

## 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

None

## INDICATIONS AND USAGE

LIVALO is a HMG-CoA reductase inhibitor indicated for:

- Patients with primary hyperlipidemia 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 patients with severe renal impairment (glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>), not yet on hemodialysis. LIVALO should not be used in this patient population.
- 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 renal impairment (glomerular filtration rate 30 to < 60 mL/min/1.73 m<sup>2</sup>) and 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, 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 enzymes abnormalities and monitoring:** Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and 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](http://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)
- Fibrates:** Use with fibrate products may increase the risk of adverse skeletal muscle effects (5.1, 7.4)

## 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 renal impairment and patients receiving hemodialysis (2.2, 8.6) Patients with severe renal impairment not receiving hemodialysis have not been studied. LIVALO should not be used in this patient population (5.1, 8.6)

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

Revised [6/2011]

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## 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<sup>®</sup> 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 patients with severe renal impairment (glomerular filtration rate  $< 30$  mL/min/1.73 m<sup>2</sup>) not on hemodialysis. LIVALO should not be used in this patient population.

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 renal impairment (glomerular filtration rate 30 to  $< 60$  mL/min/1.73 m<sup>2</sup>) and 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. LIVALO should not be used in patients with severe renal impairment (glomerular filtration rate  $< 30$  mL/min/1.73 m<sup>2</sup>) not yet on hemodialysis.

#### 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 and any elevation of dose and periodically (e.g., semiannually) thereafter.

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.

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)*].

## 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  $\geq 2\%$  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  $\geq 2.0\%$  of Patients Treated with LIVALO and > Placebo in Short-Term Controlled Studies**

| Adverse Reactions* | Placebo<br>N= 208 | LIVALO<br>1 mg<br>N=309 | LIVALO<br>2 mg<br>N=951 | LIVALO<br>4 mg<br>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.

## 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 Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors may be increased with concurrent administration of 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)].

### 7.5 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)].

### 7.6 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  $\leq 36\%$  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  $\geq 0.3$  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 renal impairment (glomerular filtration rate 30 to  $< 60$  mL/min/1.73 m<sup>2</sup>) and 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.



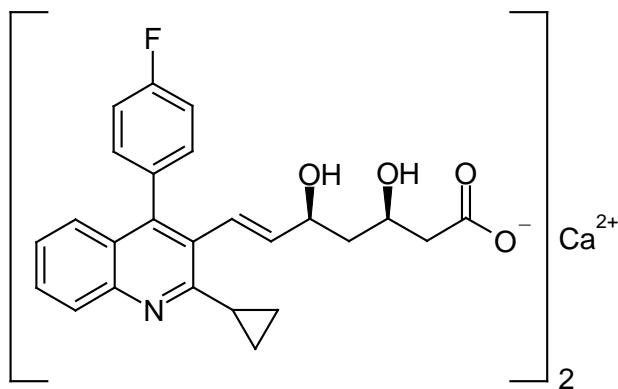
## 10 OVERDOSAGE

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, 6E)-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  $AUC_{0-inf}$  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 <sup>14</sup>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<sub>max</sub> 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<sub>max</sub> and AUC.

**Gender:** In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C<sub>max</sub> 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<sub>max</sub> 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 to <60 mL/min/1.73 m<sup>2</sup>) and end stage renal disease receiving hemodialysis, pitavastatin AUC<sub>0-inf</sub> is 79 and 86% higher than those of healthy volunteers, respectively, while pitavastatin C<sub>max</sub> 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. The effect of mild and severe renal impairment on pitavastatin exposure is unknown.

**Hepatic Impairment:** The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. The ratio of pitavastatin C<sub>max</sub> between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers was 2.7. The ratio of pitavastatin AUC<sub>inf</sub> between patients with moderate hepatic impairment and healthy volunteers was 3.8. The ratio of pitavastatin C<sub>max</sub> between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteers was 1.3. The ratio of pitavastatin AUC<sub>inf</sub> between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean pitavastatin t<sub>1/2</sub> 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 <sub>max</sub> * |
|----------------------|---|----------------|------------------------------|
| 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%                        |
| 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%                         |
| 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 <sub>max</sub> * |
|----------------------|---|-------------|----------------|------------------------------|
| Atazanavir           | Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days   |             | ↑ 6%           | ↑ 13%                        |
| 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%                        |
| 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%                         |
| 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

## 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 <sup>#</sup> | -43   | -35   | -31 | -18 | 5     |

<sup>#</sup> 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<br>2 mg daily        | 315                   | -38   | -30   | -28 | -14 | 4     | -35       |
| LIVALO<br>4 mg daily        | 298                   | -45   | -35   | -32 | -19 | 5     | -41       |
| Atorvastatin<br>10 mg daily | 102                   | -38   | -29   | -28 | -18 | 3     | -35       |
| Atorvastatin<br>20 mg daily | 102                   | -44   | -36   | -33 | -22 | 2     | -41       |
| Atorvastatin<br>40 mg daily | -----Not Studied----- |       |       |     |     |       |           |
| Atorvastatin<br>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<br>2 mg daily       | 307                   | -39   | -30   | -28 | -16 | 6     | -36       |
| LIVALO<br>4 mg daily       | 319                   | -44   | -35   | -32 | -17 | 6     | -41       |
| Simvastatin<br>20 mg daily | 107                   | -35   | -27   | -25 | -16 | 6     | -32       |
| Simvastatin<br>40 mg daily | 110                   | -43   | -34   | -31 | -16 | 7     | -39       |
| Simvastatin<br>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<br>1 mg daily       | 207                   | -31   | -25   | -22 | -13 | 1     | -29       |
| LIVALO<br>2 mg daily       | 224                   | -39   | -31   | -27 | -15 | 2     | -36       |
| LIVALO<br>4 mg daily       | 210                   | -44   | -37   | -31 | -22 | 4     | -41       |
| Pravastatin<br>10 mg daily | 103                   | -22   | -17   | -15 | -5  | 0     | -20       |
| Pravastatin<br>20 mg daily | 96                    | -29   | -22   | -21 | -11 | -1    | -27       |
| Pravastatin<br>40 mg daily | 102                   | -34   | -28   | -24 | -15 | 1     | -32       |
| Pravastatin<br>80 mg daily | -----Not Studied----- |       |       |     |     |       |           |

*Active-controlled study with simvastatin in patients with  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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<br>4 mg daily       | 233                   | -44   | -34   | -31 | -20 | 7     | -40       |
| Simvastatin<br>40 mg daily | 118                   | -44   | -34   | -31 | -15 | 5     | -39       |
| Simvastatin<br>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.

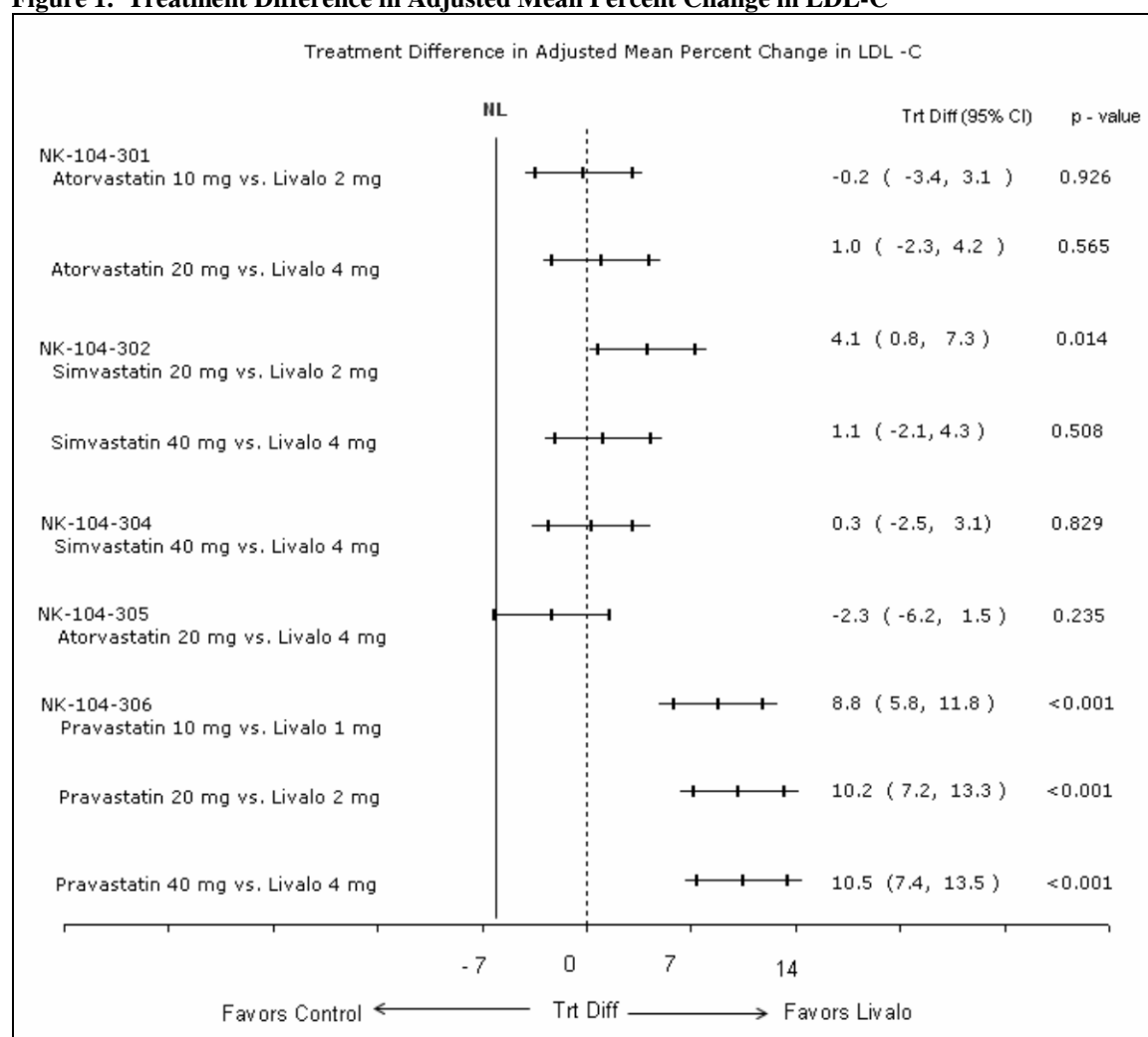
Lipid results are shown in Table 9. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit so that 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<br>4 mg daily        | 274                   | -41   | -32   | -28 | -20 | 7     | -36       |
| Atorvastatin<br>20 mg daily | 136                   | -43   | -34   | -32 | -27 | 8     | -40       |
| Atorvastatin<br>40 mg daily | -----Not Studied----- |       |       |     |     |       |           |
| Atorvastatin<br>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 enzymes be checked before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

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Product of Japan

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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

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/s/

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ERIC C COLMAN  
06/16/2011