LIVALO® (pitavastatin) Tablet
1 mg, 2 mg, and 4 mg

Kowa Pharmaceuticals America, Inc.

Montgomery, AL 36117

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Package Insert – Product Labeling

Version of October 2013
Version 8.0

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 or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) (1.1)

Limitations of Use (1.2):

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

- Tablets: 1 mg, 2 mg, and 4 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most frequent adverse reactions (rate ≥2.0% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Kowa Pharmaceuticals America, Inc. at 1-877-334-3464 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS *

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Primary Hyperlipidemia and Mixed Dyslipidemia

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

1.2 Limitations of Use

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

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

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

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

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

2.2 Dosage in Patients with Renal Impairment

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

2.3 Use with Erythromycin

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)]*.
Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors coadministered with colchicine, and caution should be exercised when prescribing LIVALO with colchicine [see *Drug Interactions* (7.7)].
There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.
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.

5.2 Liver Enzyme Abnormalities
Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including LIVALO. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.
In placebo-controlled Phase 2 studies, ALT >3 times the upper limit of normal was not observed in the placebo, LIVALO 1 mg, or LIVALO 2 mg groups. One out of 202 patients (0.5%) administered LIVALO 4 mg had ALT >3 times the upper limit of normal.
It is recommended that liver enzyme tests be performed before the initiation of LIVALO and if signs or symptoms of liver injury

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LIVALO, promptly interrupt therapy. If an alternate etiology is not found do not restart LIVALO.
As with other HMG-CoA reductase inhibitors, LIVALO should be used with caution in patients who consume substantial quantities of alcohol. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of LIVALO *[see Contraindications (4)]*.

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

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the label:
- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) *[see Warnings and Precautions (5.1)]*.

- Liver Enzyme Abnormalities *[see Warning and Precautions (5.2)]*.

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

6.1 Clinical Studies Experience
Because clinical studies on LIVALO are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of LIVALO cannot be directly compared with that in the clinical studies of other HMG-CoA reductase inhibitors and may not reflect the frequency of adverse reactions observed in clinical practice.
Adverse reactions reported in ≥ 2% of patients in controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had treatment duration of up to 12 weeks.
Table 1. Adverse Reactions* Reported by ≥2.0% of Patients Treated with LIVALO and > Placebo in Short-Term Controlled Studies

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

* Adverse reactions by MedDRA preferred term.

Other adverse reactions reported from clinical studies were arthralgia, headache, influenza, and nasopharyngitis.
The following laboratory abnormalities have also been reported: elevated creatine phosphokinase, transaminases, alkaline phosphatase, bilirubin, and glucose.
In controlled clinical studies and their open-label extensions, 3.9% (1 mg), 3.3% (2 mg), and 3.7% (4 mg) of pitavastatin-treated patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: elevated creatine phosphokinase (0.6% on 4 mg) and myalgia (0.5% on 4 mg).
Hypersensitivity reactions including rash, pruritus, and urticaria have been reported with LIVALO.

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of LIVALO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Adverse reactions associated with LIVALO therapy reported since market introduction, regardless of causality assessment, include the following: abdominal discomfort, abdominal pain, dyspepsia, nausea, asthenia, fatigue, malaise, hepatitis, jaundice, fatal and non-fatal hepatic failure, dizziness, hypoesthesia, insomnia, depression, interstitial lung disease, erectile dysfunction and muscle spasms.
There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of

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