HMG-CoA Reductase Inhibitor

# LIVALO

(Pitavastatin Calcium 2mg & Pitavastatin Calcium 4mg)

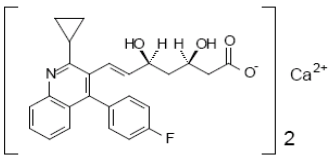
**Livalo 2: Reg. No. DKL1925202817A1**

**Livalo 4: Reg. No. DKL1925202817B1**

## (COMPOSITION AND DESCRIPTION)

## PHYSICOCHEMISTRY

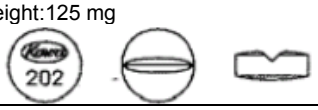
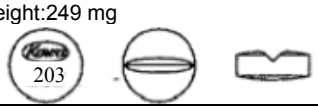
**Nonproprietary Name:** Pitavastatin calcium
**Chemical Name:** (+)-Monocalcium bis{(3R,5S,6E)-7-[2-cyclopropyl- 4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}
**Chemical Structure:**




**Molecular Formula:** $C_{50}H_{46}CaF_2N_2O_8$
**Molecular Weight:** 880.98

## DESCRIPTION:

A white to pale yellowish odorless powder. It is freely soluble in pyridine or in tetrahydrofuran, soluble in ethylene glycol, slightly soluble in methanol, very slightly soluble in ethanol (99.5) or in water, practically insoluble in acetonitrile or in diethyl ether. It dissolves in dilute hydrochloric acid.

| Brand Name | | LIVALO 2 | LIVALO 4 |
|---|---|---|---|
| Active Ingredient | | Each tablet contains 2 mg of pitavastatin calcium | Each tablet contains 4 mg of pitavastatin calcium |
| Inactive Ingredients | | Lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminometasilicate, magnesium stearate, triethyl citrate, hydrated silicon dioxide, titanium oxide, carnauba wax, food yellow No. 5 (sunset yellow FCF) | |
| Color / Dosage Form | | Slightly light-colored yellow-red round scored film-coated tablet with a secant line. | Light yellow, round scored film-coated tablet with a secant line. |
| Appearance | | Diameter: 7.1㎜ Thickness: 2.9㎜<br>Weight:125 mg<br>  | Diameter: 8.6㎜ Thickness: 3.9㎜<br>Weight:249 mg<br>  |
| ID Code | | 202 | 203 |

## (ACTIONS)

## CLINICAL PHARMACOLOGY

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.

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).

   **Diabetes Mellitus**:
   In an open-label prospective controlled study in 1269 Japanese patients with impaired glucose tolerance randomised to lifestyle modification with or without Livalo 1mg or 2mg daily, 45.7% of patients in the control group developed diabetes in comparison to 39.9% of patients in the Livalo group over a 2.8 year period, hazard ratio 0.82 [95% CI 0.68-0.99].

A meta-analysis of 4815 non-diabetic patients included in randomised controlled double-blind studies of at least 12-weeks duration (weighted mean follow-up 17.3 weeks [SD 17.7 weeks]) demonstrated a neutral effect for Livalo on the risk of new-onset diabetes (0.98% of control patients and 0.50% of Livalo patients developed diabetes, relative risk 0.70 [95% CI 0.30-1.61]) whilst 6.5% (103/1579) of control patients were treated with placebo; the rest were treated with statins including atorvastatin, pravastatin and simvastatin.

**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 pitava
statin, 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.

**Pediatric:**
A 12-week study in pediatric patients 8 to 16 years of age treated with pitavastatin 1 mg, 2 mg and 4 mg administered once daily, showed a dose-dependent increase in pitavastatin plasma concentrations at trough (for 2 mg and 4 mg doses) and 1 hour post dose. A dose-dependent increase in pitavastatin lactone plasma concentrations was observed at trough and 1 hour post dose.

**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 $AUC_{o\text{-}inf}$ 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 pharmacokinetics study, patients with severe renal impairment (glomerular filtration rate 15 – 29 mL/min/1.73 $m^2$) not receiving hemodyalisis were administered a single dose of LIVALO 4 mg. The $AUC_{o\text{-}inf}$ 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 1. 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 4 mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800 mg/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 2. 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 4 mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800 mg/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 4 mg QD on Days 1-5 and 12164 + darunavir/ritonavir 800 mg/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

## (NON CLINICAL STUDIES)

**NON CLINICAL TOXICOLOGY**

**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.

**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.

## (CLINICAL STUDIES)

**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 3). 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 3. 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 4). 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 4. 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 4. 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 5). 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 5. 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 5. 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 6). 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 6. 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 6. 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 7). 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 7. 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 7. 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.

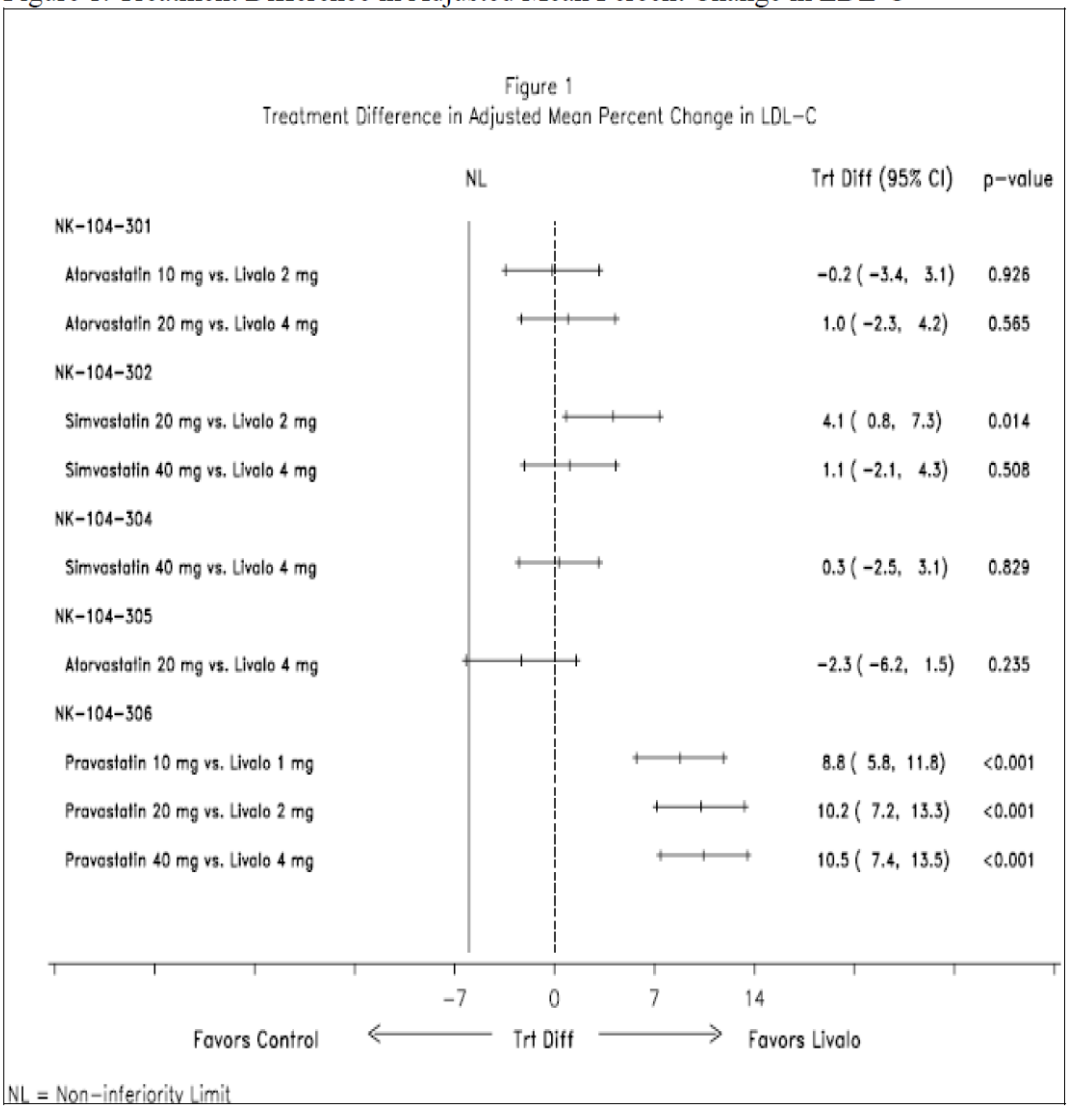
Lipid results are shown in Table 8. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%). The two treatment groups were not statistically different on LDL-C. However, the lower limit of the CI was -6.2%, slightly exceeding the -6% non-inferiority limit so that the non-inferiority objective was not achieved.

**Table 8. 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.

**HeFH in Pediatric Patients**

In a double-blind, placebo-controlled, 12-week trial, 82 pediatric patients (36 boys and 46 girls), 8 to 16 years of age with genetically confirmed HeFH, fasting low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL or LDL-C ≥160 mg/dL with an additional cardiovascular risk factor (male gender, a family history of premature CV disease, presence of low HDL (<45 mg/dL) or high TG (>150 mg/dL), presence of high lipoprotein (a) (>75 nmol/L), presence of type 2 diabetes mellitus or presence of hypertension) were randomized to LIVALO 1 mg, 2 mg, and 4 mg. Mean LDL-C at baseline was 235 mg/dL (range 160.5 mg/dL to 441mg/dL). Approximately 39% of patients were Tanner Stage 1 at baseline.

LIVALO significantly reduced plasma LDL-C, non-HDL-C, TC, and Apo-B compared to placebo. The reductions in LDL-C, Apo-B, TC, and non-HDL-C were dose dependent. There was no statistically significant improvement in HDL-C or TG at any LIVALO dose. See the lipid results in Table 9.

**Table 9. Lipid Response in Pediatric Patients with HeFH (Mean % Change from Baseline at Week 12)**

| Treatment | N | LDL-C | Apo-B | TC | TG*# | HDL-C* | non-HDL-C |
|---|---|---|---|---|---|---|---|
| Placebo | 19 | -1 | -3 | -1 | -3 | -1 | -1 |
| LIVALO 1 mg daily | 20 | -21 | -20 | -16 | -14 | 7 | -21 |
| LIVALO 2 mg daily | 24 | -30 | -25 | -25 | -15 | -3 | -29 |
| LIVALO 4 mg daily | 19 | -38 | -28 | -30 | 5 | -2 | -36 |

*Difference from placebo not statistically significant
# Median Percent Change from Baseline at Week 12

The long-term efficacy of LIVALO initiated in childhood to reduce morbidity and mortality in adulthood has not been

established.

## (INDICATIONS)

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. 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.

**2. Heterozygous Familial Hypercholesterolemia (HeFH)**
Pediatric patients aged 8 years and older with Heterozygous Familial Hypercholesterolemia (HeFH) to reduce elevated TC, LDL-C and Apo B.

**3. 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.

## (DOSAGE AND ADMINISTRATION)

**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.

Use in children should only be carried out by physicians experienced in the treatment of hyperlipidaemia and progress should be regularly reviewed.

**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 hemodyalisis, 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. A recommended dosage for pediatric patients with renal impairment has not been established.

**3. Use with Erythromycin**
In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded *[see Drug Interactions]*.

**4. Use with Rifampin**
In patients taking rifampin, a dose of LIVALO 2 mg once daily should not be exceeded *[see Drug Interactions]*.

## (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 angioedema, rash, pruritus, and urticaria have been reported with LIVALO *[see Adverse Reactions]*.
- Patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels *[see Warnings and Precautions, Use in Specific Populations]*.
- 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) and Nonclinical Toxicology]*.
- 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 and Nonclinical Toxicology]*.
- Co-administration with cyclosporine *[see Drug Interactions and Clinical Pharmacology]*.

## (WARNINGS AND PRECAUTIONS)

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, Use in Specific Populations and Clinical Pharmacology]*.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness, elevated serum creatine kinase, muscle fiber necrosis without inflammation, and anti -HMG-CoA reductase (HMGCR) antibody positive, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents. Patients should be carefully monitored.

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 or if muscle signs and symptoms persist after discontinuing LIVALO

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 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

There have been rare postmarketing reports of fatal and non-fatal hapatic 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]*.

3. **Endocrine Function**
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, include LIVALO.

4. **Diabetes Mellitus**
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk of hyperglycaemia (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m$^2$, raised triglycerides, hypertension), should be monitored both clinically and biochemically according to national guidelines. However, there has been no confirmed signal of a diabetes risk for pitavastatin either in post-marketing safety surveillance studies or in prospective studies.

5. **Pediatric population**
There is limited data on the long term effect on growth and sexual maturation in pediatric patients.

## (ADVERSE REACTION)

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]*.
- Liver Enzyme Abnormalities *[see Warning and Precautions]*.

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.

**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 in Adults with Primary Hyperlipidemia and Mixed Dyslipidemia
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 10. These studies had treatment duration of up to 12 weeks.

**Table 10. 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.

Adverse Reactions in Pediatric Patients Aged 8 Years and Older with HeFH
In a 12-week, double-blind, placebo-controlled trial of LIVALO 1 mg, 2 mg, and 4 mg once daily in 82 pediatric patients 8 years to 16 years of age with HeFH and a 52-week open-label trial in 85 pediatric patients with HeFH, the safety profile was similar to that observed in the adult population.

**Post marketing experience**
The following adverse reactions have been identified during post approval use of LIVALO. Because therse 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 impairement (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 non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptoms resolution (median of 3 weeks).

There have been rare reports of angioedema and immune-mediated necrotizing myopathy associated with statin use [see Warning and Precaution]

## (DRUG INTERACTIONS)

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

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 and Clinical Pharmacology]*.

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 and Clinical Pharmacology]*.

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

5. **Other 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 other fibrates *[see Warnings and Precautions, and Clinical Pharmacology]*.

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].*

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]*. However, patients receiving warfarin should have their PT and INR monitored when pitavastatin is added to their therapy.

8. **Pediatric population**
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the pediatric population is not known.

## (USE IN SPECIFIC POPULATIONS)

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]*.

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.

2. **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]*.

3. **Pediatric Use**
The safety and effectiveness of LIVALO as an adjunctive therapy to diet to reduce elevated TC, LDL-C, and Apo B in pediatric patients aged 8 years and older with HeFH have been established. Use of LIVALO for this indication is supported by a 12-week, double-blind, placebo-controlled trial in 82 pediatric patients 8 to 16 years of age with HeFH [see CLINICAL STUDIES] and a 52-week open-label trial in 85 pediatric patients with HeFH.
The safety and effectiveness of LIVALO in pediatric patients have not been established in pediatric patients younger than 8 years of age with HeFH or in pediatric patients with other types of hyperlipidemia (other than HeFH).

4. **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.

5. **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. A recommended dosage for pediatric patients with renal impairment has not been established *[see Dosage and Administration and Clinical Pharmacology]*.

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

## (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.

## (STORAGE)

Store below 30°C. Protect from light.
Livalo Tablet 2mg shelf life: 3 years
Livalo Tablet 4mg shelf life: 3 years

## (PACKAGING)

LIVALO Tablets 2mg: Box, 1 pouch @ 3 blisters @ 10 film-coated tablets
LIVALO Tablets 4mg: Box, 1 pouch @ 3 blisters @ 10 film-coated tablets

**ON DOCTOR'S PRESCRIPTION ONLY**
**HARUS DENGAN RESEP DOKTER**

Manufactured by and under license from
KOWA COMPANY, LTD.
Nagoya, Japan

Imported, packaged and released by
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

**Date of Package Insert**
August, 2022

# Informasi Produk Untuk Pasien

# LIVALO® Tablet 2 mg, 4 mg

Pitavastatin Calcium

## Apa yang terdapat dalam brosur ini

Informasi yang tercantum di dalam brosur mengenai 'LIVALO® Tablet 2 mg dan 4 mg' ini hanya merupakan informasi umum dan ditujukan untuk menunjang petunjuk yang diberikan oleh dokter Anda.

Brosur ini tidak dapat menggantikan peran atau saran tenaga kesehatan. Semua keputusan yang Anda ambil harus Anda diskusikan dengan tenaga kesehatan, berkaitan dengan kebutuhan medis Anda yang spesifik.

**Anda sebaiknya selalu berkonsultasi dengan dokter atau tenaga kesehatan lain untuk mendiskusikan masalah kesehatan atau kondisi medis, dan meminta saran lebih lanjut.**

**Simpan brosur ini dengan obat Anda. Anda mungkin perlu membacanya lagi.**

## Apa kegunaan obat ini

LIVALO® Tablet 2 mg dan 4 mg (Pitavastatin Calcium) digunakan untuk hiperlipidemia primer dan dislipidemia campuran pada pasien dewasa, serta hiperkolesterolemia familial heterozigot pada anak usia 8 tahun keatas.

Hiperlipidemia primer adalah suatu kelainan metabolisme lemak yang dikarenakan oleh kelainan genetik/ keturunan.

Dislipidemia (kelainan metabolisme lemak) campuran adalah suatu keadaan yang ditandai oleh adanya peningkatan kadar lemak (kolesterol dan trigliserida (suatu jenis lemak utama) dalam darah yang jumlahnya melewati batas normal.

Hiperkolesterolemia familial merupakan kondisi kelebihan kolesterol dalam darah yang disebabkan oleh faktor genetik/keturunan.

## Bagaimana cara kerja obat ini

Zat aktif LIVALO® Tablet 2 mg dan 4 mg yaitu Pitavastatin Calcium, bekerja dengan menghambat enzim HMG-CoA reduktase, suatu enzim yang berperan dalam proses pembentukan kolesterol di dalam tubuh. Dengan dihambatnya enzim tersebut, pembentukan kolesterol di dalam tubuh pun menjadi terhambat dan kadar lemak dalam darah menjadi turun.

## Sebelum penggunaan obat ini

**Anda tidak boleh menggunakan obat ini jika**:

- Mempunyai riwayat alergi dengan komposisi dalam obat ini.
- Merupakan pasien dengan penyakit hati aktif (terdapat kelainan pada hasil tes fungsi hati), contohnya terdapat peningkatan kadar suatu enzim bernama transaminase dalam darah yang belum jelas penyebabnya.
- Merupakan ibu yang sedang menyusui, hamil atau kemungkinan akan hamil.
- Sedang mengkonsumsi obat siklosporin.
- Sedang mengalami nyeri atau nyeri otot yang berulang atau tidak dapat dijelaskan.

Sebelum Anda menggunakan obat ini:

- Pastikan dokter Anda tahu jika Anda memiliki masalah jantung, hati dan ginjal.
- Pastikan dokter Anda melakukan tes darah untuk mengecek kadar kolesterol Anda dan melakukan tes fungsi hati sebelum Anda mengkonsumsi obat ini.
- Sangat penting untuk menginformasikan kepada dokter Anda jika Anda mengkonsumsi obat lain, termasuk obat yang dijual bebas, vitamin atau suplemen herbal serta informasikan pula riwayat kesehatan Anda.

## Cara penggunaan obat ini

- Gunakan LIVALO® Tablet 2 mg dan 4 mg sesuai petunjuk dokter atau apoteker Anda. Rentang dosis yang dianjurkan adalah 1 mg sampai 4 mg dengan dosis awal adalah 2 mg dan maksimum 4 mg.
- Penggunaan pada anak-anak hanya boleh dilakukan sesuai dengan petunjuk dokter yang berpengalaman pada pengobatan hiperlipidemia dan kemajuan pengobatan harus ditinjau secara teratur.
- Jika Anda adalah pasien dengan gangguan ginjal menengah (secara medis ditunjukkan dengan laju fltrasi glomerulus 30 sampai 59 mL/menit/1.73 $m^2$), gangguan ginjal parah (secara medis ditunjukkan dengan laju filtrasi glomerulus 15 sampai 29 mL/menit/1.73 $m^2$) yang tidak menjalani cuci

darah dan sedang menjalani cuci darah, dosis awal yang dianjurkan adalah 1 mg sekali sehari dan maksimum 2 mg sekali sehari.
- Jika Anda sedang mengkonsumsi obat Eritromisin, dosis yang diperbolehkan adalah 1 mg sekali sehari, tidak boleh lebih.
- Jika Anda sedang mengkonsumsi obat Rifampisin, dosis yang diperbolehkan adalah 2 mg sekali sehari, tidak boleh lebih.
- Keluarkan obat dari kemasan terlebih dahulu.
- Anda harus meminum obat bersamaan dengan segelas air putih.
- Obat harus ditelan seluruhnya. Tidak boleh dihancurkan, dilarutkan, atau dikunyah.
- Usahakan Anda mengkonsumsi obat ini pada waktu yang sama setiap harinya secara teratur, dapat sebelum atau sesudah makan.
- Jika Anda lupa meminum obat ini, minumlah sesegera mungkin ketika Anda ingat. Sebaiknya Anda menyimpan obat ini di tempat yang mudah terlihat dan mudah dijangkau.

## Selama penggunaan obat ini

- Konsultasikan pada dokter jika Anda mengalami gejala alergi, seperti ruam atau gatal-gatal.
- Konsultasikan pada dokter jika Anda mengalami nyeri otot, lemas, atau nyeri yang diikuti dengan rasa tidak enak atau demam, atau jika gejala pada otot tersebut tidak hilang setelah penghentian obat ini.
- Konsultasikan pada dokter jika Anda merasakan keletihan yang tidak biasa, kehilangan nafsu makan, nyeri perut bagian atas, urin berwarna gelap, atau kekuningan pada kulit atau mata.
- Konsultasikan pada dokter jika terjadi peningkatan kadar gula darah.
- Pastikan dokter Anda melakukan tes darah untuk mengecek kadar kolesterol Anda dan melakukan tes fungsi hati selama Anda mengkonsumsi obat ini. Dosis dapat berubah sesuai dengan hasil tes tersebut.
- Teraturlah dalam berkonsultasi dengan dokter sehingga kemajuan pengobatan Anda bisa terpantau.
- Jangan berhenti minum obat ini tanpa berkonsultasi dengan dokter Anda terlebih dahulu.
- Jika Anda membeli obat-obatan, konsultasikanlah kepada dokter atau apoteker Anda bahwa obat-obatan tersebut aman untuk digunakan bersamaan dengan LIVALO® Tablet 2 mg atau 4 mg ini.
- Obat ini untuk Anda. Jangan pernah memberikannya kepada orang lain bahkan jika kondisi mereka tampaknya sama seperti kondisi Anda.

## Efek samping

Obat dapat menyebabkan efek samping yang tidak diinginkan meskipun tidak semua orang mengalaminya. Konsultasikanlah kepada dokter atau apoteker jika salah satu efek samping berikut berlanjut atau menjadi bermasalah:

- Sakit punggung
- Konstipasi
- Diare
- Nyeri otot
- Nyeri di kaki dan tangan

Efek samping lain yang tidak tercantum dalam brosur ini mungkin terjadi. Periksakanlah kepada dokter atau apoteker Anda jika Anda memiliki gejala yang tidak diinginkan.

## Setelah penggunaan obat

- Simpan obat ini dalam suhu ruangan, di tempat yang kering dan jauhkan dari jangkauan anak-anak.
- Jangan menggunakan dan menyimpan obat-obatan yang kedaluwarsa atau tidak diinginkan. Bawa obat-obatan tersebut ke apotek setempat untuk dimusnahkan.

## Deskripsi produk

LIVALO® Tablet 2 mg merupakan tablet bulat salut selaput berwarna kuning-merah sedikit terang dan terdapat garis potong pada bagian tengah.

LIVALO® Tablet 4 mg merupakan tablet bulat salut selaput berwarna kuning terang dan terdapat garis potong pada bagian tengah.

Ukuran kemasan:
Box berisi 30 tablet (10 tablet x 3 blister)

Komposisi:
Lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminometasilicate, magnesium stearate, triethyl citrate, hydrated silicon dioxide, titanium oxide, carnauba wax, food yellow No. 5 (sunset yellow FCF)

No. Reg:
Livalo 2mg : DKL1925202817A1
Livalo 4mg : DKL1925202817B1

HARUS DENGAN RESEP DOKTER

## Dibawah lisensi dan diproduksi oleh:

KOWA COMPANY, LTD
Nagoya, Japan

## Diimpor, dikemas dan dirilis oleh:

PT Mitsubishi Tanabe Pharma Indonesia

Bandung 40612, Indonesia.

Version: MTID/PIL/LIVALO/2021/001

Referensi :

1. Produk Informasi Livalo 2 mg dan 4 mg
2. http://www.livalorx.com/

Versi revisi: Agustus 2022