08 vs. 24.06). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0.3%] vs. 31 [0.3%]).

  There was a slightly higher frequency of cases of Alzheimer's disease or Alzheimer's type dementia in patients on simvastatin (n=6) compared to placebo (n=3). When looking at all patients with potential diagnoses of dementia including Alzheimer's disease, confusion, disorientation, dementia or cognitive impairment, there was no difference in the frequency of patients in the simvastatin group (n=35; 0.34%) compared to placebo (n=33; 0.32%).
- **SEARCH:** Assessment of cognitive function, using the TICS-m score, was a tertiary endpoint for the folate arm of the trial. It was performed in 8891 subjects – 4473 on simvastatin 80 mg and 4418 on simvastatin 20 mg – at the final visit. There was no difference in mean TICS-m score between treatment groups (24.3 ± 4.1 for simvastatin 80 mg vs. 24.3 ± 4.3 for simvastatin 20 mg), and no difference in percentages of patients with scores <20, ≥20, <22, ≥22, <25, ≥25, <30, ≥30 between treatment groups. The TICS-m score reflects memorizing ability in large part. Verbal fluency scores also did not differ among patients allocated to simvastatin 80 mg and simvastatin 20 mg. Hearing thresholds were assessed at final follow-up and did not differ between the simvastatin groups.

  The incidence of memory loss attributed to study treatment was 17 (0.3%) in patients allocated to simvastatin 80 mg, and 8 (0.1%) in patients allocated to simvastatin 20 mg.

It should also be noted that while no formal neurocognitive assessment was performed in the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), there was noted a

statistically significant increase in the reported adverse event of confusional state in subjects allocated to rosuvastatin 20 mg (n=8 [0.2%]) versus subjects allocated to placebo (n=4 [0.04%]).

DMEP was aware of a Phase III efficacy study of atorvastatin that had been conducted in patients with mild to moderate Alzheimer's Disease. The clinical study report for this study (Study A2581078) was requested from the sponsor and consulted to the Division of Neurology Products (DNP) for review. DNP's findings were as follows:

> *The results of Study A2581078, an adequately-designed Phase III efficacy and safety study of atorvastatin (Lipitor) in patients with mild to moderate Probable Alzheimer's Disease, provide no evidence that the administration of Lipitor results in cognitive worsening in this population; neither was there any evidence of a worsening of global function in those treated with atorvastatin in this study.*

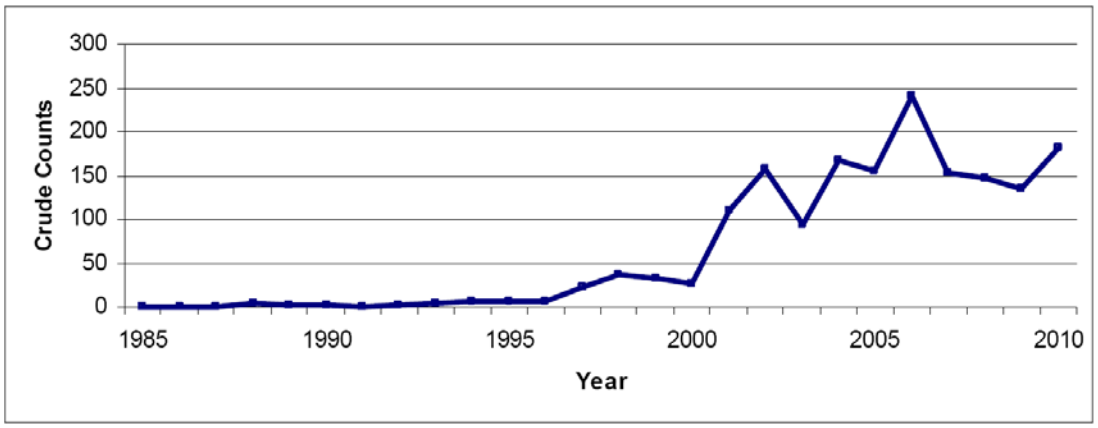
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to a consumer report of transient global amnesia (TGA) with atorvastatin. At that time, OSE determined that the calculated reporting rate for statin-associated TGA (0.12-0.55 per 100,000 patient years) was well below the background incidence rate (3.4-32/100,000 population per year). As memory loss was already included in the statin labels, no labeling change was recommended at that time.

OSE's updated review of AERS focused on reports of serious cases of memory impairment, using the following High Level Terms (HLT):

- Mental Impairment (excluding dementia and memory loss)
- Memory Loss (excluding dementia)
- Amnestic Symptoms
- Confusion and Disorientation

Through January 1, 2011 there were 1,698 U.S. serious reports (crude counts) in AERS.

Figure 1. Number of U.S. Serious Statin* Reports (Crude Counts) Associated with Cognitive Change†, by Year Received. Source: AERS, Initial Marketing Approval Through January 1, 2011 (n=1,698)



*Includes single ingredient and combination statin products approved by FDA.
†Reports identified in AERS using four HLTs: Mental Impairment (excluding dementia & memory loss), Memory Loss (excluding dementia), Amnestic Symptoms, and Confusion and Disorientation

Further case review was limited to 182 reports received by FDA in 2010. Of those reports, 57 unique cases described transient cognitive change as the primary adverse event. Sixty nine percent (n=125) of the cases were excluded because they reported multiple events such as rhabdomyolysis, renal failure, and confusion (n=81), were duplicates (n=18), hearsay (n=3), reported by attorneys (n=5), or solicited reports (n=16).

Characteristics of the 57 cases included:

- Age: median of 62 years (30-85)
- Sex: 62% male
- Exposure time: median of 3 years (1 month-12 years)

The literature review included case series of transient cognitive impairment associated with statin use, as well as observational studies on the association between statin use and the incidence of dementia. The observational evidence was summarized based on a meta-analysis by Zhou and colleagues:

> *After conducting a systematic review, the authors identified four cohort studies and three case control studies which examined the association between statin use and dementia. The average observation period ranged from three to nine years. Three case control studies suggested statin use may lower the incidence of dementia; while the remaining four cohort studies failed to demonstrate an association between statin use and incident dementia. A pooled analysis also failed to demonstrate an association between statin use and incident dementia.*

OSE further noted:

Results from three prospective cohort studies published within the last year provide similar conflicting results. Analyses of Baltimore Longitudinal Study of Aging and the Ginkgo Evaluation of Memory Study suggested that statin use is associated with a lower risk of dementia. A nested case control study in the Neurological Disorders in Central Spain cohort failed to detect an association between statin use and cross sectional performance on a neuropsychological test battery.

Table 5. Observational Studies Summary: Statin Use and Cognition

Author (Publication Date)	Study Design	Total Sample Size (% Exposed to Statins)	Outcome	Key Result
Zhou (2007)	Meta-Analysis – Observational Studies	10523 (12%)	Incident Dementia	Adjusted OR=0.77 (95%: 0.45-1.30)
Beydoun (2010)	Cohort Study	1604 (7%)	Incident Dementia	Adjusted HR=0.21 (95%: 0.09-0.48)
Betterman (2011)	Cohort Study	3069 (25%)	Incident Dementia	Adjusted HR=0.79 (95%: 0.65-0.96)
Benito-Leon (2010)	Nested Case-Control	548 (25%)	Neuropsychological Test Performance	No treatment effect observed in any test neuropsychological test administered (global cognition, verbal fluency, psychomotor speed, confrontational naming, verbal memory, logical memory)

OSE concluded:

The postmarket statin reports associated with transient cognitive change generally describe individuals over the age of 50 years who experience notable (sometimes described as "dramatic"), but ill defined memory loss or impairment (e.g., "lost my mind") that is reversible upon discontinuation of statin therapy. The statin exposure time to onset of the event is highly variable (1 day to years). These cases do not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease.

Like the previous (2002) OSE review, the analyzed data in this review did not reveal any discernible dose event or age (the reported age at the time of event is similar to the age of the population using statins) trends or effects between statins and other drugs; few reports described neurologic follow-up or standardized testing results. Findings from this review (and the 2002 OSE review) are also similar to patient survey results recently published by the University of California San Diego (UCSD) Statin Effects Study investigators. Cognitive issues were reported for all statins, with atorvastatin and simvastatin most frequently reported. The time to onset was variable (1 day to 10 years). Ninety percent reported symptom improvement after the statin was discontinued. Complete recovery time varied from 1 day to several years (median time to first noted improvement was 2.5 weeks). Of 29 participants who underwent rechallenge, 19 reported recurrence of events.

An analysis of the epidemiologic evidence and clinical trials did not provide evidence that chronic statin use is associated with cognitive decline at the population level. Two studies demonstrated that exposure to statins for up to six months may prevent the acquisition of a practice effect on select neuropsychological measures. However, the clinical significance of an absent practice effect in the context of normal cognitive performance is questionable. Furthermore, no study systematically assessed patients who experienced statin associated cognitive impairment during both dechallenge and rechallenge. Such systematic studies would provide additional evidence to support a causal association and better characterize the clinical phenotype.

OSE recommended that DMEP consider statin class labeling that would characterize the nature of the cognitive changes. In response, DMEP requested that the following be added to the **Adverse Reactions, Postmarketing Experience** sub-section of all statin labels:

> 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).

(b) (4)

[redacted]

3. Drug-drug interaction with protease inhibitors – TSI #756

On July 23, 2009 TSI #756 was opened to examine the drug-drug interaction between statins and protease inhibitors.

In July 2009, the sponsor for rosuvastatin (CRESTOR) submitted a prior approval supplement (PAS) proposing to include information on increased rosuvastatin exposure when CRESTOR was co-administered with the combinations of protease inhibitors tipranavir/ritonavir, atazanavir/ritonavir or fosamprenavir/ritonavir, based on studies in the published literature. Previous CRESTOR labeling had noted a DDI with lopinavir/ritonavir (KALETRA) resulting in a dose cap of 10 mg of CRESTOR when co-administered with KALETRA.

In a January 2010 review of the PAS, it was noted that there were inconsistencies between the statin labels and the protease inhibitor labels regarding recommendations for co-administration of these products. It was therefore determined that the Office of Clinical Pharmacology (OCP) would review the relevant data on DDIs between statins and HIV and HCV protease inhibitors.

On August 3, 2011 OCP completed its review of the cross labeling initiative for drug interaction updates between protease inhibitors and statins. DMEP was requested to make changes to the atorvastatin and pravastatin labels to provide the results of DDI studies conducted with certain protease inhibitors, and in the case of atorvastatin, to provide dose caps where appropriate, based on the results of the following DDI studies:

- Tipranavir/ritonavir increases atorvastatin AUC and C_{max} 9.4-fold and 8.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and "Avoid atorvastatin" was recommended for labeling.
- Telaprevir increases atorvastatin AUC and C_{max} 7.88-fold and 10.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and "Avoid atorvastatin" was recommended for labeling.
- Darunavir/ritonavir increases atorvastatin AUC and C_{max} 3.4-fold and 2.25-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.
- Fosamprenavir increases atorvastatin AUC and C_{max} 2.3-fold and 4.04-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.

(b) (4)

(b) (4)

Based on OCP's recommendation, DMEP requested the following changes to the atorvastatin and pravastatin labels:

Atorvastatin:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS,** Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

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

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	~~Do not exceed 10 mg atorvastatin daily~~ Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (~~ritonavir plus~~ saquinavir plus ritonavir, ~~lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir))	~~Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used.~~ Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

Under **DOSAGE AND ADMINISTRATION**:

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors ~~a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir~~

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the Hepatitis C protease inhibitor (telaprevir), therapy ~~should be limited to~~ with LIPITOR ~~10 mg once daily~~ should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir ~~for doses of~~ therapy with LIPITOR should be limited to ~~exceeding~~ 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed. In patients with HIV taking nelfinavir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.

Under **5 WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle:**

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, ~~immunosuppressive drugs~~, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.

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

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

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	~~Do not exceed 10 mg atorvastatin daily~~ Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (~~ritonavir plus~~ saquinavir plus ritonavir*, or ~~lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	~~Caution when exceeding doses > 20mg atorvastatin daily. The lowest dose necessary should be used.~~ Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary

Under **DRUG INTERACTIONS, Combination of Protease Inhibitors, 7.1 Strong Inhibitors of CYP 3A4:**

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR ~~40 mg~~ with several combinations of HIV protease inhibitors, as well as with the Hepatitis C protease inhibitor telaprevir, ~~ritonavir plus saquinavir (400 mg twice daily) or LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily)~~ compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor~~s~~ tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the

dose of LIPITOR should not exceed 20 mg and should be used with caution. ~~caution should be used when the LIPITOR dose exceeds 20 mg~~.

Under **12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin:**

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑9.4 fold	↑8.6 fold
Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑74%	↑2.2-fold
Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑2.3-fold	↑4.04-fold
Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑2.53-fold	↑2.84-fold
Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑3.4-fold	↑2.25-fold
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑7.88-fold	↑10.6-fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
#, ‡ Ritonavir Saquinavir 400 mg BID/saquinavir ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑3.9-fold	↑4.3-fold

‡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.

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
~~#Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days~~	~~20 mg QD for 4 days~~	~~↑ 5.9 fold~~	~~↑ 4.7 fold~~

Under **12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs:**

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in Cmax
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓27%	↓18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

Pravastatin:

Under **12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 3: Effect of Coadministered Drugs on the Pharmacokinetics of Pravastatin:**

Coadministered Drug and Dosing Regimen	Pravastatin		
	Dose (mg)	Change in AUC	Change in C_{max}
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days	40 mg single dose	↑81%	↑63%
Kaletra 400 mg/100 mg BID for 14 days	20 mg OD for 4 days	↑33%	↑26%

Under **12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 4: Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs**

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C_{max}
20 mg OD for 4 days	Kaletra 400 mg/100 mg BID for 14 days	No change	No change

A December 6, 2011 OCP review of DDI's with lovastatin noted that available data support a contraindication with strong CYP3A4 inhibitors, such as the HIV protease inhibitors. The data were summarized as follows:

- *According to the Guidance for Industry Drug Interaction Studies, lovastatin is listed as one of the sensitive in vivo CYP3A4 substrates. Therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure because lovastatin is extensively metabolized by CYP3A4 isozyme.*
- *Literature survey indicates that itraconazole increases lovastatin exposure up to 15- to 20-fold and the drug interaction seems to result in rhabdomyolysis. Itraconazole is the representative strong CYP3A4 inhibitor and therefore, the effect of itraconazole on lovastatin exposure can be extrapolated to other strong CYP3A4 inhibitors listed in the Guidance as well as the FDA website.*

- *Strong CYP3A4 inhibitors are contraindicated for simvastatin because of the significant drug interaction and its potential for the increased risk on the rhabdomyolysis. Physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Meanwhile, itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Therefore, concomitant use of lovastatin with HIV protease inhibitors, as well as the HCV protease inhibitors boceprevir and telaprevir, will be contraindicated.

Lovastatin:

Under **CONTRAINDICATIONS:**

Concomitant administration with strong CYP3A4 inhibitors, e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** **Strong inhibitors of CYP3A4:**

Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a strong inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.~~ Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**:**

Interacting Agents	**Prescribing Recommendations**
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	~~Avoid~~ Contraindicated with lovastatin

Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., ~~below~~ itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, bocprevir, telaprevir, nefazodone), and erythromycin, and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin.

~~**Itraconazole**~~
~~**Ketoconazole**~~
~~**Erythromycin**~~
~~**Clarithromycin**~~
~~**Telithromycin**~~
~~**HIV protease inhibitors**~~
~~**Nefazodone**~~
~~**Large quantities of grapefruit juice (>1 quart daily)**~~

4. Increases in HbA1c and fasting plasma glucose – TSI #891

On April 8, 2010 TSI #891 was opened to evaluate the effect of statins on increases in HbA1c and fasting plasma glucose. This was based on findings from the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-exposed subjects compared to placebo-exposed subjects. High-dose atorvastatin had previously been associated with worsening glycemic control in the PROVE-IT TIMI 22 substudy.

Several articles from the published literature were also considered, including:

- Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet.*2010;375:735-742
- Sukhija R et al. Effect of Statins on Fasting Plasma Glucose in Diabetic and Nondiabetic Patients. *Journal of Investigative Medicine.*2009;57(3): 495-499
- Rajpathak SN et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. *Diabetes Care.*2009;32:1924-1929
- Koh KK et al. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. *JACC.*2010;55(12):1209-1216
- Thongtang N et al. Effects of Maximal Atorvastatin and Rosuvastatin Treatment on Markers of Glucose Homeostasis and Inflammation. *Am J Cardiol.*2011;107:387-392
- Kostapanos MS et al. Do Statins Beneficially or Adversely Affect Glucose Homeostasis? *Current Vascular Pharmacology.*2010;8:612-631
- Mills EJ et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170255 patients from 76 randomized trials. *Q J Med.*2011;104:109-124

- Culver AL et al. Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative. *Arch Intern Med*. Published online January 9, 2012.

The Sattar meta-analysis, which looked at 13 statin trials with 91,140 participants, reported that "statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity (I^2=11%) between trials."

The Rajpathak meta-analysis, which looked at 6 statin trials with 57,593 participants, reported a "small increase in diabetes risk" (relative risk [RR] 1.13; 95% CI 1.03-1.23), with "no evidence of heterogeneity across trials".

The Mills meta-analysis, which looked at 76 randomized clinical trials (RCTs) with 170,255 participants, reported that 17 RCTs reported on increased risk of development of incident diabetes (Odds ratio [OR] 1.09; 95% CI 1.02-1.17, p=0.001, I^2=11%).

Culver et al looked at postmenopausal women participating in the Women's Health Initiative (WHI) to investigate whether the incidence of new-onset diabetes mellitus is associated with statin use. The study involved 153,840 women. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83); the multivariate-adjusted HR was 1.48; 95% CI, 1.38-1.59. The association was observed for all types of statin medications.

At the time of approval of the JUPITER supplement, the following labeling was required for CRESTOR:

> **5.5 Endocrine Effects**
> Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

The data for an effect of statins on incident diabetes, and increases in HbA1c and/or fasting plasma glucose seem to indicate a class effect; however, given the limitations of epidemiological data, and the findings from the West of Scotland Coronary Prevention Study (WOSCOPS) clinical trial, which suggested that pravastatin may decrease the incidence of diabetes by 30%, the division did not seek a labeling change for pravastatin.

Therefore, based on clinical trial data, epidemiological data, and the published literature, the following labeling change was requested for all statins except pravastatin:

> **5.X Endocrine Function:**
> Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including <<STATIN>>.

5. Drug-drug interaction with ranolazine – TSI #988

TSI #988 was opened by the Division of Cardiovascular and Renal Products (DCRP) in July 2010 when during routine data monitoring of the AERS database for cases of ranolazine and torsades de pointes, a signal was identified for rhabdomyolysis in patients receiving ranolazine and statins.

Nine cases of drug interaction were related to concomitant use of ranolazine and a statin. Of those nine cases, seven (all male) involved the statin associated adverse events of rhabdomyolysis (6) and myalgia (1). Four of those six patients were stable on long-term statin therapy prior to the initiation of ranolazine. Most cases involved the use of simvastatin.

According to the OCP review:

> *Ranolazine and SV are both cleared via CYP3A metabolism. Hence, concomitant administration of the two may lead to pharmacokinetic DDI. Administration of ranolazine (1000 mg twice daily) with SV (80 mg once daily) resulted in a ~2-fold increase in C_{max} and ~1.5-fold increase in AUC of SV and SVA, at steady state. Increased systemic exposure to SV and SVA has been associated with increased risk of myopathy and rhabdomyolysis. The 80 mg dose of SV has been shown to be associated with increased incidence of myopathy and rhabdomyolysis. In addition, there is little gain in effectiveness of the 80 mg over 40 mg dose. The DMEP regulatory briefing held on 6/4/2010 suggested progressive removal of 80 mg dose of simvastatin from the market, leaving 40 mg as the highest available dose. Therefore, given the 2-fold increase in systemic exposure expected on concomitant administration of ranolazine and SV, limiting the dose of SV to 20 mg will avoid exposures similar or greater to that observed with 80 mg.*
>
> *In addition, for other statins which are primarily metabolized by CYP3A (e.g., lovastatin and atorvastatin), concomitant medications which are CYP3A inhibitors are expected to elevate statin exposure, and risk of myopathy. However, at present, definitive data (such as available with simvastatin) is not available for other statins, in order to recommend dose-adjustments.*

On June 8, 2011, in conjunction with the approval of new dosing restrictions with the 80 mg dose of simvastatin, DMEP approved a dose cap of simvastatin 20 mg when simvastatin is coadministered with ranolazine.

In addition, the current ranolazine label recommends a dose adjustment of sensitive CYP3A4 substrates such as lovastatin based on the 2-fold simvastatin exposure increase by ranolazine.

Based on the information above, the following recommendations for labeling changes were made:

Mevacor:

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis***:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration.

Under **PRECAUTIONS,** *Other Drug Interactions*:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine.

Altoprev:

Advicor:

6. Myopathy with concomitant administration with colchicine

In June 2010, a Regulatory Briefing was conducted to discuss the increased risk of myopathy, including rhabdomyolysis, associated with the use of simvastatin 80

mg, based on DMEP's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial. In preparation for the briefing, OSE noted an interaction between statins and colchicine resulting in an increased risk of myopathy. Colchicine, a substrate of P-glycoprotein and CYP3A4, carried the following information in its label:

> **5.4 Neuromuscular Toxicity**
> Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

This was based on reports from the literature as summarized in the table below, and adapted from a 2008 OCP review of NDA 22-352 (Colstat [colchicine tablets]).

Lipid Lowering Agents			
HMG-CoA Reductase Inhibitors	Simvastatin: Baker *et al.* (2004); Hsu *et al.* (2002)	Both are CYP3A4 and P-gp substrates; P-gp inhibition by simvastatin	Acute myopathy or rhabdomyolysis (could be attributed to either drug)
	Fluvastatin: Atasoyu *et al.* (2005)	Synergistic myotoxicity *via* PK & PD mechanism; fluvastatin is not a P-gp inhibitor	
	Pravastatin: Alayli *et al.* (2005)	Synergistic myotoxicity *via* PK & PD mechanism; pravastatin is not a P-gp inhibitor	
	Atorvastatin: Tufan *et al.* (2006)	Both are CYP3A4 substrates; P-gp inhibition by atorvastatin	
Fibrates	Gemfibrozil; Atmaca *et al.*, 2002	Synergistic toxic effect of both drugs	
	Fenofibrate & Diltiazem: Sinsawaiwong *et al.*, 1997	Mechanism-based inhibition of CYP3A4 by diltiazem.	

On June 8, 2011, the following changes were approved for the simvastatin-containing drugs:

> **5 WARNINGS AND PRECAUTIONS**
> **5.1 Myopathy/Rhabdomyolysis**
> Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.
>
> **7 DRUG INTERACTIONS**
> **7.7 Colchicine**
> Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

In order to harmonize and update the appropriate statin labels, similar labeling changes were requested for atorvastatin, pravastatin, and fluvastatin. Furthermore, because of physicochemical and pharmacokinetic similarities between lovastatin and simvastatin, similar labeling changes were requested for lovastatin.

7. Myopathy with concomitant administration with fibrates

A National Institutes of Health (NIH) funded trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial, was reviewed by DMEP and discussed at an Advisory Committee meeting on May 19, 2011. ACCORD-Lipid evaluated the occurrence of major adverse cardiovascular events (MACE), a composite of nonfatal heart attack, nonfatal stroke, and cardiovascular death in patients receiving simvastatin plus fenofibrate, compared to simvastatin alone. The trial found that there was no difference in cardiovascular outcomes between the two groups (Hazard Ratio = 0.92; 95% Confidence Interval: 0.79-1.08; p=0.32).

This was the second failed cardiovascular outcome trial for fenofibrate. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (Hazard Ratio = 0.89; 95% Confidence Interval: 0.75-1.05; p=0.04) versus placebo.

The absence to date of proven cardiovascular benefit with fenofibrates must be viewed in the context of observational data showing an increase in the risk of myopathy with fenofibrates, especially when co-administered with a statin. In 2011, OSE conducted a review of observational data on rhabdomyolysis with fenofibrates and gemfibrozil in combination with statins. Their review looked at 3 studies:

- Graham DJ, Staffa JA, Shatin D et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.
- Amend KL, Landon J, Thyagarajan V, Niemcryk S, McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45:1230-1239.
- Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol* 2010;106:1594-1601.

According to the OSE review, the best available evidence suggests that fenofibrate-statin combination is associated with an increased hazard rate for rhabdomyolysis (HR, 3.26, 95% CI, 1.21-8.80) relative to statin monotherapy. There also appears to be a differential risk associated with the gemfibrozil-statin combination therapy versus the fenofibrate-statin combination therapy, with a

numerically higher rate of rhabdomyolysis observed with gemfibrozil-statin combination therapy (HR, 11.93, 95% CI, 3.96-35.93) compared to statin monotherapy.

Most statin labels contain language in the FPI (Warnings and Precautions and Drug Interactions sections) regarding the increased risk of myopathy, including rhabdomyolysis, when statins and fibrates are co-administered. In order to highlight this increased risk, as well as to note the differential risk between gemfibrozil-statin combination therapy and fenofibrate-statin combination therapy, all sponsors of statin drugs with labels in the PLR format (i.e., all except the lovastatin products) were requested to add the following information to the Highlights page. The following language was also provided in the Drug Interactions section of the PI's, depending on the level of risk determined for each statin product:

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

Other Lipid-lowering Medications: Use with other 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 <<STATIN>>.

7.X Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: <<Contraindicated or Avoid>> with <<STATIN>>
Other fibrates: Caution should be used when prescribing with <<STATIN>>

7.X Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of <<STATIN>> with gemfibrozil should be avoided.

7.X Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, <<STATIN>> should be administered with caution when used concomitantly with other fibrates.

8. Myopathy with concomitant administration with lipid-modifying doses of niacin

In March 2010, DMEP approved a labeling revision for simvastatin based on interim results from an ongoing clinical trial - the Heart Protection Study 2 (HPS2) – Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE), a cardiovascular outcome trial being conducted in 20,000 patients with vascular disease from the UK, China and Scandinavia to investigate whether combining niacin with a new drug (laropiprant) that minimizes niacin's flushing effect can reduce the risk of serious heart attacks and strokes among people already taking treatment to lower their LDL-cholesterol. The interim HPS2 – THRIVE results showed that the incidence of myopathy was higher in patients of

Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%) taking 40 mg simvastatin plus cholesterol-modifying doses (≥1 g/day) of a niacin-containing product. The exact mechanism of this drug interaction is not fully understood.

Drug-drug interaction studies report an increase in simvastatin exposure of 41-64% with co-administration of simvastatin and ER niacin. According to OCP, the cause of the observed changes in exposure of simvastatin due to ER niacin is not well established as this is not due to changes in the known pathways (e.g., via CYP3A4 or OATP1B1). Furthermore, a PK study of simvastatin in Chinese subjects showed no significant differences in Chinese and non-Asian subjects in simvastatin C_{max} and $AUC_{0\text{-last}}$, and simvastatin acid $AUC_{0\text{-last}}$ or C_{max}.

The OCP Genomics Group further noted that the SLCO1B1 genotype that has been associated with statin-induced myopathy, is less prevalent in Asian populations than European populations and, therefore, does not seem to explain the higher myopathy risk rates among Chinese subjects in HPS2-THRIVE.

So, it remains unclear if this increased risk of myopathy with statin and niacin co-administration is unique to Chinese subjects, or applies to other Asians and non-Asians as well.

Furthermore, in the AIM-HIGH study, which compared ER-niacin with simvastatin to simvastatin alone in reducing the residual cardiovascular risk in patients with established cardiovascular disease, "there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels".

The lack of clear benefit in conjunction with uncertainty as to the nature of the increased risk of myopathy in patients treated with niacin plus a statin led FDA to believe that this risk needed to be highlighted in statin labeling.

The labeling approved for simvastatin in March 2010 noted that patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.

In June 2011, in conjunction with labeling revisions required based on the Agency's review of the SEARCH trial, this language was modified to note that "caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products."

Most statin labels contain information in the FPI (Warnings and Precautions and Drug Interactions sections) noting that "The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with niacin; a reduction in

<<STATIN>> dosage should be considered in this setting." All sponsors of statin drugs with labels in the PLR format were requested to modify the HIGHLIGHTS page, with corresponding changes to the FPI if indicated, as follows:

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

Other Lipid-lowering Medications: Use with other 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 <<STATIN>>.

7.X Niacin

The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with lipid-modifying doses (≥1 g/day) of niacin; a reduction in <<STATIN>> dosage should be considered in this setting.

9. Update to lovastatin drug-drug interactions and dose caps

Subsequent to the June 2011 labeling revisions to the simvastatin-containing products which were largely based on the SEARCH clinical trial data and the increased risk of myopathy associated with the 80 mg dose of simvastatin, a review of drug-drug interactions with lovastatin was conducted. The physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Lovastatin is a sensitive *in vivo* CYP3A4 substrate; therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure. According to OCP:

> *Itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Based on available studies from the literature, as well as extrapolation from simvastatin data, the following changes to the lovastatin label were recommended:

Under **CONTRAINDICATIONS:**

> Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).

Under **WARNINGS, *Myopathy/Rhabdomyolysis*, Strong ~~Potent~~ inhibitors of CYP3A4:**

> Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a potent inhibitor of~~

~~CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin.~~ Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

~~The use of lovastatin concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.~~ ~~Concomitant use of other medicines labeled as having a potent strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk.~~ If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis:***

Gemfibrozil~~, particularly with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with gemfibrozil.~~ The combined use of lovastatin with gemfibrozil should be avoided~~, unless the benefits are likely to outweigh the increased risks of this drug combination~~.

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin): ~~The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with other fibrates or ≥1 g/day of niacin.~~ Caution should be used when prescribing other fibrates or lipid-lowering doses (≥1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

~~Cyclosporine or d~~Danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with ~~cyclosporine or~~ danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patients receiving ~~cyclosporine or~~ danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Amiodarone~~ or verapamil~~: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone ~~or verapamil~~. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone~~ or verapamil~~ should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is

increased when ~~either~~ amiodarone ~~or verapamil~~ is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Under **WARNINGS**, ***Myopathy/Rhabdomyolysis:***

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

Amiodarone ~~or verapamil~~: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone ~~or verapamil~~. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone ~~or verapamil~~ should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when ~~either~~ amiodarone ~~or verapamil~~ is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

~~Cyclosporine, or d~~Danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with ~~cyclosporine, or~~ danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patient receiving ~~cyclosporine, or~~ danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Under **WARNINGS,** ***Myopathy/Rhabdomyolysis,*** Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis**:**

Interacting Agents	**Prescribing Recommendations**
Ketoconazole Itraconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	~~Avoid~~ Contraindicated with lovastatin
Gemfibrozil Cyclosporine	Avoid with lovastatin
~~Gembibrozil~~ ~~Other fibrates~~ ~~Lipid-lowering doses (≥1 g/day) of nicacin~~ ~~Cyclosporine~~ Danazol Diltiazem Verapamil	Do not exceed 20 mg lovastatin daily
Amiodarone ~~Verapamil~~	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Under **PRECAUTIONS**, *Drug Interactions, CYP3A4 Interactions*:

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. ~~Potent~~ Strong inhibitors of CYP3A4 (e.g., ~~below~~ itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and erythromycin), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin

~~**Itraconazole**~~
~~**Ketoconazole**~~
~~**Erythromycin**~~
~~**Clarithromycin**~~
~~**Telithromycin**~~
~~**HIV protease inhibitors**~~
~~**Nefazodone**~~
~~**Large quantities of grapefruit juice (>1 quart daily)**~~

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Under **PRECAUTIONS**, *Other Drug Interactions:*

Cyclosporine ~~or Danazol~~: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine ~~or danazol particularly with higher doses of lovastatin~~.

Danazol, Diltiazem, or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, diltiazem, or verapamil particularly with higher doses of lovastatin.

Amiodarone ~~or Verapamil~~: The risk of myopathy/rhabdomyolysis is increased when either amiodarone ~~or verapamil~~ is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.

Under **PRECAUTIONS,** *Endocrine Function*:

Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ~~ketoconazole,~~ spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

Under **DOSAGE AND ADMINISTRATION:**

Dosage in Patients taking ~~Cyclosporine, or~~ Danazol, Diltiazem, or Verapamil
In patients taking ~~cyclosporine, or~~ danazol, diltiazem, or verapamil concomitantly with lovastatin, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Dosage in Patients taking Amiodarone ~~or Verapamil~~
In patients taking amiodarone ~~or verapamil~~ concomitantly with MEVACOR, the dose should not exceed 40 mg/day.

Concomitant Lipid-Lowering Therapy
MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. ~~If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥ 1g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day~~.

Under **CLINICAL PHARMACOLOGY**:

	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid†
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0 96	2 80
Itraconazole‡	12	200 mg QD for 4 days	40 mg on Day 4	> 36§	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14 8§	15 4
Grapefruit Juice¶ (high dose)	10	200 mL of double-strength TID#	80 mg single dose	15.3	5.0
Grapefruit Juice¶ (low dose)	16	8 oz (about 250 mL) of single-strengthÞ for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not describedß	10 mg QD for 10 days	5- to 8-fold	NDà
	Number of Subjects	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Lovastatin**	**AUC Ratio* (with / without coadministered drug) No Effect = 1.00**	
				Total Lovastatin acide	
Diltiazem	10	120 mg BID for 14 days	20 mg	3 57è	

* Results based on a chemical assay

† Lovastatin acid refers to the β-hydroxyacid of lovastatin

‡ The mean total AUC of lovastatin without itraconazole phase could not be determined accurately Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone

§ Estimated minimum change

¶ The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied

Double-strength: one can of frozen concentrate diluted with one can of water Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3

Þ Single-strength: one can of frozen concentrate diluted with 3 cans of water Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3

ß Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study

10. Update to simvastatin and lovastatin drug-drug interaction:

In May 2011, the hepatitis C protease inhibitors boceprevir and telaprevir were approved. These protease inhibitors have been characterized as being strong CYP3A4 inhibitors. Because simvastatin is contraindicated with strong CYP3A4 inhibitors, and because the simvastatin label individually lists strong CYP3A4 inhibitors with which simvastatin is contraindicated, these two recently approved protease inhibitors will be added to the list in all simvastatin-containing products (Zocor, Vytorin, and Simcor).

Because of the physicochemical and pharmacokinetic similarities between simvastatin and lovastatin, and consistent with changes being made to the lovastatin labeling which include a new contraindication with strong CYP3A4 inhibitors, the labeling for lovastatin will be modified to add boceprevir and telaprevir to the list of strong CYP3A4 inhibitors with which lovastatin is contraindicated.

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/s/

AMY G EGAN
02/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022363Orig1s008, 009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22363
Submission Date(s)	December 9, 2011
Brand Name	Livalo®
Generic Name	Pitavastatin
Reviewers	Sang M. Chung, Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Kowa Pharmaceuticals America, Inc.
Submission Type	Prior Approval Supplement (PAS) – Request for change to labeling information
Formulation Strength(s)	1 mg, 2 mg and 4 mg tablets

Table of Contents

1 Summary of Important Clinical Pharmacology Findings

The sponsor submitted the PAS for labeling change related to drug interaction based on two post-approval trials. The proposed labeling (Section 1.3) is acceptable.

Background information related to potential mechanisms for drug interaction: Pitavastatin is mainly metabolized through glucuronidation (isozymes; UGT1A3 and UGT2B7) and two additional metabolic isozymes (i.e., CYP2C9 and 2C8) are involved in its metabolism. Its absolute bioavailability is 51%. Darunavir is primarily metabolized by CYP3A and ritonavir is a strong CYP3A inhibitor. Darunavir is approved only as co-administration with ritonavir. Absolute bioavailability of darunavir is 37% and is increased to 82% with ritonavir. *In vivo* data suggest that darunavir/ritonavir is an inhibitor of the p-glycoprotein transporter. Both diltiazem and combination of darunavir and ritonavir are listed as moderate CYP3A4 inhibitors in the Drug Interaction Guidance (link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)

1.1 The effect of multiple dose darunavir/ritonavir on multiple dose pitavastatin in healthy subjects (Study NK-104-4.06)

Pharmacokinetic interaction between pitavastatin and combination of darunavir and ritonavir (darunavir/ritonavir) was evaluated in an open-label, fixed-sequence, multiple-dose following pitavastatin 4 mg QD for 5 days with and without darunavir/ritonavir 800/100 mg QD for 5 days in healthy subjects (n=27).

Pitavastatin pharmacokinetics was characterized on Day 5 and 16, and darunavir/ritonavir pharmacokinetics was characterized on Day 11 and 16. Study design, treatments and investigational products are summarized in Table 1. Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose on Days 5 and 16 for pitavastatin and its lactone metabolites, and at pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose on Days 11 and 16 for darunavir/ritonavir pharmacokinetics. Steady-state pharmacokinetics was estimated using non-compartmental analysis. Disposition of subjects are summarized in Table 2. One subject (Subject 115) was discontinued because of the AE of maculopapular rash after receiving darunavir/ritonavir only.

Mean (SD) pitavastatin and its lactone plasma concentration-time profiles are shown in Figure 1. Their pharmacokinetic parameters and statistical analysis are summarized in Table 3. The pitavastatin AUC and Cmax were decreased by 28% and 4%, respectively, by co-administration of rarunavir/ritonavir compared to those of pitavastatin alone (Table 3). Pitavastatin lactone AUC and Cmax were decreased by 32% and 24%, respectively by the same treatment effect (Table 3). Pitavastatin did not significantly affect both darunavir and ritonavir pharmacokinetics (Table 4). Pharmacokinetic parameters based on the arithmetic mean (SD) are summarized in Attachment 1.4.1.

Table 1 summary of study design, treatments and investigational products

DAY		-30 to -1	-1	1 to 5	6 to 11	12 to 16	17
Procedures		Screening	Admission				Discharge
Treatments	Pitavastatin			4 mg QD		4 mg QD	
	Darunavir / ritonavir				800/100 mg QD	800/100 mg QD	

Products	lot number
Pitavastatin, 4-mg tablets	3087858
Darunavir (Prezista) 400 mg	1CG592
ritonavir (Norvir) 100 mg	014612E

Table 2 Subject disposition (Study NK-104-4.06)

Disposition	Number (%) Subjects
Number Enrolled	28
Number Treated	28 (100)
Number Completed	27 (96.4)
Number Discontinued	1 (3.6)
Reason for	
Adverse Event	1 (3.6)
Populations	
Safety	28 (100)
Pharmacokinetic	27 (96.4)

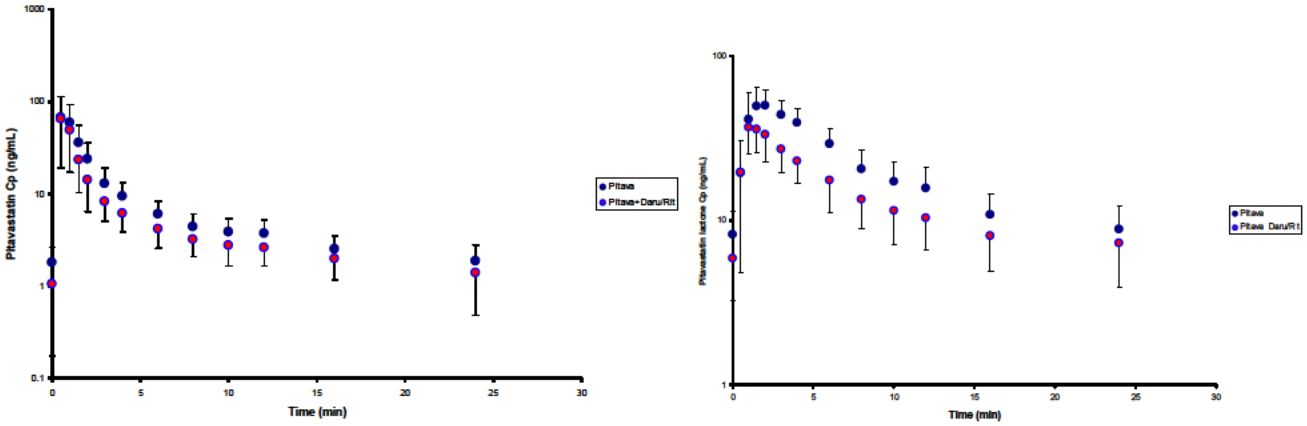

Figure 1 **Mean (SD) pitavastatin (left) and its lactone (right) plasma concentration-time profiles by treatments following 4 mg QD for 5 days (Study NK-104-4.06)**

Table 3 Pitavastatin and its lactone pharmacokinetic parameters (Study NK-104-4.06)

Analyte	Parameter (unit)	N	Geometric Mean		Ratio[a]	90% CI of Ratio
			Pitavastatin + Darunavir/Ritonavir	Pitavastatin Only		
Pitavastatin	C_{max} (ng/mL)	27	68.44	71.52	0.96	0.84–1.09
	$AUC_{0-\tau}$ (ng•h/mL)	27	132.81	178.64	0.74	0.69–0.80
Pitavastatin Lactone	C_{max} (ng/mL)	27	38.77	51.28	0.76	0.70–0.82
	$AUC_{0-\tau}$ (ng•h/mL)	27	311.98	456.41	0.68	0.63–0.74

[a] Ratio of the geometric means was estimated by exponentiating the least squares mean difference between pitavastatin with darunavir/ritonavir and pitavastatin only.

Table 4 Darunavir and ritonavir pharmacokinetic parameters (Study NK-104-4.06)

Analyte	Parameter (unit)	N	Geometric Mean		Ratio[a]	90% CI of Ratio
			Darunavir/Ritonavir + Pitavastatin	Darunavir/Ritonavir Only		
Darunavir	C_{max} (ng/mL)	27	6039.10	5702.08	1.06	1.00–1.12
	$AUC_{0-\tau}$ (ng•h/mL)	27	66954.17	64855.61	1.03	0.95–1.12
Ritonavir	C_{max} (ng/mL)	27	847.57	830.53	1.02	0.94–1.11
	$AUC_{0-\tau}$ (ng•h/mL)	27	6134.27	5665.44	1.08	1.01–1.16

[a] Ratio of the geometric means was estimated by exponentiating the least squares mean difference between darunavir/ritonavir with pitavastatin and darunavir/ritonavir only.

1.2 The effect of multiple dose diltiazem (Cardizem LA) on multiple dose pitavastatin in healthy subjects (Study NK-104-4.07)

Pharmacokinetic interaction between pitavastatin and diltiazem was evaluated in an open-label, fixed-sequence, multiple-dose following pitavastatin 4 mg QD for 5 days with and without diltiazem 240 mg QD for 5 days in healthy subjects (n=26) (Study NK-104.4.07).

Pitavastatin pharmacokinetics was characterized on Day 5 and 15, and diltiazem and its N-desmethyl and desacetyl metabolites pharmacokinetics was characterized on Day 10 and 15. Study design, treatments and investigational products are summarized in Table 5. Blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose on Days 5 and 15 for pitavastatin and its lactone metabolites, and at pre-dose, 0.5, 1, 1.5, 3, 6, 8, 10, 12, 14, 16, 18, 20, and 24 hours post-dose on Days 10 and 15 for diltiazem and its metabolites pharmacokinetics. Steady-state pharmacokinetics was

estimated using non-compartmental analysis. Disposition of subjects are summarized in Table 6. One subject (Subject 128) withdrew consent because of personal reasons.

Mean (SD) pitavastatin and its lactone plasma concentration-time profiles are shown in Figure 2. Pitavastatin pharmacokinetic parameters and statistical analysis are summarized in Table 7. Pitavastatin AUC and Cmax were increased by 10% and 15%, respectively, by co-administration of diltiazem compared to those of pitavastatin alone (Table 7). Pitavastatin lactone AUC and Cmax were increased by 11% and 12%, respectively by the same treatment effect (Table 7). Pitavastatin did not significantly affect diltiazem and its metabolites pharmacokinetics (Table 8). Pharmacokinetic parameters based on the arithmetic mean (SD) are summarized in Attachment 1.4.2.

Table 5 summary of study design, treatments, and investigational products (Study NK-104.4.07)

DAY		**-30 to -1**	**-1**	**1 to 5**	**6 to 10**	**11 to 15**	**16**
Procedures		Screening	Admission				Discharge
Treatments	Pitavastatin			4 mg QD		4 mg QD	
	Diltiazem				240 mg QD	240 mg QD	

Products	**lot number**
Pitavastatin, 4-mg tablets	3087858
Diltiazem (Cardizem LA) 240 mg	10L075P

Table 6 Subject disposition (Study NK-104.4.07)

Disposition	**Number (%) Subjects**
Number Enrolled	28
Number Treated	28 (100)
Number Completed	27 (96.4)
Number Discontinued	1 (3.6)
Reason for	
Adverse Event	1 (3.6)
Populations	
Safety	28 (100)
Pharmacokinetic	27 (96.4)

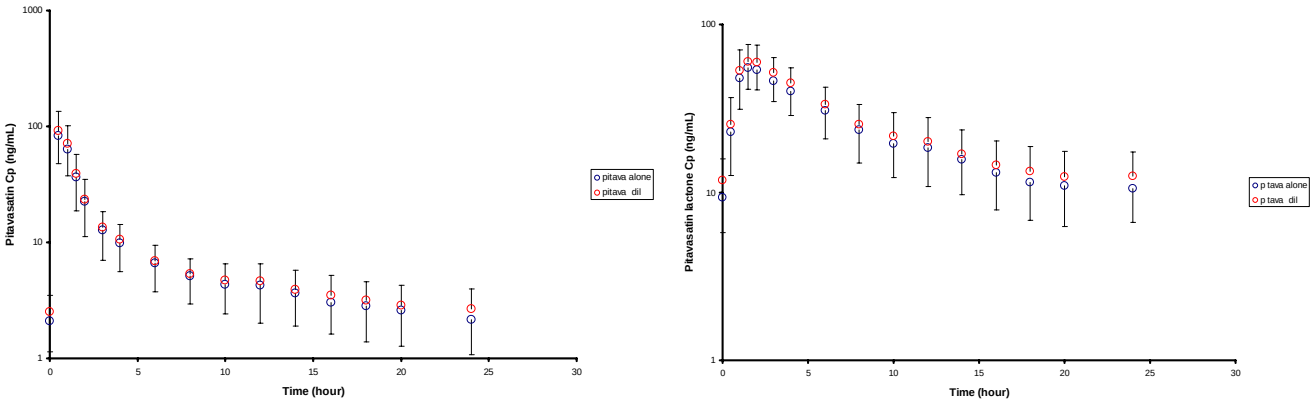

Figure 2 **Mean (SD) pitavastatin (left) and its lactone (right) plasma concentration-time profiles by treatments following 4 mg QD for 5 days (Study NK-104.4.07)**

Table 7 **Pitavastatin and its lactone pharmacokinetic parameters (Study NK-104-4.07)**

Analyte	Parameter (unit)	n	Geometric Mean		Ratio[a]	90% CI of Ratio
			Pitavastatin + Diltiazem	Pitavastatin Only		
Pitavastatin	C_{max} (ng/mL)	26	92.56	80.72	1.15	1.02 – 1.29
	$AUC_{0-\tau}$ (ng•h/mL)	26	213.99	194.99	1.10	1.03 – 1.17
Pitavastatin Lactone	C_{max} (ng/mL)	26	61.30	54.95	1.12	1.05 – 1.18
	$AUC_{0-\tau}$ (ng•h/mL)	26	563.37	507.56	1.11	1.04 – 1.18

a Ratio of the geometric means was estimated by exponentiating the least squares mean difference between pitavastatin with diltiazem and pitavastatin only.

Table 8 **Diltiazem and its metabolites pharmacokinetic parameters (Study NK-104-4.07)**

	Analyte Parameter (unit)	n	Geometric Mean		Ratio[a]	90% CI of Ratio
			Pitavastatin and Diltiazem	Diltiazem Only		
Diltiazem	C_{max} (ng/mL)	26	191.67	205.81	0.93	0.85 – 1.02
	$AUC_{0-\tau}$	26	2999.11	3051.28	0.98	0.91 – 1.07
N-Desmethyl Diltiazem	C_{max} (ng/mL)	26	55.50	56.16	0.99	0.93 – 1.05
	$AUC_{0-\tau}$	26	995.65	982.11	1.01	0.96 – 1.07
Desacetyl Diltiazem	C_{max} (ng/mL)	26	20.64	20.31	1.02	0.95 – 1.09
	$AUC_{0-\tau}$	26	405.57	399.59	1.01	0.94 – 1.09

a Ratio of the geometric means was estimated by exponentiating the least squares mean difference between diltiazem with pitavastatin and diltiazem only.

1.3 Labeling *(red text indicates the sponsor's proposal.)*

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max*}
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Darunavir/Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16	↓ 26%	↓ 4%
Lopinavir/Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24	↓ 20%	↓ 4 %
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓ 0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15	↑ 10%	↑ 15%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days	↑ 15%	↓ 12%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

*Data presented as x-fold change represent the ratio between co-administration and pitavastatin alone (i.e., 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).
† Considered clinically significant *[see Dosage and Administration (2) and Drug Interactions (7)]*
BID = twice daily; QD = once daily

Table 3. Effect of Pitavastatin Co-Administration on Systemic Exposure to Other Drugs

Co-administered drug	Dose regimen		Change in AUC*	Change in C_{max}*
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Darunavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 3%	↑ 6%
Lopinavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 9%	↓ 7%
Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 11%	↓ 11%
Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 8%	↑ 2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	Enalapril	↑ 12%	↑ 12%
		Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 - 7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑ 7%	↑ 3%
		S-warfarin	↑ 6%	↑ 3%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days		↑ 9%	↑ 2%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days		↓ 3%	↓ 4%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15		↓ 2%	↓ 7%
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days		↓ 15%	↓ 18%

Data presented as % change represent % difference relative to the investigated drug alone (i.e., 0% = no change).
BID = twice daily; QD = once daily

1.4 Attachment

1.4.1 Study NK-104-4.06

Pitavastatin and its lactone pharmacokinetic parameters: arithmetic mean (SD)

Pharmacokinetic Parameter (unit)	Treatment Analyte							
	Pitavastatin Only				Pitavastatin and Darunavir/Ritonavir			
	n	Pitavastatin	n	Pitavastatin Lactone	n	Pitavastatin	n	Pitavastatin Lactone
$AUC_{0-\tau}$ (ng•h/mL)	27	192.00 (80.8)	27	472.21 (127.1)	27	143.08 (60.3)	27	326.35 (103.3)
C_{max} (ng/mL)	27	80.21 (39.3)	27	52.94 (14.8)	27	77.04 (41.2)	27	40.21 (11.3)
T_{max} (h)[a]	27	0.50 (0.50–2.00)	27	2.00 (1.00–3.00)	27	0.50 (0.50–1.50)	27	1.00 (0.50–2.05)

[a] T_{max} is reported as median (minimum, maximum).

Darunavir and ritonavir pharmacokinetic parameters: arithmetic mean (SD)

Pharmacokinetic Parameter (unit)	Treatment Analyte							
	Darunavir/Ritonavir Only				Pitavastatin and			
	n	Darunavir	n	Ritonavir	n	Darunavir	n	Ritonavir
$AUC_{0-\tau}$ (ng•h/mL)	27	67442 (19695)	27	6232 (2776)	27	70095 (22140)	27	6807 (3226)
C_{max} (ng/mL)	27	5815 (1253)	27	901.44 (362.4)	27	6168 (1304)	27	936.74 (454.0)
T_{max} (h)[a]	27	2.00 (1.00–4.00)	27	3.00 (2.00–4.03)	27	2.00 (1.00–4.12)	27	3.00 (2.00–4.12)

[a] T_{max} is reported as median (minimum, maximum).

2.0 CLINICAL STUDY SYNOPSIS

Name of Company: Kowa Research Institute, Inc.		**Volume:**	(For National Authorities Use only)
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Name of Active Ingredient: Pitavastatin			
Title of Study:	Drug-Drug Interaction Study to Assess the Effects of Steady-State Darunavir/Ritonavir on Steady-State Pitavastatin in Healthy Adult Volunteers		
Investigator:	The principal investigator, Matthew Medlock, MD, enrolled 28 subjects at 1 study site.		
Study Center:	PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, Texas, 78744		
Publication (reference):	None		
Study Period: 20 April 2011 – 10 June 2011		**Phase of Development:** 4	
Date of First Subject Enrolled: 20 April 2011 **Date of Last Subject Completed:** 10 June 2011			

Objectives:

Primary Objective: The primary objective of the study was to investigate any potential pharmacokinetic (PK) interactions of darunavir/ritonavir 800 mg/100 mg on the pharmacokinetics of pitavastatin 4 mg.

Secondary Objectives: The secondary objectives of the study were:

- To investigate any potential effect on the safety of pitavastatin 4 mg by the addition of darunavir/ritonavir 800 mg/100 mg,
- To investigate any potential effect on the safety of darunavir/ritonavir 800 mg/100 mg by the addition of pitavastatin 4 mg, and
- To investigate any potential PK interaction of pitavastatin 4 mg on the pharmacokinetics of darunavir/ritonavir 800 mg/100 mg.

Exploratory Objective: Genetic testing was performed on Day 17 of the study. Collection of the blood samples for genetic testing was optional and was discussed with subjects before they provided consent for this testing.

Methodology: This was a Phase 4, single-center, open-label, fixed-sequence, multiple-dose, 2-way drug-drug interaction study to determine the PK interaction of darunavir/ritonavir on the pharmacokinetics of pitavastatin.

Each subject qualified for entry into the study within 30 days before admission into the clinical unit. Subjects were checked into the clinical unit on Day –1 for baseline assessments. There was 1 treatment period, with each subject receiving a once-daily dose of pitavastatin 4 mg on Days 1 through 5 and Days 12 through 16 and a once-daily dose of darunavir/ritonavir 800 mg (two 400-mg tablets)/100 mg (one 100-mg tablet) on Days 6 through 16. On Days 1 through 4, 6 through 10, and 12 through 15, study drug was administered 30 minutes before a standard breakfast. On Days 5, 11, and 16, subjects fasted at least 8 hours before receiving study drug and remained fasted for 4 hours after dosing.

Serial blood samples for PK assessments were collected before dosing and up to 24 hours after dosing on Days 5 and 16 for pitavastatin and its lactone metabolite and before dosing and up to 24 hours after dosing on Days 11 and 16 for darunavir and ritonavir. Subjects were discharged from the clinical unit on Day 17 after all PK sampling and safety assessments were completed.

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Number of Subjects (planned and analyzed): Up to 28 healthy adult subjects were planned, 28 subjects were enrolled, and 27 subjects completed the study. Twenty-seven subjects were included in the PK statistical analyses and 28 subjects were included in the safety analyses.

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible for the study if all of the following criteria were met:

1) Subject provided written informed consent before any study-specific evaluation was performed.
2) Subject was a healthy adult male or female volunteer aged 18 to 45 years, inclusive.
3) Subject had a body mass index (BMI) of 18 to 30 kg/m^2, inclusive.
4) Subject had hematology, serum chemistry, and urinalysis test results within the reference ranges or showing no clinically relevant deviations, as judged by the investigator at Screening.
5) All female subjects must have had a negative serum pregnancy test at Screening and upon check-in to the clinical unit. Female subjects of childbearing potential must have used one of the following acceptable birth control methods as specified before enrollment and throughout the study:
   - Surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months before the first dose of study drug;
   - Intrauterine device in place for at least 3 months before the first dose of study drug and throughout the study;
   - Barrier method (condom, diaphragm) with spermicide for at least 14 days before the first dose of study drug and throughout the study;
   - Surgical sterilization of the male partner (vasectomy at least 6 months before the first dose of study drug);
   - Hormonal contraceptives with a barrier method for at least 3 months before the first dose of study drug and throughout the study;
   - Postmenopausal women with amenorrhea for at least 2 years and with a documented serum follicle-stimulating hormone level greater than 35 mIU/mL were eligible.
6) Subject was able and willing to comply with the protocol and study procedures.
7) Subject was able and willing to abstain from alcohol, grapefruit, caffeine, caffeine-containing products, St John's wort, and herbal supplements for 4 days before Day 1 until after completion of this study.
8) Subject was a nonsmoker or had quit smoking at least 6 months before the first dose of study drug and until study completion.

Diagnosis and Main Criteria for Exclusion:

Subjects were excluded from the study if any of the following criteria were met:

1) Subject had clinically relevant abnormalities in the screening or check-in assessments.
2) Subject had a supine blood pressure after resting for 5 minutes that was higher than 140 mm Hg systolic or 90 mm Hg diastolic, or lower than 90 mm Hg systolic or 60 mm Hg diastolic.
3) Subject had a supine heart rate after resting for 5 minutes that was outside the range of 40 to

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90 beats per minute.

4) Subject had received an investigational drug within 30 days before the first dose of study drug.

5) Subject had an active or recurring clinically significant disorder of the skin, head, ears, eyes, nose, throat, respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, genitourinary, neurologic, hematologic, musculoskeletal, immunologic, or psychological/psychiatric systems, or other disease requiring medical treatment.

6) Subject had a history of cancer other than nonmelanomatous skin malignancies.

7) Subject had a positive test result at Screening for human immunodeficiency virus (1 or 2) antibody, hepatitis B surface antigen, or hepatitis C virus antibody.

8) Subject had any surgery of the gastrointestinal tract likely to affect drug absorption, distribution, metabolism, or excretion.

9) Subject had a previous allergy or intolerance to treatment with pitavastatin, darunavir, ritonavir, sulfonamides, or any drugs in these classes.

10) Subject had a history of drug or alcohol abuse.

11) Subject had a clinically significant illness within 4 weeks before the first dose of study drug.

12) Subject had donated more than 450 mL of blood within 30 days before the first dose of study drug.

13) Subject had a positive test result for drugs of abuse (opiates, methadone, cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, oxycodone), cotinine, or alcohol. Documentation of prescriptive use of medications containing any of these drugs was acceptable.

14) Subject had a positive serum pregnancy test at Screening or Check-in (Day –1).

15) Any medication (with the exception of acetaminophen or vitamin supplements) must have been stopped at least 14 days before the first dose of study drug. The use of any known inhibitors or inducers of cytochrome P450 (CYP) enzyme 2C9 (CYP2C9), CYP3A4, or organic anion transporting polypeptide 1B1 (OATP1B1) was prohibited within 30 days before the first dose of study drug.

16) Subject was a member of the professional or ancillary personnel involved in the study.

17) Subjects who, in the opinion of the investigator, should not have participated in the study.

Test Product, Dose, Mode of Administration, and Lot or Batch Numbers:

- Pitavastatin, 4-mg tablets for oral administration; lot number: 3087858
- Darunavir (Prezista) 400 mg (lot number: 1CG592) and ritonavir (Norvir) 100 mg (lot number: 014612E) tablets for oral administration were obtained commercially.

Duration of Treatment: Subjects received pitavastatin once daily on Days 1 through 5 and Days 12 through 16 (10 doses); subjects received darunavir/ritonavir once daily on Days 6 through 16 (11 doses).

Reference Therapy, Dose, Mode of Administration, and Batch Number: None.

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Treatment and Administration: Each subject received a once-daily dose of pitavastatin 4 mg on Days 1 through 5 and Days 12 through 16 and a once-daily dose of darunavir/ritonavir 800 mg (two 400-mg tablets)/100 mg (one 100-mg tablet) on Days 6 through 16. On Days 1 through 4, 6 through 10, and 12 through 15, study drug was administered 30 minutes before a standard breakfast. On Days 5, 11, and 16, subjects fasted at least 8 hours before receiving study drug and remained fasted for 4 hours after dosing.

Criteria for Evaluation:

Pharmacokinetics: The following plasma PK parameters were calculated for pitavastatin, its lactone metabolite, darunavir, and ritonavir: area under the concentration versus time curve over 1 dosing interval at steady state ($AUC_{0-\tau}$), maximum observed plasma concentration (C_{max}), and time of observed maximum plasma concentration (T_{max}). Apparent oral clearance at steady state (CL_{ss}/F) and apparent volume of distribution (V_d/F) were calculated for the parent compounds pitavastatin, darunavir, and ritonavir.

Safety: Safety assessments included adverse event (AE) reporting, clinical laboratory test results (including hematology, serum chemistry [including lipid measures], and urinalysis), vital sign measurements (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), 12-lead electrocardiogram (ECG) recordings, and physical examination findings.

Pharmacogenetics: Samples for optional genotype testing for variations in the solute carrier organic anion transporter family member 1B1 (SLCO1B1) were collected on Day 17.

Statistical Methods:

Complete statistical methodology was presented in a separate statistical analysis plan.

Pharmacokinetics:

Plasma concentrations of pitavastatin, its lactone metabolite, darunavir, and ritonavir were summarized for each time point and treatment by analyte. Individual plasma concentration versus time profiles were presented graphically by treatment/analyte group. Pharmacokinetic parameters derived from plasma samples were summarized by analyte and treatment.

Pitavastatin and pitavastatin lactone log-transformed parameters (C_{max} and $AUC_{0-\tau}$) in the presence of darunavir/ritonavir were compared to the log-transformed parameters in the absence of darunavir/ritonavir using an analysis of variance. In addition, darunavir/ritonavir log-transformed parameters in the presence of pitavastatin were compared to darunavir/ritonavir log-transformed parameters in the absence of pitavastatin.

A linear mixed model using treatment as a fixed effect and subject as a random effect on the log-transformed PK parameters ($AUC_{0-\tau}$ and C_{max}) for pitavastatin, pitavastatin lactone, and darunavir/ritonavir was performed. Geometric mean ratios and 90% confidence intervals (CI) for C_{max} and $AUC_{0-\tau}$ of each analyte were presented. No clinically significant interaction was concluded if the 90% CIs for the ratios of geometric means for C_{max} and $AUC_{0-\tau}$ of the parent drugs were entirely contained within the range of 80% to 125%.

Safety:

Demographics and baseline characteristics were summarized. A summary of all AEs was presented by treatment and overall. The incidence of treatment-emergent AEs (TEAEs) by treatment and overall was summarized as follows: TEAEs, TEAEs leading to discontinuation, relationship of TEAEs to study drug, severity of TEAEs, treatment-emergent serious AEs (SAEs), and treatment-emergent SAEs leading to death. Clinical laboratory results (including lipid measures), vital sign measurements, and 12-lead ECG results and changes from Baseline were summarized by scheduled time points. All AE, clinical laboratory, vital sign, 12-lead ECG, and physical examination data were presented in data listings.

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RESULTS

Demographics and Disposition:

Twenty-eight subjects were enrolled and 27 subjects completed the study. One subject (Subject 115) was discontinued because of the AE of maculopapular rash after receiving darunavir/ritonavir only. Overall, the majority of subjects enrolled in the study were white, ranged in age from 19 to 42 years, and had a mean BMI of 24.46 kg/m^2. Twenty-one males and 7 females participated in the study.

Pharmacokinetics:

Statistical Analysis of Pharmacokinetic Parameters of Pitavastatin and its Lactone Metabolite (Pharmacokinetic Population)

Analyte	Parameter (unit)	N	Geometric Mean		Ratio[a]	90% CI of Ratio
			Pitavastatin with Darunavir/Ritonavir	Pitavastatin Only		
Pitavastatin	C_{max} (ng/mL)	27	68.44	71.52	0.96	0.84–1.09
	AUC_{0-t} (ng•h/mL)	27	132.81	178.64	0.74	0.69–0.80
Pitavastatin Lactone	C_{max} (ng/mL)	27	38.77	51.28	0.76	0.70–0.82
	AUC_{0-t} (ng•h/mL)	27	311.98	456.41	0.68	0.63–0.74

Data source: Statistical Table 14.2.3.

Abbreviations: CI, confidence interval.

[a] Ratio of the geometric means was estimated by exponentiating the least squares mean difference between pitavastatin with darunavir/ritonavir and pitavastatin only.

Note: The linear mixed model was performed on the natural log-transformed parameters C_{max} and AUC_{0-t} and included treatment as a fixed effect and subject as a random effect.

There was no drug interaction effect of darunavir/ritonavir on the peak exposure of pitavastatin. Coadministration of pitavastatin with darunavir/ritonavir slightly decreased the AUC of pitavastatin by approximately 26%. The 90% CI of the geometric least squares mean ratio for AUC_{0-t} was (0.69, 0.80). The 90% CI of the geometric least squares mean ratio for C_{max} was (0.84, 1.09), which is entirely contained within the criterion range of (0.80, 1.25) specified in the analysis plan as sufficient to indicate the absence of clinically significant interaction.

There was a weak (greater than or equal to a 25% decrease, but less than 100% decrease) drug interaction effect of darunavir/ritonavir on the total and peak exposures of pitavastatin lactone (inactive metabolite) (decreases of approximately 32% and 24%, respectively). The 90% CIs of the geometric least squares mean ratio for AUC_{0-t} and C_{max} were outside the range of 0.80 to 1.25, with values of (0.63, 0.74) and (0.70, 0.82), respectively.

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Statistical Analysis of Pharmacokinetic Parameters of Darunavir and Ritonavir (Pharmacokinetic Population)

Analyte	Parameter (unit)	N	Geometric Mean		Ratio[a]	90% CI of Ratio
			Darunavir/Ritonavir with Pitavastatin	Darunavir/Ritonavir Only		
Darunavir	C_{max} (ng/mL)	27	6039.10	5702.08	1.06	1.00–1.12
	AUC_{0-t} (ng•h/mL)	27	66954.17	64855.61	1.03	0.95–1.12
Ritonavir	C_{max} (ng/mL)	27	847.57	830.53	1.02	0.94–1.11
	AUC_{0-t} (ng•h/mL)	27	6134.27	5665.44	1.08	1.01–1.16

Data source: Statistical Table 14.2.4.

Abbreviations: CI, confidence interval.

[a] Ratio of the geometric means was estimated by exponentiating the least squares mean difference between darunavir/ritonavir with pitavastatin and darunavir/ritonavir only.

Note: The linear mixed model was performed on the natural log-transformed parameters C_{max} and AUC_{0-t} and included treatment as a fixed effect and subject as a random effect.

There was no drug interaction effect of pitavastatin on the total and peak exposures of either darunavir or ritonavir (increases of approximately 3% and 6% for total and peak exposures of darunavir and increases of approximately 8% and 2% for total and peak exposures of ritonavir, respectively). The 90% CIs of the geometric least squares mean ratio for AUC_{0-t} and C_{max} for darunavir (AUC_{0-t}, 1.03 [0.95, 1.12] and C_{max}, 1.06 [1.00, 1.12]) and for ritonavir (AUC_{0-t}, 1.08 [1.01, 1.16] and C_{max}, 1.02 [0.94, 1.11]) were entirely contained within the range of 0.80 to 1.25.

Safety:

Overall, 13 of 28 subjects (46.4%) reported TEAEs. Treatment-emergent AEs were reported by 2 subjects (7.1%) during treatment with pitavastatin only, 10 subjects (35.7%) during treatment with darunavir/ritonavir only, and 7 subjects (25.9%) during treatment with pitavastatin and darunavir/ritonavir. The most frequently reported TEAEs were each reported by 3 subjects (10.7%) and included diarrhea, headache, myalgia, and oropharyngeal pain. Six of 28 subjects (21.4%) reported treatment-related TEAEs. Treatment-related TEAEs were reported by 1 subject (3.6%) during treatment with pitavastatin only, 4 subjects (14.3%) during treatment with darunavir/ritonavir only, and 3 subjects (11.1%) during treatment with pitavastatin and darunavir/ritonavir. Diarrhea was the most frequently reported treatment-related TEAE (3 subjects overall, 10.7%); all other treatment-related TEAEs were each reported by 1 subject.

All TEAEs were mild in severity except in 1 subject who experienced a headache of moderate severity while receiving darunavir/ritonavir only. All TEAEs resolved by the end of the study. One subject was discontinued from the study due to an AE of maculopapular rash during treatment with darunavir/ritonavir only. There were no severe AEs, SAEs, or deaths.

There were no clinically significant findings in any of the other safety assessments (clinical laboratory test results, vital sign measurements, ECG results, and physical examinations).

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CONCLUSIONS

- Total exposure of pitavastatin at steady state was weakly affected by coadministration of darunavir/ritonavir (decrease of approximately 26%) (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 0.74 [0.69, 0.80]).
- Peak exposure of pitavastatin at steady state as measured by C_{max} was not affected by coadministration of darunavir/ritonavir (decrease of approximately 4%) (geometric mean ratio [90% CI]: C_{max}, 0.96 [0.84, 1.09]).
- Total exposure of pitavastatin lactone (inactive metabolite) at steady state was weakly affected by coadministration of darunavir/ritonavir (decrease of approximately 32%) (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 0.68 [0.63, 0.74]).
- Peak exposure of pitavastatin lactone (inactive metabolite) at steady state was weakly affected by coadministration of darunavir/ritonavir (decrease of approximately 24%) (geometric mean ratio [90% CI]: C_{max}, 0.76 [0.70, 0.82]).
- Total and peak exposures of darunavir and ritonavir at steady state were not affected by coadministration of pitavastatin as seen by increases of approximately 3% and 6% for total and peak exposures of darunavir, respectively (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 1.03 [0.95, 1.12] and C_{max}, 1.06 [1.00, 1.12]) and increases of approximately 8% and 2% for total and peak exposures of ritonavir (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 1.08 [1.01, 1.16] and C_{max}, 1.02 [0.94, 1.11]).
- Overall, multiple doses of pitavastatin alone and pitavastatin coadministered with darunavir/ritonavir were safe and well tolerated in the healthy subjects in this study.

1.4.2 Study NK-104-4.07

Pitavastatin and its lactone pharmacokinetic parameters: arithmetic mean (SD) (Study NK-104.4.07)

Pharmacokinetic Parameter (unit)	Treatment Analyte							
	Pitavastatin Alone				Pitavastatin and Diltiazem			
	n	Pitavastatin	n	Pitavastatin Lactone	n	Pitavastatin	n	Pitavastatin Lactone
$AUC_{0-\tau}$ (ng•h/mL)	26	208.92 (86.54)	26	530.60 (168.71)	26	227.02 (84.76)	26	587.63 (178.43)
C_{max} (ng/mL)	26	86.19 (33.23)	26	57.15 (16.44)	26	98.52 (37.01)	26	63.57 (17.49)
T_{max} (h)[a]	26	0.50 (0.50 – 1.00)	26	1.50 (1.00 – 2.00)	26	0.50 (0.50 – 1.00)	26	1.50 (1.00 – 3.00)
$t_{1/2}$ (h)	21	14.84 (12.07)	20	12.99 (8.64)	18	15.56 (8.40)	15	12.71 (4.89)
CL_{ss}/F (L/h)	26	21.77 (7.19)	NA	NA	26	19.71 (6.26)	NA	NA
V_d/F (L)	21	459.62 (297.74)	NA	NA	18	421.28 (214.44)	NA	NA

a T_{max} is reported as median (minimum, maximum).

Darunavir and ritonavir pharmacokinetic parameters: arithmetic mean (SD) (Study NK-104.4.07)

	Treatment Analyte											
	Diltiazem Alone						Pitavastatin and Diltiazem					
	n	Diltiazem	n	N-Desmethyl Diltiazem	n	Desacetyl Diltiazem	n	Diltiazem	n	N-Desmethyl Diltiazem	n	Desacetyl Diltiazem
$AUC_{0-\tau}$ (ng•h/mL)	26	3220.29 (1027.78)	26	1018.03 (270.17)	26	673.08 (1118.93)	26	3132.03 (932.36)	26	1019.34 (222.38)	26	610.39 (828.14)
C_{max} (ng/mL)	26	214.38 (62.36)	26	57.47 (12.34)	26	32.24 (49.77)	26	199.17 (55.73)	26	56.46 (10.50)	26	30.10 (38.99)
T_{max} (h)[a]	26	10.00 (6.00 – 16.00)	26	14.00 (8.00 – 14.20)	26	14.00 (0.00 – 20.00)	26	11.00 (6.00 – 14.00)	26	14.00 (8.00 – 16.00)	26	14.00 (0.00 – 24.10)
$t_{1/2}$ (h)	24	10.69 (4.08)	24	13.26 (4.69)	19	29.66 (30.33)	24	10.70 (4.12)	24	15.39 (8.45)	13	23.51 (15.55)
CL_{ss}/F (L/h)	26	83.86 (34.92)	NA	NA	NA	NA	26	83.69 (26.20)	NA	NA	NA	NA
V_d/F (L)	24	1297.83 (709.92)	NA	NA	NA	NA	24	1190.97 (402.07)	NA	NA	NA	NA

Abbreviation: NA, not applicable.

[a] T_{max} is reported as median (minimum, maximum).

Note: The pharmacokinetic (PK) parameters CL_{ss}/F and V_d/F were estimated only for diltiazem. The PK parameters $t_{1/2}$ and V_d/F were not reported and were set to missing for $R^2<0.90$.

2.0 CLINICAL STUDY SYNOPSIS

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Title of Study:	Drug-Drug Interaction Study to Assess the Effects of Steady-State Cardizem LA (Diltiazem Hydrochloride) and Steady-State Pitavastatin on Their Respective Pharmacokinetics in Healthy Adult Volunteers
Investigator:	The principal investigator, Sabiha Mondal, MD, enrolled 28 subjects at 1 study site.
Study Center:	PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, Texas, 78744
Publication (reference):	None

Study Period: 05 May 2011 – 12 July 2011 **Phase of Development:** 4

Date of First Subject Enrolled: 05 May 2011

Date of Last Subject Completed: 12 July 2011

Objectives:

Primary Objective: The primary objective of the study was to investigate any potential pharmacokinetic (PK) effects of diltiazem 240 mg on the pharmacokinetics of pitavastatin 4 mg.

Secondary Objectives: The secondary objectives of the study were:

- To investigate any potential effects on the safety of pitavastatin 4 mg when administered with diltiazem 240 mg,
- To investigate any potential effects on the safety of diltiazem 240 mg when administered with pitavastatin 4 mg, and
- To investigate any potential PK effects of pitavastatin 4 mg on the pharmacokinetics of diltiazem 240 mg.

Methodology: This was a Phase 4, single-center, open-label, fixed-sequence, multiple-dose, 2-way drug-drug interaction study to investigate any potential PK effects of diltiazem on the pharmacokinetics of pitavastatin.

Each subject qualified for entry into the study within 30 days before admission into the clinical unit. Subjects checked into the clinical unit on Day –1 for baseline assessments. There was 1 treatment period, with each subject receiving a once-daily dose of pitavastatin 4 mg on Days 1 through 5 and on Days 11 through 15 and a once-daily dose of diltiazem 240 mg on Days 6 through 15. On Days 1 through 4, 6 through 9, and 11 through 14, study drug was administered 30 minutes before a standard breakfast. On Days 5, 10, and 15, subjects fasted at least 8 hours before receiving study drug and continued to fast for 4 hours after dosing.

Serial blood samples for PK assessments were collected before dosing and up to 24 hours after dosing on Days 5 and 15 for pitavastatin and its lactone metabolite and before dosing and up to 24 hours after dosing on Days 10 and 15 for diltiazem and its major metabolites, N–desmethyl diltiazem and desacetyl diltiazem. Subjects were discharged from the clinical unit on Day 16 after all PK sampling and safety assessments were completed.

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Number of Subjects (planned and analyzed): Up to 28 healthy adult subjects were planned, 28 subjects were enrolled, and 27 subjects completed the study. Twenty-six subjects (92.9%) were included in the PK statistical analyses, and 28 subjects (100.0%) were included in the safety analyses.

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible for the study if all of the following criteria were met:

1) Subject provided written informed consent before any study-specific evaluation was performed.
2) Subject was a healthy adult male or female volunteer aged 18 to 45 years, inclusive.
3) Subject had a body mass index of 18 to 30 kg/m^2, inclusive.
4) Subject had hematology, serum chemistry, and urinalysis test results within the reference ranges or showing no clinically relevant deviations, as judged by the investigator at Screening.
5) All female subjects had a negative serum pregnancy test at Screening and upon check-in to the clinical unit. Female subjects of childbearing potential used one of the following acceptable birth control methods as specified before enrollment and throughout the study:
   - Surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months before the first dose of study drug;
   - Intrauterine device in place for at least 3 months before the first dose of study drug and throughout the study;
   - Barrier method (condom, diaphragm) with spermicide for at least 14 days before the first dose of study drug and throughout the study;
   - Surgical sterilization of the male partner (vasectomy at least 6 months before the first dose of study drug);
   - Hormonal contraceptives with a barrier method for at least 3 months before the first dose of study drug and throughout the study;
   - Postmenopausal women with amenorrhea for at least 2 years and with a documented serum follicle-stimulating hormone level >35 mIU/mL were eligible.
6) Subject was able and willing to comply with the protocol and study procedures.
7) Subject was able and willing to abstain from alcohol, grapefruit-containing food or beverages, caffeine, caffeine-containing products, St John's wort, and herbal supplements for 4 days before Day 1 until after completion of this study.
8) Subject was a nonsmoker or had quit smoking at least 6 months before the first dose of study drug and until study completion.

Diagnosis and Main Criteria for Exclusion:

Subjects were excluded from the study if any of the following criteria were met:

1) Subject had clinically relevant abnormalities in the screening or check-in assessments.
2) Subject had a supine blood pressure after resting for 5 minutes that was higher than 140 mm Hg systolic or 90 mm Hg diastolic, or lower than 95 mm Hg systolic or 65 mm Hg diastolic.
3) Subject had a supine heart rate after resting for 5 minutes that was outside the range of 60 to

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90 beats per minute.

4) Subject had received an investigational drug within 30 days before the first dose of study drug.

5) Subject had an active or recurring clinically significant disorder of the skin, head, ears, eyes, nose, throat, respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, genitourinary, neurologic, hematologic, musculoskeletal, immunologic, or psychological/psychiatric systems, or other disease requiring medical treatment.

6) Subject had a previous history (or evidence at Screening) of sick sinus syndrome or second/third degree atrioventricular block.

7) Subject had a history of cancer other than nonmelanomatous skin malignancies.

8) Subject had a positive test result at Screening for human immunodeficiency virus (1 or 2) antibody, hepatitis B surface antigen, or hepatitis C virus antibody.

9) Subject had any surgery of the gastrointestinal tract likely to affect drug absorption, distribution, metabolism, or excretion.

10) Subject had a previous allergy or intolerance to treatment with pitavastatin, diltiazem, or any drugs in these classes.

11) Subject had a history of drug or alcohol abuse.

12) Subject had a clinically significant illness within 4 weeks before the first dose of study drug.

13) Subject had donated more than 450 mL of blood within 30 days before the first dose of study drug.

14) Subject had a positive test result for cotinine, drugs of abuse (opiates, methadone, cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and oxycodone) or alcohol. Documentation of prescriptive use of medications containing any of these drugs was acceptable.

15) Subject was a member of the professional or ancillary personnel involved in the study.

16) Subject had taken any medication (with the exception of acetaminophen or vitamin supplements) within 14 days before the first dose of study drug.

17) Subject had taken any known inhibitors or inducers of cytochrome P4502C9 (CYP2C9), CYP3A4, or organic anion transporting polypeptide 1B1 (OATP1B1) within 30 days before the first dose of study drug.

18) Subjects who, in the opinion of the investigator, should not have participated in the study.

Test Product, Dose, Mode of Administration, and Lot or Batch Numbers:

- Pitavastatin, 4-mg tablets for oral administration; Lot number: 3087858
- Diltiazem (Cardizem LA) 240 mg tablets for oral administration were obtained commercially. Lot number: 10L075P

Duration of Treatment: Subjects received pitavastatin on Days 1 through 5 and Days 11 through 15; subjects received diltiazem on Days 6 through 15.

Reference Therapy, Dose, Mode of Administration, and Batch Number: None.

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Treatment and Administration: Each subject received a once-daily dose of pitavastatin 4 mg on Days 1 through 5 and Days 11 through 15 and a once-daily dose of diltiazem 240 mg on Days 6 through 15. On Days 1 through 4, 6 through 9, and 11 through 14, study drug was administered 30 minutes before a standard breakfast. On Days 5, 10, and 15, subjects fasted at least 8 hours before receiving study drug and continued to fast for 4 hours after dosing. On days when both pitavastatin and diltiazem were given, diltiazem was given first.

Criteria for Evaluation:

Pharmacokinetics: The following plasma PK parameters were calculated for pitavastatin and its lactone metabolite, diltiazem, N-desmethyl diltiazem, and desacetyl diltiazem: area under the concentration versus time curve over 1 dosing interval at steady state ($AUC_{0-\tau}$), maximum observed plasma concentration (C_{max}), time to achieve maximum observed plasma concentration (T_{max}), apparent terminal elimination half-life ($t_{1/2}$), and first-order terminal phase rate constant (K_el). Apparent clearance at steady state (CL_{ss}/F) and apparent volume of distribution (V_d/F) were calculated for the parent compounds pitavastatin and diltiazem.

Safety: Safety assessments included adverse event (AE) reporting, clinical laboratory test results (including hematology, serum chemistry [including lipid measures], and urinalysis), vital sign measurements (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), 12-lead electrocardiogram (ECG) recordings, and physical examination findings.

Statistical Methods:

Complete statistical methodology was presented in a separate statistical analysis plan.

Pharmacokinetics:

Plasma concentrations of pitavastatin, its lactone metabolite, diltiazem, N–desmethyl diltiazem, and desacetyl diltiazem were summarized for each time point and treatment by analyte. Mean and individual plasma concentration versus time profiles were presented graphically by treatment/analyte group. Pharmacokinetic parameters derived from plasma samples were summarized by analyte and treatment.

Pitavastatin and pitavastatin lactone natural log-transformed parameters (C_{max} and $AUC_{0-\tau}$) in the presence of diltiazem were compared with the natural log-transformed parameters in the absence of diltiazem using a linear-mixed model. In addition, natural log-transformed parameters for diltiazem and its N–desmethyl and desacetyl metabolites in the presence of pitavastatin were compared with the natural log-transformed parameters in the absence of pitavastatin.

A mixed-effects analysis of variance was performed on natural log-transformed PK parameters ($AUC_{0-\tau}$ and C_{max}) of pitavastatin, pitavastatin lactone, diltiazem, N–desmethyl diltiazem, and desacetyl diltiazem with treatment as a fixed effect and subject as a random effect. Geometric mean ratios and 90% confidence intervals (CI) for C_{max} and $AUC_{0-\tau}$ of each analyte were presented. No clinically significant interaction was concluded if the 90% CIs for the ratios of geometric means for C_{max} and $AUC_{0-\tau}$ of the parent drugs were entirely contained within the range of 0.80 to 1.25.

Safety:

Demographics and baseline characteristics were summarized. A summary of all AEs was presented by treatment and overall. The incidence of treatment-emergent AEs (TEAEs) by treatment and overall was summarized as follows: TEAEs, TEAEs leading to discontinuation, TEAEs related to study drug,

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severity of TEAEs, treatment-emergent serious AEs (SAEs), and treatment-emergent SAEs leading to death. Clinical laboratory results (including lipid measures), vital sign measurements, and 12-lead ECG results and changes from Baseline were summarized by scheduled time points. All AE, clinical laboratory, vital sign, 12-lead ECG, and physical examination data were presented in data listings.

RESULTS

Demographics and Disposition:

Twenty-eight subjects were enrolled and 27 subjects (96.4%) completed the study. One subject (Subject 128) was discontinued because of personal reasons. All 28 subjects were included in the safety population, and 26 subjects (92.9%) were included in the PK population. Overall, the majority of subjects enrolled in the study were white (22 of 28 subjects; 78.6%), ranged in age from 19 to 45 years, and had a mean body mass index of 25.79 kg/m^2. There were more male than female subjects (17 males and 11 females), and 50.0% of subjects were each Hispanic or Latino or not Hispanic or Latino. Twelve subjects (42.9%) had abnormal medical history findings that primarily involved the head, eyes, ears, nose, and throat and gastrointestinal body systems (5 subjects, 17.9% each); no finding was considered clinically significant. Four female subjects (14.3%) reported taking concomitant medications or ongoing prior medications for birth control; no other concomitant medications were reported during the study.

Pharmacokinetics:

Statistical Analysis of Pharmacokinetic Parameters of Pitavastatin and its Lactone Metabolite (Pharmacokinetic Population)

Analyte	Parameter (unit)	n	Geometric Mean		Ratio[a]	90% CI of Ratio
			Pitavastatin and Diltiazem	Pitavastatin Only		
Pitavastatin	C_{max} (ng/mL)	26	92.56	80.72	1.15	1.02–1.29
	$AUC_{0-\tau}$ (ng•h/mL)	26	213.99	194.99	1.10	1.03–1.17
Pitavastatin Lactone	C_{max} (ng/mL)	26	61.30	54.95	1.12	1.05–1.18
	$AUC_{0-\tau}$ (ng•h/mL)	26	563.37	507.56	1.11	1.04–1.18

Abbreviation: CI, confidence interval.

[a] Ratio of the geometric means was estimated by exponentiating the least squares mean difference between pitavastatin with diltiazem and pitavastatin only.

Note: The linear-mixed model was performed on the natural log-transformed parameters C_{max} and $AUC_{0-\tau}$ and included treatment as a fixed effect and subject as a random effect.

There was no drug interaction effect of diltiazem on the total exposure ($AUC_{0-\tau}$) of pitavastatin with a 10% increase in the AUC of pitavastatin. The 90% CI of the geometric mean ratio for $AUC_{0-\tau}$ (1.03, 1.17) was entirely contained within the criterion range (0.80, 1.25) sufficient to indicate the absence of a clinically significant interaction. However, the upper bound of the 90% CI of the geometric mean ratio for C_{max} fell slightly outside the criterion range indicating a weak effect of diltiazem on peak exposure with a geometric mean ratio of 1.15 (an increase of 15%).

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There was no drug interaction effect of diltiazem on the C_{max} and $AUC_{0-\tau}$ exposures of pitavastatin lactone (inactive metabolite) (increases of approximately 12% and 11%, respectively). The 90% CIs of the geometric mean ratios for $AUC_{0-\tau}$ and C_{max} were inside the range of 0.80 to 1.25, with values of (1.05, 1.18) and (1.04, 1.18), respectively.

Statistical Analysis of Pharmacokinetic Parameters of Diltiazem, N-Desmethyl Diltiazem, and Desacetyl Diltiazem (Pharmacokinetic Population)

Analyte	Parameter (unit)	n	Geometric Mean		Ratio[a]	90% CI of Ratio
			Pitavastatin and Diltiazem	Diltiazem Only		
Diltiazem	C_{max} (ng/mL)	26	191.67	205.81	0.93	0.85–1.02
	$AUC_{0-\tau}$ (ng·h/mL)	26	2999.11	3051.28	0.98	0.91–1.07
N-Desmethyl Diltiazem	C_{max} (ng/mL)	26	55.50	56.16	0.99	0.93–1.05
	$AUC_{0-\tau}$ (ng·h/mL)	26	995.65	982.11	1.01	0.96–1.07
Desacetyl Diltiazem	C_{max} (ng/mL)	26	20.64	20.31	1.02	0.95–1.09
	$AUC_{0-\tau}$ (ng·h/mL)	26	405.57	399.59	1.01	0.94–1.09

Abbreviation: CI, confidence interval.

[a] Ratio of the geometric means was estimated by exponentiating the least squares mean difference between diltiazem with pitavastatin and diltiazem only.

Note: The linear-mixed model was performed on the natural log-transformed parameters C_{max} and AUC_{0-t} and included treatment as a fixed effect and subject as a random effect.

There was no drug interaction effect of pitavastatin on the total and peak exposures of diltiazem (decreases of 2% and 7% in $AUC_{0-\tau}$ and C_{max}, respectively) or its metabolites, N-desmethyl diltiazem (an increase of 1% and a decrease of 1% in $AUC_{0-\tau}$ and C_{max}, respectively) and desacetyl diltiazem (increases of 1% and 2% in $AUC_{0-\tau}$ and C_{max}, respectively). The 90% CIs of the geometric mean ratios for $AUC_{0-\tau}$ and C_{max} were entirely contained within the range of 0.80 to 1.25.

Safety:

Overall, 15 of 28 subjects (53.6%) reported TEAEs. Treatment-emergent AEs were reported by 10 subjects (35.7%) during treatment with pitavastatin only, 7 subjects (25.0%) during treatment with diltiazem only, and 4 subjects (14.8%) during treatment with pitavastatin and diltiazem. Overall, the most frequently reported TEAEs were headache (5 subjects, 17.9%), presyncope (3 subjects, 10.7%), and nasopharyngitis and cough (2 subjects each, 7.1%). All other TEAEs were each reported by 1 subject.

Seven of 28 subjects (25.0%) reported treatment-related TEAEs: 3 subjects (10.7%) during treatment with pitavastatin, 6 subjects (21.4%) during treatment with diltiazem only, and 1 subject (3.7%) during treatment with pitavastatin and diltiazem. Headache was the most frequently reported treatment-related TEAE (4 subjects, 14.3%); all other treatment-related TEAEs were each reported by 1 subject.

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All TEAEs were mild in severity, and with the exception of a TEAE of pregnancy reported in 1 subject, all TEAEs resolved by the end of the study. No subject was discontinued due to an AE, and there were no SAEs or deaths.

The only clinically significant abnormal laboratory finding was a positive serum pregnancy test result for 1 subject obtained at the End-of-Study visit. There were no clinically significant findings in any of the other safety assessments (other clinical laboratory test results, vital sign measurements, ECG results, and physical examinations).

CONCLUSIONS

- The total exposure of pitavastatin at steady state was not affected by coadministration of diltiazem (an increase of 10%) (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 1.10 [1.03, 1.17]).
- There was a marginal increase of 15% in the peak exposure of pitavastatin with coadministration of diltiazem (geometric mean ratio [90% CI]: C_{max}, 1.15 [1.02, 1.29]).
- The total and peak exposures of pitavastatin lactone (inactive metabolite) were not affected by coadministration of diltiazem as seen by increases of 11% and 12% for total and peak exposures of pitavastatin lactone, respectively (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 1.11 [1.04, 1.18] and C_{max}, 1.12 [1.05, 1.18]).
- The total and peak exposures of diltiazem at steady state were not affected by coadministration of pitavastatin as seen by decreases of 2% and 7% for total and peak exposures of diltiazem, respectively (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 0.98 [0.91, 1.07] and C_{max}, 0.93 [0.85, 1.02]) .
- The total and peak exposures of N-desmethyl diltiazem were not affected by coadministration of pitavastatin as seen by an increase of 1% and a decrease of 1% for total and peak exposures of N-desmethyl diltiazem, respectively (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 1.01 [0.96, 1.07] and C_{max}, 0.99 [0.93, 1.05]). Similarly, the total and peak exposures of desacetyl diltiazem were not affected by coadministration of pitavastatin as seen by increases of 1% and 2% for total and peak exposures of desacetyl diltiazem, respectively (geometric mean ratio [90% CI]: $AUC_{0-\tau}$, 1.01 [0.94, 1.09] and C_{max}, 1.02 [0.95, 1.09]).
- Overall, multiple doses of pitavastatin alone and pitavastatin coadministered with diltiazem were safe and well tolerated by the healthy subjects in this study.

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/s/

SANG M CHUNG
01/18/2012

JAYABHARATHI VAIDYANATHAN
01/18/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022363Orig1s008, 009

OTHER REVIEW(S)

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: 22363/S-008 and S-009

Name of Drug: Livalo (pitavastatin) Tablets

Sponsor: Kowa Pharmaceuticals America, Inc. US Agent for Kowa Company Limited

Submission Date: September 21, 2011 (S-008) and December 23, 2011 (S-009);

Final PI: February 14, 2012 (email)

Background and Summary:

Primary Hyperlipidemia and Mixed Dyslipidemia

LIVALO® is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

Livalo is supplied in the tablet dose strengths of 1 mg, 2 mg, and 4 mg.

The last approved supplement, S-007, was a Prior Approval supplement that provided for a second manufacturing facility (Kowa Company Limited Facility in Nagoya, Japan) for the drug product. The change to the (b) (4) for this CMC supplement (S-007) was the addition of the Nagoya manufacturing facility language to the final page of the labeling document.

Supplement-008 provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **CLINICAL PHARMACOLOGY,** and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Livalo (pitavastatin) package insert.

Supplement-009 provides changes to the **CLINICAL PHARMACOLOGY**, **Pharmacokinetics** subsection of the Livalo package insert to add information on protease inhibitors and Diltiazem LA.

Review:

A track change version including all labeling changes since the last approved label and a final, clean version of the PI and PPI have been attached to the approval letter.

The Agency will issue one approval action letter referencing both supplements S-008 and S-009. The PI submitted on February 14, 2012 (by email) was accepted by Dr. Egan.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/2.22.12
(See appended electronic signature page)

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

/s/

MARGARET A SIMONEAU
02/22/2012