1. NAME OF THE MEDICINAL PRODUCT

LIVALO Film-coated Tablets 2mg / LIVALO Film-coated Tablets 4mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Each tablet contains 2.0mg (for LIVALO Film-coated Tablets 2mg) or 4.0mg (for LIVALO Film-coated Tablets 4mg) of pitavastatin calcium (as hydrate)
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

LIVALO Film-coated Tablets 2mg: Slightly light-colored yellow-red, round and scored film-coated tablet embossed “Kowa 202” on one face and scored on the reverse. LIVALO Film-coated Tablets 2mg can be divided into equal halves.
LIVALO Film-coated Tablets 4mg: Light-colored yellow, round and scored film-coated tablet embossed “Kowa 203” on one face and scored on the reverse. LIVALO Film-coated Tablets 4mg can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Patients with primary hyperlipidemia including familial hypercholesterolaemia 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) and children aged 10 years and older with familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate.
Since there is no experience of use in homozygous cases of familial hypercholesterolemia, administration of LIVALO should be considered as a treatment supplementary to non-drug therapy such as LDL-apheresis and only when treatment with LIVALO is judged indispensable.

4.2 Posology and method of administration

For oral use only and should be swallowed whole tablet, or half tablet of 2mg if requiring 1mg of pitavastatin calcium. If halving of tablets is necessary, the tablets should only be halved when a dose is required. 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: Starting dose is 2mg of pitavastatin calcium orally once daily. The dosage may be adjusted according to the patient’s age and symptoms. When lowering of the LDL-C level is insufficient, the dosage may be increased to a maximum of 4mg per day. Adjustment of dose should be made at intervals of 4 weeks or more.

Special populations
Elderly: No dosage adjustment is required (see sections 5.1 and 5.2).
Paediatric population: The usual dosage for children aged 10 years and older is 1mg of pitavastatin calcium orally once daily. The dosage may be adjusted according to the patient’s symptoms. When lowering of the LDL-C level is insufficient, the dosage may be increased to a maximum of 2mg per day. Adjustment of dose should be made at intervals of 4 weeks or more. Safety of pitavastatin calcium in low birth weight infants, newborns, infants, and children under 10 years of age has not been established (pitavastatin calcium has not been used in children under 10 years of age in Japan and has not been used in children under 6 years of age in Europe) .
Use of LIVALO should be considered only for those who are considered appropriate to receive LIVALO under the supervision of adequately trained and experienced physicians for the treatment of paediatric familial hypercholesterolemia. When LIVALO is used in children, attention should be given to the frequency or intensity of exercise and creatine kinase (CK) level elevation, and LIVALO should be administered with caution (Since the frequency and intensity of exercise tends to be higher in children, myopathy is more likely to develop in this population) .
Patients with impaired renal function: 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 receiving hemodialysis: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily.
Patients with impaired hepatic function: LIVALO is contraindicated in patients with active liver disease which may include unexplained persistent elevations of hepatic transaminase levels (see sections 4.3).

4.3 Contraindications

LIVALO is contraindicated:

- in patients with known hypersensitivity to pitavastatin or to any of the excipients
- in patients with active liver disease or unexplained persistent elevations in serum transaminases
- in patients with myopathy
- in patients receiving concomitant ciclosporin
- during pregnancy, while breastfeeding and in women of child bearing potential not taking appropriate contraceptive precautions

4.4 Special warnings and precautions for use

Muscle Effects

In common with other HMG-CoA reductase inhibitors (statins), there is the potential for myalgia, myopathy and, rarely, rhabdomyolysis to develop. Patients should be asked to report any muscle symptoms. 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 (>5 times the upper limit of normal (>5x ULN)) are noted, a confirmatory test should be performed within 5 to 7 days.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum CK, which persist despite discontinuation of statin treatment.

LIVALO must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of LIVALO and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Before Treatment

In common with other statins, LIVALO should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatinine kinase 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 (over 70 years) 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 muscle pain, weakness or cramps immediately. CK levels should be measured and treatment stopped if CK levels are elevated (>5x ULN). Stopping treatment should be considered if muscular symptoms are severe even if CK levels are ≤5x 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 >3x ULN was not observed in the placebo, pitavastatin 1 mg, or pitavastatin 2 mg groups. One out of 202 patients (0.5%) administered pitavastatin 4 mg had ALT >3x ULN.

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

There have been rare post-marketing 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 section 4.3).

New Onset Diabetes

Increases in HbA1c and fasting serum glucose levels have been reported with statins, and at high risk of future diabetes, statins 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 TG, 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 (see section 5.1).

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). 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.

Cognitive impairment

There have been rare post-marketing 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 non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Myasthenia Gravis/Ocular Myasthenia
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. LIVALO should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Other effects
A temporary suspension of LIVALO is recommended for the duration of treatment with erythromycin, other macrolide antibiotics or fusidic acid (see section 4.5). LIVALO should be used with caution in patients taking drugs known to cause myopathy (e.g. fibrates or niacin see section 4.5).
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.

4.5 Interaction with other medicinal products and other forms of interaction
Pitavastatin is actively transported into human hepatocytes by multiple hepatic transporters (including organic anion transporting polypeptide, OATP), which may be involved in some of the following interactions.

Ciclosporin: Co-administration of a single dose of ciclosporin with LIVALO at steady state resulted in a 4.6-fold increase in pitavastatin AUC. The effect of steady state ciclosporin on steady state pitavastatin is not known. LIVALO is contraindicated in patients being treated with ciclosporin (see section 4.3).

Erythromycin: Erythromycin significantly increased pitavastatin exposure. In patients taking erythromycin, a dose of LIVALO 1 mg once daily should not be exceeded.

Gemfibrozil and other 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 (see section 4.4). 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.

Niacin: Interaction studies with pitavastatin 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 when used concomitantly with niacin.

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with systemic fusidic acid is necessary, LIVALO treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Rifampicin: Rifampicin significantly increased pitavastatin exposure. In patients taking rifampicin, a dose of LIVALO 2 mg once daily should not be exceeded.

Warfarin: The steady-state pharmacokinetics and pharmacodynamics (INR and PT) of warfarin in healthy volunteers was unaffected by the co-administration of LIVALO 4mg daily. However, as for other statins, patients receiving warfarin should have their prothrombin time or INR monitored when LIVALO is added to their therapy.

4.6 Fertility, pregnancy and lactation
Pregnancy
LIVALO is contraindicated during pregnancy (see section 4.3). Women of childbearing potential must take appropriate contraceptive precautions during treatment with LIVALO. Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the fetus, the potential risk for inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. If the patient is planning to become pregnant, treatment should be stopped at least one month prior to conception. If a patient becomes pregnant during use of LIVALO, treatment must be discontinued immediately.

Breastfeeding
LIVALO is contraindicated during breastfeeding (see section 4.3). Pitavastatin is excreted in rat milk. It is not known whether it is excreted in human milk.

Fertility
No current data

4.7 Effects on ability to drive and use machines
There is no pattern of adverse events that suggests that patients taking LIVALO will have any impairment of ability to drive and use hazardous machinery, but it should be taken into account that there have been reports of dizziness and somnolence during treatment with LIVALO.

4.8 Undesirable effects

Summary of the safety profile

In controlled clinical trials, at the recommended doses, less than 4% of pitavastatin treated patients were withdrawn due to adverse events. The most commonly reported adverse event overall was nasopharyngitis. The most commonly reported pitavastatin related adverse reaction in controlled clinical trials was myalgia.

Summary of adverse reactions

Adverse reactions and frequencies observed in worldwide controlled clinical trials and extension studies, at the recommended doses, are listed below by system organ class. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) very rare (<1/10,000) and not known.

Table 1: **Adverse reactions and frequencies observed in worldwide controlled clinical trials and extension studies at the recommended doses by system organ class**

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not Known
Blood and the lymphatic system disorders	–	–	Anaemia	–	–	–
Metabolism and nutrition disorders	–	–	Anorexia	–	–	–
Psychiatric disorders	–	–	Insomnia	–	–	–
Nervous system disorders	–	Headache	Dizziness, Dysgeusia, Somnolence	–	–	–
Eye disorders	–	–	–	Visual acuity reduced	–	–
Ear and labyrinth disorders	–	–	Tinnitus	–	–	–
Gastrointestinal disorders	–	Constipation, Diarrhoea, Dyspepsia, Nausea	Abdominal Pain, Dry Mouth, Vomiting	Glossodynia, Pancreatitis acute	–	–
Hepato-biliary disorders	–	–	Transaminases (aspartate aminotransferase, alanine aminotransferase) increased	Jaundice cholestatic	–	–
Skin and subcutaneous tissue disorders	–	–	Pruritus, Rash	Urticaria, Erythema	–	–
Musculoskeletal, connective tissue and bone disorders	–	Myalgia, Arthralgia	Muscle spasms	–	–	Immune-mediated necrotizing myopathy (see section 4.4)
Renal and urinary disorders	–	–	Pollakiuria	–	–	–
General disorders and administration site conditions	–	–	Asthenia, Malaise, Fatigue, Peripheral Oedema	–	–	–

Elevated blood creatinine kinase of >3x ULN occurred in 49 out of 2,800 (1.8%) patients receiving pitavastatin in the controlled clinical trials. Levels of ≥10x ULN with concurrent muscle symptoms were rare and only observed in one patient out of 2,406 treated with 4mg pitavastatin (0.04%) in the clinical trial programme.

In a double-blind, randomized, controlled, 52 weeks trial, 252 HIV-infected patients with dyslipidemia were treated with either pitavastatin 4mg once daily (n=126) or another statin (n=126). All patients were taking antiretroviral therapy (excluding darunavir) and had HIV-1 RNA less than 200 copies/mL and CD4 count greater than 200 cell/μL for at least 3 months prior to randomization. The safety profile of pitavastatin was generally consistent with that observed in the clinical trials described above. One patient (0.8%) treated with pitavastatin had a peak creatine phosphokinase value exceeding 10x ULN, which resolved spontaneously. Four patients (3%) treated with pitavastatin had at least one ALT value exceeding 3x but less than 5x ULN, none of which led to drug discontinuation. Virologic failure was reported for four patients (3%) treated with pitavastatin, defined as a confirmed measurement of HIV-1 RNA exceeding 200 copies/mL that was also more than a 2-fold increase from baseline.

Paediatric population

In Japanese clinical studies, no adverse reactions were found in any patients (14 subjects). In European clinical studies, adverse reactions were found in 20 out of 128 patients (15.6%). The main symptoms were headache, abdominal pain, and myalgia (at the time of approval for paediatric use).

Post Marketing Experience

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 1mg or 2mg pitavastatin and not 4mg. 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.

Hepato-biliary disorders
Rare: Hepatic function abnormal, Liver disorder

Musculoskeletal, connective tissue disorders
Rare: Myopathy, Rhabdomyolysis

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 LIVALO treated patients at all recommended doses. Reports of rhabdomyolysis, with and without acute renal failure, including fatal rhabdomyolysis have also been received. Unsolicited reports of the following events have also been received (the frequency is based on that observed in post-marketing studies):

Nervous system disorders
Uncommon: Hypoaesthesia

Gastrointestinal disorders
Rare: Abdominal discomfort

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 (see section 4.4)
- New Onset Diabetes: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI >30 kg/m^2, raised TG, history of hypertension)

4.9 Overdose
There is no specific treatment in the event of overdose. The patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC Code: C10A A08
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 TC and LDL-C concentrations in the blood. Its sustained inhibition of hepatic cholesterol synthesis reduces very low density lipoprotein (VLDL) secretion into the blood, reducing plasma TG levels.
Pharmacodynamic Effects
LIVALO reduces elevated LDL-C, TC and TG and increases HDL-C. It reduces Apo-B, and produces variable increases in Apo-A1 (see Table 2). It also reduces non-HDL-C and elevated TC/HDL-C, and Apo-B/Apo-A1 ratios.

Table 2: Dose response in patients with primary hypercholesterolaemia (Adjusted mean percent change from baseline over 12 weeks)

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

*unadjusted

Clinical efficacy
In controlled clinical studies which enrolled a total of 1,687 patients with primary hypercholesterolaemia and mixed dyslipidaemia, including 1,239 patients treated at the therapeutic doses (mean baseline LDL-C about 4.8 mmol/L), pitavastatin consistently reduced LDL-C, TC, non-HDL-C, TG and Apo-B concentrations and elevated HDL-C and Apo-A1 concentrations. TC/HDL-C and Apo-B/Apo-A1 ratios were reduced. LDL-C was reduced by 38 to 39% with pitavastatin 2mg and 44 to 45% with pitavastatin 4mg.

The majority of patients taking 2mg achieved the European Atherosclerosis Society (EAS) treatment target for LDL-C (<3 mmol/L). In a controlled clinical trial in 942 patients aged ≥65 years (434 treated with pitavastatin 1mg, 2mg or 4mg) with primary hypercholesterolaemia and mixed dyslipidaemia (mean baseline LDL-C about 4.2 mmol/L), LDL-C values were reduced by 31.4%, 39.0% and 44.3%, respectively, and about 90% of patients reached the EAS treatment target. More than 80% of the patients were taking concomitant medications, but the incidence of adverse events was similar in all treatment groups and fewer than 5% of patients withdrew from the study due to adverse events. Safety and efficacy findings were similar in patients in the different age subgroups (65-69, 70-74, and ≥75 years).
In controlled clinical trials which enrolled a total of 761 patients (507 treated with pitavastatin 4mg) who had primary hypercholesterolaemia or mixed dyslipidaemia, with 2 or more cardiovascular risk factors (mean baseline LDL-C about 4.1 mmol/L), or mixed dyslipidaemia with type 2 diabetes (mean baseline LDL-C about 3.6 mmol/L), approximately 80% achieved the relevant EAS target (either 3 or 2.5 mmol/L, depending on risk). LDL-C was reduced by 44% and 41%, respectively, in the patient groups.
In long term studies of up to 60 weeks duration in primary hypercholesterolaemia and mixed dyslipidaemia, EAS target attainment has been maintained by persistent and stable reductions of LDL-C, and HDL-C concentrations have continued to increase. In a study in 1,346 patients who had completed 12 weeks of statin therapy (LDL-C reduction 42.3%, EAS target attainment 69%, HDL-C elevation 5.6%), values after a further 52 weeks of treatment with pitavastatin 4mg were LDL-C reduction 42.9%, EAS target attainment 74%, HDL-C elevation 14.3%.
In an extension to the two year surveillance study conducted in Japan (LIVS-01, see section 4.8), 6,582 patients with hypercholesterolaemia who had received treatment with pitavastatin 1, 2, or 4mg for 2 years, were continued on treatment for a further 3 years (5 years total treatment). During this 5 year study, LDL-C reduction (-30.5%) was maintained from 3 months for the duration of the study, HDL-C values increased by 1.7% at 3 months to 5.7% at 5 years, with greater HDL-C increases seen in patients with lower baseline HDL-C values (<40 mg/dL), e.g. serum levels increased by 11.9% at 3 months to 28.9% after 5 years were observed.

Atherosclerosis
The JAPAN-ACS study compared the effects of 8 to 12 months treatment with pitavastatin 4mg or atorvastatin 20mg on coronary plaque volume in 251 patients undergoing percutaneous coronary intervention for acute coronary syndrome, guided by intravascular ultrasound. This study demonstrated approximately 17% reduction in plaque volume for both treatments (-16.9 ± 13.9% with pitavastatin and -18.1 ± 14.2% with atorvastatin). Non-inferiority was proven between pitavastatin and atorvastatin and vice versa. In both cases, plaque regression was associated with negative vessel remodelling (113.0 to 105.4 mm^3). There was no significant correlation between LDL-C reduction and plaque regression in this study, in contrast to the findings in placebo-controlled studies.
The beneficial effects on mortality and morbidity have not yet been evaluated.

Diabetes Mellitus
In an open-label prospective controlled study in 1,269 Japanese patients with impaired glucose tolerance randomised to lifestyle modification with or without pitavastatin 1mg or 2mg daily, 45.7% of patients in the control group developed diabetes in comparison to 39.9% of patients in the pitavastatin group over a 2.8 year period, hazard ratio 0.82 [95% CI 0.68-0.99].
A meta-analysis of 4,815 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.

Paediatric Population
In a clinical study, pitavastatin calcium 1 or 2 mg was administered once daily for 52 weeks before breakfast in male Japanese children aged 10 to 15 years with familial hypercholesterolemia. The results of an analysis of covariance model with repeated measurements, treatment and week (8 and 12 weeks) as factors and baseline LDL-C as a covariate revealed that the least squares means of LDL-C percent change [95% confidence interval] were -27.258 [-34.003 to -20.513]% in the 1 mg group (7 subjects) and -34.273 [-41.018 to -27.528]% in the 2 mg group (7 subjects), indicating a significant reduction in LDL-C level ($p < 0.001$), and the effect persisted until 52 weeks.
In a double-blind, randomized, multi-centre, placebo-controlled study NK-104-4.01EU (n=106; 48 male and 58 female) children and adolescent patients (≥6 years of age and <17 years of age) with high-risk hyperlipidaemia (fasting plasma LDL-C levels ≥160 mg/dL (4.1 mmol/L), or LDL-C ≥130 mg/dL (3.4 mmol/L) with additional risk factors) received pitavastatin 1mg, 2mg, 4mg or placebo daily for 12 weeks. At study entry, the majority of the patients were diagnosed with heterozygous familial hypercholesterolaemia, approximately 41% of the patients were 6 to <10 years old and approximately 20%, 9%, 12%, and 9% were Tanner stage II, III, IV, and V, respectively. Mean LDL-C was reduced 23.5%, 30.1%, and 39.3% by pitavastatin 1, 2 and 4 mg, respectively, compared to 1.0% for placebo.
In a 52-week open-label extension and safety study NK-104-4.02EU (n=113, including 87 patients from the 12-week placebo-controlled study; 55 male and 58 female) children and adolescent patients (≥6 years of age and <17 years of age) with high-risk hyperlipidaemia received pitavastatin for 52 weeks. All patients started treatment with pitavastatin 1mg daily, and the dose of pitavastatin may have been up-titrated to 2mg and 4 mg to achieve an optimum LDL-C treatment target of <110 mg/dL (2.8 mmol/L) based on LDL-C values at Week 4 and Week 8. At study entry, approximately 37% of the patients were 6 to <10 years old and approximately 22%, 11%, 12%, and 13% were Tanner stage II, III, IV, and V, respectively. The majority of patients (n=103) were up-titrated to 4mg pitavastatin daily. Mean LDL-C was reduced 37.8% at the Week 52 endpoint. In total, 47 patients (42.0%) achieved the AHA minimal LDL-C target of <130 mg/dL and 23 patients (20.5%) achieved the AHA ideal LDL-C target of <110 mg/dL at Week 52. The reduction in mean LDL-C at the Week 52 endpoint was 40.2% for patients ≥6 to <10 years of age (n=42), 36.7% for patients ≥10 to <16 years of age (n=61), and 34.5% for patients ≥16 to <17 years of age (n=9). Patient gender did not

appear to have an effect on response. In addition mean TC was decreased 29.5% and mean TG was decreased 7.6% at the Week 52 endpoint.

5.2 Pharmacokinetic properties

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 geometolic 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.

Biotransformation: 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.

Elimination: 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.

Special populations

Elderly: In a pharmacokinetic study which compared healthy young and elderly (≥65 years) volunteers, pitavastatin AUC was 1.3-fold higher in elderly subjects. This has no effect on the safety or efficacy of LIVALO 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.

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.

Paediatric: Fifty-two-week repeated oral administration of pitavastatin calcium (1 or 2 mg) once a day before breakfast in 7 male Japanese children with familial hypercholesterolemia was performed. The plasma concentrations of the unchanged pitavastatin 1 hour after the administration are 22.79 ± 11.34ng/mL (mean ± S.D.) for 1mg and 32.17 ± 17.65ng/mL for 2mg, respectively.

Renal insufficiency: For patients with moderate renal disease and those on haemodialysis increases in AUC values were 1.8-fold and 1.7-fold respectively. In another pharmacokinetic study, patients with severe renal impairment not receiving haemodialysis were administered a single dose of LIVALO 4 mg. The $AUC_{0\text{-}inf}$ and the Cmax were 36 and 18% higher, respectively, compared with those of healthy volunteers. (see section 4.2).

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.

Drug-Drug Interactions:

Table 3: Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in Cmax*
Ciclosporin	Pitavastatin 2 mg QD for 6 days + ciclosporin 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 †
Rifampicin	Pitavastatin 4 mg QD + rifampicin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Darunavir/ Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16	↓ 26%	↓ 4%
Lopinavir/ Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ ritonavir 400 mg/100 mg BID on Days 9-24	↓ 20%	↓ 4%
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓ 0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%

Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15	↑10%	↑15%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice for 4 days	↑ 15%	↓12%
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

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

Table 4: Effect of Pitavastatin Co-Administration on Systemic Exposure to Other Drugs

Co-administered drug	Dose regimen		Change in AUC*	Change in Cmax*
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Darunavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ ritonavir 800mg/100 mg QD on Days 6-16		↑ 3%	↑ 6%
Lopinavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ ritonavir 400 mg/100 mg BID on Days 9-24		↓ 9%	↓ 7%
Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ ritonavir 400 mg/100 mg BID on Days 9-24		↓ 11%	↓ 11%
Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ ritonavir 800mg/100 mg QD on Days 6-16		↑ 8%	↑ 2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg	Enalapril	↑ 12%	↑ 12%
	daily for 5 days	Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 -7 mg) for 8 days	R-warfarin	↑ 7%	↑ 3%
	+ pitavastatin 4 mg QD for 9 days	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%
Rifampicin	Pitavastatin 4 mg QD + rifampicin 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose hydrate, low substituted hydroxypropylcellulose, hypromellose, magnesium aluminometasilicate, magnesium stearate, triethyl citrate, hydrated silicon dioxide, titanium oxide, carnauba wax, Sunset yellow FCF, and (LIVALO Film-coated Tablets 4mg only) yellow ferric oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

LIVALO Film-coated Tablets 2mg: 36 months
LIVALO Film-coated Tablets 4mg: 36 months

6.4 Special precautions for storage

Do not store above 30ºC.
To protect from light keep blister in the outer carton.

6.5 Nature and contents of container

LIVALO Film-coated Tablets 2mg and 4mg: Packaged in PVC/Aluminium blister in cartons of 30 tablets (10 tablets X 3 blister)

7. PRODUCT OWNER

KOWA COMPANY, LTD.
6-29, Nishiki 3-chome,
Naka-ku, Nagoya, Aichi, Japan

8. REGISTRATION NUMBER

LIVALO Film-coated Tablets 2mg: SIN15859P
LIVALO Film-coated Tablets 4mg: SIN15860P

9. DATE OF REVISION OF THE TEXT

January 2024