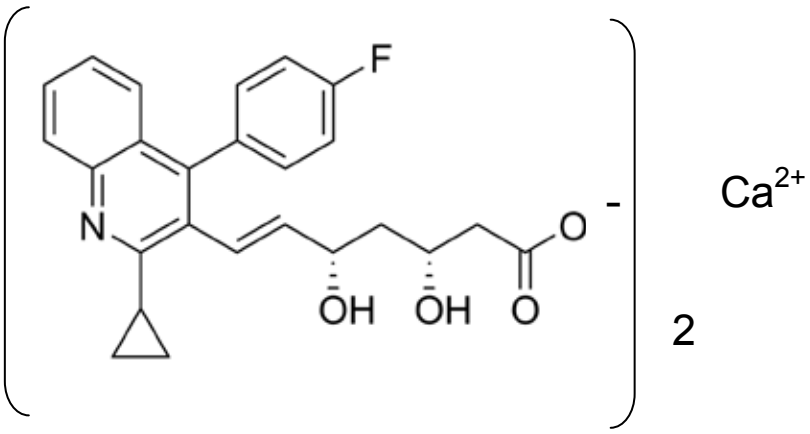
PRODUCT INFORMATION
LIVALO®

NAME OF THE MEDICINE

Pitavastatin calcium

Chemical Structure

Pitavastatin calcium is chemically identified as (+)monocalcium bis{(3R, 5S, 6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}. The structural formula is:



Empirical formula: $C_{50}H_{46}CaF_2N_2O_8$

MW= 880.98

CAS Number

CAS 147526-32-7 (147511-69-1 for free pitavastatin)

DESCRIPTION

Pitavastatin is odourless 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, hydroxypropylcellulose, hypromellose, aluminium magnesium silicate, magnesium stearate, and film coating containing the following inactive ingredients: hypromellose, titanium dioxide, triethyl citrate, and colloidal anhydrous silica.

PHARMACOLOGY

Mechanism of Action

Pitavastatin competitively inhibits HMG-CoA reductase, the rate-limiting enzyme in the biosynthesis of cholesterol, and inhibits cholesterol synthesis in the liver. As a result the expression of LDL receptors in the liver is increased, promoting the uptake of circulating LDL from the blood, decreasing total cholesterol (TC) and LDL-cholesterol (LDL-C) concentrations

in the blood. Its sustained inhibition of hepatic cholesterol synthesis reduces VLDL secretion into the blood, reducing plasma triglyceride (TG) levels.

Pharmacodynamics

Pitavastatin reduces elevated LDL-C, total cholesterol and triglycerides and increases HDL-cholesterol (HDL-C). It reduces apolipoprotein B (Apo-B), and produces variable increases in Apo-A1. It also reduces non-HDL-C and elevated TC/HDL-C, and Apo-B/Apo-A1 ratios. A variety of clinical and pathological studies have demonstrated that elevated cholesterol and lipoprotein levels TC, LDL-C and Apo B promote human atherosclerosis and are risk factors for developing cardiovascular disease. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the levels of TC and LDL-C and inversely with the level of HDL-C.

In a randomised, double-blind, placebo-controlled, 4-way parallel, active-comparator study with moxifloxacin in 174 healthy participants, pitavastatin 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).

Pharmacokinetics

Absorption

Pitavastatin is rapidly absorbed from the upper gastrointestinal tract and peak plasma concentrations are achieved within one hour after oral administration. Absorption is not affected by food. Unchanged drug undergoes enterohepatic circulation and is well absorbed from the jejunum and ileum. The absolute bioavailability of pitavastatin is 51%.

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 133 L. Pitavastatin is actively transported into hepatocytes, the site of action and metabolism, by multiple hepatic transporters including OATP1B1 and OATP1B3. Plasma AUC is variable with an approximately 4-fold range between the highest and lowest values. Studies with SLCO1B1 (the gene which encodes OATP1B1) suggests that polymorphism of this gene could account for much of the variability in AUC. Pitavastatin is not a substrate for p-glycoprotein.

Metabolism

Unchanged pitavastatin is the predominant drug moiety in plasma. The principal metabolite is the inactive lactone which is formed via an ester-type pitavastatin glucuronide conjugate by UDP glucuronosyltransferase (UGT1A3 and 2B7). In vitro studies, using 13 human cytochrome P450 (CYP) isoforms, indicate that the metabolism of pitavastatin by CYP is minimal; CYP2C9 (and to a lesser extent CYP2C8) is responsible for the metabolism of pitavastatin to minor metabolites.

Excretion

Unchanged pitavastatin is rapidly cleared from the liver in the bile, but undergoes enterohepatic recirculation, contributing to its duration of action. Less than 5% of pitavastatin is excreted in the urine. The plasma elimination half-life ranges from 5.7 hours (single dose) to 8.9 hours (steady state) and the apparent geometric mean oral clearance is 43.4 L/h after single dose.

Effect of Food

The maximum plasma concentration of pitavastatin was reduced by 43% when it was taken with a high-fat meal, but AUC was unchanged.

Race

There was no difference in the pharmacokinetic profile of pitavastatin between Japanese and Caucasian healthy volunteers when age and body weight was taken into account.

Elderly

In a pharmacokinetic study which compared healthy young and elderly volunteers, pitavastatin AUC was 1.3-fold higher in elderly subjects. This has no effect on the safety or efficacy of pitavastatin in elderly patients in clinical trials.

Gender

In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin AUC was increased 1.6-fold in women. This has no effect on the safety or efficacy of Livalo in women in clinical trials.

Renal Impairment

For patients with stage 3 kidney disease (glomerular filtration rate (GFR) 30-59 mL/min/1.73m^2) and those on haemodialysis increases in AUC values were 1.8-fold and 1.7-fold respectively. (see 'Dosage and Administration')

Hepatic Impairment

For patients with mild (Child-Pugh A) hepatic impairment AUC was 1.6 times that in healthy subjects, while for patients with moderate (Child-Pugh B) hepatic impairment AUC was 3.9-fold higher. Dose restrictions are recommended in patients with mild and moderate hepatic impairment (see 'Dosage and Administration'). Pitavastatin is contraindicated in patients with severe hepatic impairment.

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. (see 'Interactions with other medicines').

Warfarin

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

CLINICAL STUDIES

Primary Hypercholesterolaemia or Mixed Dyslipidaemia

Livalo reduces TC, LDL-C, ApoB, non high-density lipoprotein cholesterol (non HDL-C) and TG, and increases HDL-C in patients with primary hypercholesterolaemia or mixed dyslipidaemia. The clinical trial program showed that Livalo is effective in a wide variety of patient populations regardless of race, age or sex.

Dose-ranging study: A multicenter, randomised, double-blind, placebo-controlled, dose-ranging study was performed to evaluate the efficacy of Livalo compared with placebo in 251 patients with primary hypercholesterolaemia (Table 1). Livalo given as a single daily dose for 12 weeks reduces elevated LDL-C, total-C and TG and increases HDL-C. It reduces Apo-B, and produces variable increases in Apo-A1 (see Table 1). It also reduces non-HDL-C and elevated TC/HDL-C, and Apo-B/Apo-A1 ratios.

Table 1. Dose-Response in Patients with Primary Hypercholesterolaemia (Adjusted Mean % Change from Baseline over 12 Weeks)

Treatment	N	LDL-C	TC*	TG	HDL-C	Apo-B	Apo-A1
Placebo	51	-4.0	-1.3	-2.1	2.5	0.3	3.2
LIVALO 1mg	52	-33.3	-22.8	-14.8	9.4	-24.1	8.5
LIVALO 2mg	49	-38.2	-26.1	-17.4	9.0	-30.4	5.6
LIVALO 4mg	50	-46.5	-32.5	-21.2	8.3	-36.1	4.7

* unadjusted

Active-controlled study with atorvastatin (NK-104-301): Livalo was compared with the HMG-CoA reductase inhibitor, atorvastatin in a randomised, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 817 patients with primary hypercholesterolaemia or mixed dyslipidaemia. (baseline TG <4.6 mmol/L and LDL 4.2-5.7 mmol/L). Patients were eligible for inclusion if they were male or female aged 18 to 75 years, with primary hypercholesterolaemia or mixed dyslipidaemia, LDL-C ≥4.2 and ≤5.7 mmol/L and TG ≤ 4.6 mmol/L. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomised to a 12-week treatment with either Livalo or atorvastatin (Table 5). Non-inferiority of Livalo 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 2. For the percent change from baseline to endpoint in LDL-C, Livalo was non-inferior to atorvastatin for the two pair-wise 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 2. Response by Dose of LIVALO and Atorvastatin in Patients with Primary Hypercholesterolaemia or Mixed Dyslipidaemia (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 randomised, multicenter, double-blind, double-dummy, active-controlled, non-inferiority Phase 3 study of 843 patients with primary hypercholesterolaemia or mixed dyslipidaemia (baseline LDL 4.8 mmol/L). The same inclusion criteria were applied as for NK-104-301. Patients entered a 6- to 8-week wash-out/dietary lead-in period and then were randomised to a 12 week treatment with either Livalo or simvastatin (Table 6). Non-inferiority of Livalo 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 3. 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%; p-value 0.014) and 1% (-2%, 4%; p-value 0.509), respectively.

Table 3. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hypercholesterolaemia or Mixed Dyslipidaemia (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 randomised, multicenter, double-blind, double-dummy, parallel group, active-controlled non-inferiority Phase 3 study of 942 elderly patients (≥ 65 years) with primary hypercholesterolaemia or mixed dyslipidaemia. Patients entered a 6- to 8-week washout/dietary lead-in period, and then were randomised to a once daily dose of Livalo or pravastatin for 12 weeks (Table 4). 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. Livalo showed superiority to pravastatin at all dose comparisons.

Lipid results are shown in Table 4. Livalo significantly reduced LDL-C compared to pravastatin as demonstrated by the following pair wise 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 4. Response by Dose of LIVALO and Pravastatin in Patients with Primary Hypercholesterolaemia or Mixed Dyslipidaemia (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 randomised, multicenter, double-blind, double-dummy, active controlled, non-inferiority Phase 3 study of 351 patients with primary hypercholesterolaemia or mixed dyslipidaemia (baseline LDL 4.3 mmol/L) with ≥2 risk factors for coronary heart disease. Inclusion criteria included: male and female patients (18 to 75 years), with primary hypercholesterolaemia or mixed dyslipidaemia, LDL-C ≥ 3.4 and ≤ 5.7 mmol/L despite dietary therapy and elevated TG ≤ 4.6 mmol/L at 2 visits during the lead-in period with ≥ 2 risk factors for coronary heart disease (smoking, hypertension, low HDL-C (< 1.0 mmol/L), family history of premature CHD, or age ≥ 45 years for men and ≥ 55 for women. After a 6- to 8-week wash-out/dietary lead-in period, patients were randomised to a 12-week treatment with either Livalo or simvastatin (Table 5). 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 show in Table 5. 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 5. Response by Dose of LIVALO and Simvastatin in Patients with Primary Hypercholesterolaemia or Mixed Dyslipidaemia 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 randomised, multicenter, double-blind, double-dummy, parallel group, active controlled, non-inferiority Phase 3 study of 410 subjects with type II diabetes mellitus and mixed dyslipidaemia (baseline LDL 3.8 mmol/L). Inclusion criteria were: males and females aged 18 to 75 years, type II diabetes mellitus, on oral hypoglycaemics or insulin but not glitazones, HbA1c ≤ 7.5%, absences of diabetic retinopathy, cataracts or diabetic nephropathy, BMI ≤ 35 kg/m^2, compliant with EAS recommended diet during lead in period (6 to 8 weeks) and LDL-C ≥2.6 and ≤5.7 mmol/L despite dietary therapy and TG ≥ 1.7 mmol/L at 2 visits during the lead-in period. Patients entered a 6- to 8-week washout/dietary lead-in period and were randomised 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 6. The treatment difference (95% CI) for LDL-C percent change from baseline was -2% (-6.2%, 1.5%, p-value 0.235). 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. This appears to be more of a statistical issue as the effect size for LDL-C reduction was similar based on dose comparisons in other studies.

Table 6. Response by Dose of LIVALO and Atorvastatin in Patients with Type II Diabetes Mellitus and Combined Dyslipidaemia (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----------						

Patients with secondary dyslipidaemias were excluded from the clinical development programme and the effect of Livalo on cardiovascular morbidity and mortality has not yet been determined.

Heterozygous Familial Hypercholesterolaemia

NK-104-09 was a open-label, uncontrolled long term Japanese study in 36 patients with heterozygous familial hypercholesterolaemia (HeFH). At week 52 LDL-C decreased by 34.4%, TC by 45.2%, TG by 34%, Apo-B by 32.4% and HDL-C increased by 5.4%

Homozygous Familial Hypercholesterolaemia

Livalo has not been investigated in patients with homozygous familial hypercholesterolaemia

INDICATIONS

Livalo is indicated as an adjunct to diet for the treatment of adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, when response to diet and other non-pharmacological measures is inadequate.

Prior to initiating therapy with Livalo, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

CONTRAINDICATIONS

Hypersensitivity to pitavastatin or to any of the excipients or other statins

Severe hepatic impairment, active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN)

Concomitant cyclosporin

Concomitant erythromycin

During pregnancy, while breast feeding and in women of child bearing potential not taking appropriate contraceptive precautions

PRECAUTIONS

Muscle Effects

In common with other HMG-CoA reductase inhibitors (statins), there is the potential for myalgia, myopathy and, rarely, rhabdomyolysis and acute renal failure to develop. The risk of muscle effects occurs at any dose but the risk increases in a dose-dependent manner.

In clinical trials doses ranging from 8 mg to 64 mg have been assessed. Significantly increased rates of rhabdomyolysis and myopathy were reported for doses of 32 mg and above. (See ‘Adverse Effects’)

The risk of myopathy may also be increased with the concomitant use of cyclosporin, erythromycin, rifampicin, atazanavir, fibrates, fusidic acid and niacin. (see 'Contraindications' and 'Interactions with Other Medicines').

Patients should be asked to report any unexplained muscle symptoms. Creatine kinase (CK) levels should be measured in any patient reporting muscle pain, muscle tenderness or weakness especially if accompanied by malaise or fever. CK should not be measured following strenuous exercise or in the presence of any other plausible cause of CK increase which may confound interpretation of the result. When elevated CK concentrations (>5x ULN) are noted, a confirmatory test should be performed within 5 to 7 days.

Before Treatment

In common with other statins, Livalo should be prescribed with caution in patients with predisposing factors for rhabdomyolysis. A CK level should be measured, to establish a reference baseline, in the following situations:

Renal impairment,

Hypothyroidism,

Personal or family history of hereditary muscular disorders,

Previous history of muscular toxicity with a fibrate or another statin,

History of liver disease or alcohol abuse,

Elderly patients with other predisposing risk factors for rhabdomyolysis,

In such situations, clinical monitoring is recommended and the risk of treatment should be considered in relation to the possible benefit. Treatment with Livalo should not be started if CK values are >5x ULN.

During Treatment

Patients must be encouraged to report unexplained muscle pain, weakness or cramps immediately. CK levels should be measured and treatment stopped if CK levels are elevated (>5x ULN). Dose reduction or stopping treatment should be considered if muscular symptoms are severe even if CK levels are ≤5 x ULN. If symptoms resolve and CK levels return to normal, then re-introduction of Livalo may be considered at a dose of 1mg and with close monitoring.

Liver Effects

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., semi-annually) 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')

Endocrine Function

HMG-CoA reductase inhibitors have been shown to interfere with cholesterol synthesis and lower circulating cholesterol levels, and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. No studies have been done to examine the effect of pitavastatin on endocrine function.

Eye Disorders

The rate of eye disorder TEAEs in all European and US 12- or 16-week Phase II and III placebo- and active-controlled studies pooled was 0.7% compared to 1.4% in the placebo group. There were no reports of cataracts in pitavastatin treated patients. In a pooled analysis of all European and US Phase II and III data, including treatment to 72 weeks, the rate of eye disorders was 1.6% and 1.5% in the 2 mg and 4 mg groups, respectively. The rate of conjunctivitis was 0.4% and for cataracts was 0.2%.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Use in the Elderly

Of the 2,800 patients randomised to Livalo 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were 65 years and older. There was an increased frequency of adverse events and serious adverse events in the elderly. However, no significant differences in efficacy or safety were observed between elderly patients and younger patients.

Other effects

A temporary suspension of Livalo is recommended for the duration of treatment with erythromycin, other macrolide antibiotics or fusidic acid (see 'Interactions with other medicines').

Livalo should be used with caution in patients taking drugs known to cause myopathy (e.g. fibrates or niacin).

The tablets contain lactose. Patients with the rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on Fertility

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 ischaemia. 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 foetuses were observed.

Use in Pregnancy

Pregnancy Category D (Teratogenic effects)

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 foetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs

during pregnancy should have little impact on long-term outcomes of primary hyperlipidaemia 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 foetal 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 foetal tissues at ≤36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation. Embryo-foetal 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-foetal 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 foetal 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 corresponds to less than or equal to human systemic exposure at 4 mg/day dose based on AUC).

Livalo may cause foetal 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 foetus and the lack of known clinical benefit with continued use during pregnancy.

Use in Lactation

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. Studies have shown that pitavastatin is readily excreted in the milk of lactating rats. 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').

Paediatric Use

Safety and effectiveness of Livalo in paediatric patients have not been established.

Use in Renal Insufficiency

For patients with Stage 3 kidney disease (GFR 30-59 mL/min/1.73m^2) and those on haemodialysis increases in AUC values were 1.8-fold and 1.7-fold respectively. Livalo has not been studied in patients with Stage 4 kidney disease (GFR < 30 mL/min/1.7m^2) not on haemodialysis. Livalo should be used with caution in patients with stage 3 or stage 4 kidney disease. Dose increments should be instituted only with close monitoring. In those with stage 4 kidney disease, 4mg dose is not recommended. (see 'Dosage and Administration' and 'Pharmacokinetics').

Use in Hepatic Insufficiency

For patients with mild (Child-Pugh A) hepatic impairment AUC was 1.6 times that in healthy subjects, while for patients with moderate (Child-Pugh B) hepatic impairment AUC was 3.9-fold

higher. Dose restrictions are recommended in patients with mild and moderate hepatic impairment. (see 'Dosage and Administration') Livalo is contraindicated in patients with severe hepatic impairment.

Carcinogenicity

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 tumours.

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 tumours 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 tumours were observed.

Genotoxicity

Pitavastatin was not mutagenic in a battery of genetic toxicology studies including the Ames mutagenicity assay with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the *in vivo* micronucleus test following a single administration in mice and multiple administrations in rat, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In a chromosome aberration assay in Chinese hamster lung cells, clastogenicity was observed at the highest doses tested which also elicited high levels of cellular cytotoxicity. Overall, the weight of evidence suggests that pitavastatin does not pose a genotoxic risk for humans.

INTERACTIONS WITH OTHER MEDICINES

The principle 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. However, interactions are possible at the level of uptake by hepatic transporters of pitavastatin into the liver. Pitavastatin is actively taken up into the liver predominantly through the OATP1B1 transporter and competition for, or inhibition of, this transporter by other drugs may lead to interactions with pitavastatin.

Cyclosporin

Co-administration of a single dose of cyclosporin with Livalo at steady state resulted in a 4.6-fold increase in pitavastatin AUC. The effect of steady state cyclosporin on steady state Livalo is not known. Livalo is contraindicated in patients being treated with cyclosporin. (see 'Contraindications')

Protease inhibitors:

Co-administration with Livalo at the same time may result in minor changes in pitavastatin AUC.

Erythromycin

Co-administration with Livalo resulted in a 2.8-fold increase in pitavastatin AUC. A temporary suspension of Livalo is recommended for the duration of treatment with erythromycin or other macrolide antibiotics.

Rifampicin

Co-administration with Livalo at the same time resulted in a 1.3-fold increase in pitavastatin AUC due to reduced hepatic uptake. A maximum daily dose of 2 mg pitavastatin is recommended with concomitant rifampicin. (see 'Pharmacology').

Enalapril

Co-administration with Livalo showed no significant pharmacokinetic interaction. No dose adjustment is required for concomitant administration of pitavastatin and enalapril.

Atazanavir

Co-administration of Livalo and atazanavir results in a 1.3-fold increase in the pitavastatin AUC, but has little effect on the pharmacokinetics of atazanavir.

Fibrates

The use of fibrates alone is occasionally associated with myopathy. Co-administration of fibrates with statins has been associated with increased myopathy and rhabdomyolysis. Livalo should be administered with caution when used concomitantly with fibrates. In pharmacokinetic studies co-administration of Livalo with Gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC, with Fenofibrate AUC increased 1.2-fold. (see 'Pharmacology').

Fusidic acid:

Although interaction studies with Livalo and fusidic acid have not been conducted, there have been reports of severe muscle problems such as rhabdomyolysis attributed to interactions between fusidic acid and statins.

Niacin

Interaction studies with Livalo and niacin have not been conducted. The use of niacin alone has been associated with myopathy and rhabdomyolysis when used as a monotherapy. Thus Livalo should be administered with caution and a reduced dose should be considered when used concomitantly with niacin.

Ezetimibe

Ezetimibe and its glucuronide metabolite inhibit the absorption of dietary and biliary cholesterol. Co administration of Livalo had no effect on plasma ezetimibe or the glucuronide metabolite concentrations and ezetimibe had no impact on pitavastalin plasma concentrations.

Inhibitors of CYP3A4

Interaction studies with itraconazole and grapefruit juice, known inhibitors of CYP3A4, had no clinically significant effect on the plasma concentrations of pitavastatin. Concomitant itraconazole resulted in a 0.77-fold reduction in the AUC of pitavastatin and grapefruit juice a 1.15-fold increase.

Digoxin

A known P-glycoprotein substrate did not interact with Livalo. During co-administration there was no significant change in either pitavastatin or digoxin concentrations.

Warfarin

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

ADVERSE EFFECTS

Of 4,798 patients enrolled in 10 controlled clinical studies and 4 subsequent open-label extension studies, 3,291 patients were administered Livalo 1 mg to 4 mg daily. The mean continuous exposure of Livalo (1 mg to 4 mg) was 36.7 weeks (median 51.1 weeks). In controlled clinical trials, at the recommended doses, less than 4% of patients treated with

Livalo were withdrawn due to adverse events. The most commonly reported pitavastatin related adverse reaction in controlled trials was myalgia.

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 7. These studies had treatment duration of up to 12 weeks.

Table 7. 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%
Diarrhoea	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.				

Elevated blood creatinine kinase of > 3 times the upper limit of normal (ULN) occurred in 49 out of 2800 (1.8%) patients receiving pitavastatin in the controlled clinical trials. Levels of ≥ 10 times ULN with concurrent muscle symptoms were rare and only observed in one patient out of 2406 treated with 4mg pitavastatin (0.04%) in the clinical trial programme.

In clinical trials for doses above the recommended dose range, adverse events reported as rhabdomyolysis and myopathy (myalgia associated with CK ≥10x ULN) were seen at doses of 8 mg and above and 16 mg and above, respectively. Nine subjects (0.3%) were reported as having rhabdomyolysis after receiving pitavastatin, two (0.4%) with 8 mg pitavastatin, one (1.0%) with 16 mg pitavastatin, three (8.8%) with 32 mg pitavastatin and three (9.1%) with 64 mg pitavastatin. (See 'Precautions')

Post-marketing data

A two year prospective post-marketing surveillance study was conducted in nearly 20,000 patients in Japan. The overwhelming majority of the 20,000 patients in the study were treated with 1 mg or 2 mg pitavastatin and not 4 mg. 10.4% of patients reported adverse events for which a causal relationship to pitavastatin could not be ruled out and 7.4% of patients withdrew from therapy due to adverse events. The myalgia rate was 1.08%. The majority of adverse events were mild. Adverse event rates were higher over 2 years in patients with a history of drug allergy (20.4%), or hepatic or renal disease (13.5%).

Adverse reactions and frequencies observed in the prospective post-marketing surveillance study but not in worldwide controlled clinical trials, at the recommended doses are listed below.

Nervous system disorders

Uncommon: Hypoaesthesia

Gastrointestinal disorders

Rare: Abdominal discomfort, abdominal pain

Skin and subcutaneous tissue disorders

Uncommon: Urticaria

Hepato-biliary disorders

Rare: Hepatic function abnormal, liver disorder

Musculoskeletal, connective tissue disorders

Rare: Myopathy, Rhabdomyolysis

General disorders and administration site conditions

Uncommon: Malaise*

Rare: Asthenia

In the post-marketing surveillance study there were two reports of rhabdomyolysis requiring hospitalisation (0.01% of patients).

In addition there are unsolicited post-marketing reports of skeletal muscle effects including myalgia and myopathy in patients treated with pitavastatin at all recommended doses. Reports of rhabdomyolysis, with and without acute renal failure, including fatal rhabdomyolysis have also been received.

Statin class effects

The following adverse events have been reported with some statins, Sleep disturbances, including nightmares; Memory loss; Sexual dysfunction; Depression; Exceptional cases of interstitial lung disease, especially with long term therapy

DOSAGE AND ADMINISTRATION

For oral use only and should be swallowed whole. Livalo can be taken at any time of the day with or without food. It is desirable that the patient takes the tablet at the same time each day. Statin therapy is generally more effective in the evening due to the circadian rhythm of lipid metabolism. Patients should be on a cholesterol lowering diet before treatment. It is important that patients continue dietary control during treatment.

Adults:

The starting dose is 2 mg once daily.

Adjustment of dose should be made at intervals of 4 weeks or more. Doses should be individualised according to LDL-C levels, the goal of therapy and patient response.

The maximum daily dose is 4mg; higher doses have been associated with increased safety risks. (see 'Precautions' and 'Adverse Effects')

Elderly:

No dosage adjustment is required (see 'Precautions – Muscle Effects & Use in the Elderly'').

Paediatric use:

Livalo should not be used in children aged below 18 years because safety and efficacy has not been established. No data are currently available.

Patients with impaired renal function:

Patients with Stage 3 kidney disease (GFR 30 to < 60 mL/min/1.73 m^2) and end–stage renal disease receiving haemodialysis 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 (GFR < 30 mL/min/1.73 m^2) not yet on haemodialysis. (see 'Precautions')

Patients with mild to moderate impaired hepatic function:

The 4mg dose is not recommended in patients with mild to moderate impaired hepatic function. A maximum daily dose of 2mg may be given with close monitoring (see 'Precautions').

Use with Rifampicin

In patients taking rifampicin, a dose of Livalo 2 mg once daily should not be exceeded. (see 'Interactions with Other Medicines').

OVERDOSAGE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

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

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

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

All presentations are packed in blisters contained in a cardboard carton.

Do not store above 25ºC. To protect from light keep blister in the outer carton.

Pack sizes: 10, 28, 30, 100

NAME AND ADDRESS OF THE SPONSOR

Abbott Australasia Pty Ltd

32-34 Lord Street

Botany NSW 2019

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

27 August 2013