# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Livazo 4mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains pitavastatin calcium equivalent to 4mg pitavastatin.
Excipient(s) include 252.34mg Lactose monohydrate.
For a full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Round white film-coated tablets embossed 'KC' on one face and '4' on the reverse.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Livazo is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combined (mixed) dyslipidaemia, when response to diet and other non-pharmacological measures is inadequate.

### 4.2 Posology and method of administration

Posology

Patients should be on a cholesterol lowering diet before treatment. It is important that all patients continue dietary control during treatment.

The usual starting dose is 1mg once daily. Adjustment of dose should be made at intervals of 4 weeks or more. Doses should be individualized according to LDL-C levels, the goal of therapy and patient response. The maximum daily dose is 4mg.

Elderly

No dose adjustment necessary in patients older than 70 years (see section 5.1 and Section 5.2).

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Paediatric population

*Children and adolescents aged 6 years and over:*
Livazo use in children should only be carried out by physicians experienced in the treatment of hyperlipidaemia and progress should be regularly reviewed.

In children and adolescents with heterozygous familial hypercholesterolaemia the usual starting dose is 1mg once daily. Adjustment of dose should be made at intervals of 4 weeks or more. Doses should be individualized according to LDL-C levels, the goal of therapy and patient response. In children 6 to 9 years of age the maximum daily dose is 2mg. In children 10 years or older the maximum daily dose is 4mg (see Sections 4.8, 5.1 and 5.2).

*Children younger than 6 years of age:*
The safety and efficacy of Livazo in children below 6 years of age has not been established and no data are available.

Patients with impaired renal function

No dosage adjustment is required in mild renal impairment but pitavastatin should be used with caution. Data with 4mg dose are limited in all grades of impaired renal function. Therefore 4mg dose should ONLY be used with close monitoring after graded dose titration. In those with severe renal impairment 4mg dose is not recommended (see Section 4.4 and Section 5.2).

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 Section 4.4 and Section 5.2).

Method of Administration

For oral use only and should be swallowed whole. Livazo 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.

If a child or adolescent is unable to swallow the tablet, where necessary, the tablet may be dispersed in a glass of water and taken immediately. To ensure accurate dosage a second volume of water should be used to rinse the glass and swallowed immediately. Tablets must not be dispersed in either acidic fruit juices or milk.

## 4.3 Contraindications

Livazo is contraindicated:

- in patients with known hypersensitivity to pitavastatin or to any of the excipients or other statins
- in patients with severe hepatic impairment, active liver disease or unexplained persistent elevations in serum transaminases (exceeding 3 times the upper limit of normal [ULN])
- in patients with myopathy
- in patients receiving concomitant ciclosporin
- during pregnancy, while breast feeding and in women of child-bearing potential not taking appropriate contraceptive precautions

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## 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. Creatine kinase (CK) levels should be measured in any patient reporting muscle pain, muscle tenderness or weakness especially if accompanied by malaise or fever.

Creatine kinase 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.

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 creatine kinase, which persist despite discontinuation of statin treatment.

Livazo 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.

2

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 Livazo 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, Livazo 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 Livazo should not be started if CK values are >5x ULN.

During Treatment

Patients must be encouraged to report muscle pain, weakness or cramps immediately. Creatine kinase 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 Livazo may be considered at a dose of 1mg and with close monitoring.

**Liver Effects**

In common with other statins, Livazo should be used with caution in patients with a history of liver disease or who regularly consume excessive quantities of alcohol. Liver function tests should be performed prior to initiating treatment with Livazo and then periodically during treatment. Livazo treatment should be discontinued in patients who have a persistent increase in serum transaminases (ALT and AST) exceeding 3x ULN.

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**Renal Effects**

Livazo should be used with caution in patients with moderate or severe renal impairment. Dose increments should be instituted only with close monitoring. In those with severe renal impairment, 4mg dose is not recommended (see section 4.2).

**Diabetes Mellitus**

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

3

**Paediatric population**
There is limited data on the long term effect on growth and sexual maturation in paediatric patients 6 years of age or older taking Livazo. Adolescent females should be counselled on appropriate contraceptive precautions during treatment with Livazo (see section 4.3, section 4.6).

**Other effects**
A temporary suspension of Livazo is recommended for the duration of treatment with erythromycin, other macrolide antibiotics or fusidic acid (see section 4.5). Livazo 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 Livazo at steady state resulted in a 4.6-fold increase in pitavastatin AUC. The effect of steady state ciclosporin on steady state Livazo is not known. Livazo is contraindicated in patients being treated with ciclosporin (see section 4.3).

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

**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. Livazo should be administered with caution when used concomitantly with fibrates (see section 4.4). In Pharmacokinetic studies co-administration of Livazo with Gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC; with Fenofibrate, AUC increased 1.2-fold.

**Niacin:** Interaction studies with Livazo and niacin have not been conducted. The use of niacin alone has been associated with myopathy and rhabdomyolysis when used as a monotherapy. Thus Livazo 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, Livazo treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

**Rifampicin:** Co-administration with Livazo at the same time resulted in a 1.3-fold increase in pitavastatin AUC due to reduced hepatic uptake.

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**Protease inhibitors:** Co-administration with Livazo at the same time may result in minor changes in pitavastatin AUC.

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

**Digoxin**, a known P-gp substrate, did not interact with Livazo. During co-administration there was no significant change in either pitavastatin or digoxin concentrations.

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

**Paediatric population**

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

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Livazo is contraindicated during pregnancy (see section 4.3). Women of childbearing potential must take appropriate contraceptive precautions during treatment with Livazo. 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. Animal studies show evidence of reproductive toxicity, but no teratogenic potential (see section 5.3). 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 Livazo, treatment must be discontinued immediately.

**Breastfeeding**

Livazo 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 Livazo 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 Livazo.

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## 4.8 Undesirable effects

**Summary of the safety profile**

In controlled clinical trials, at the recommended doses, less than 4% of Livazo treated patients were withdrawn due to adverse events. 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.

Blood and the lymphatic system disorders
*Uncommon:* Anaemia

Metabolism and nutrition disorders
*Uncommon:* Anorexia

Psychiatric disorders
*Uncommon:* Insomnia

Nervous system disorders
*Common:* Headache
*Uncommon:* Dizziness, Dysgeusia, Somnolence

Eye disorders
*Rare:* Visual acuity reduced

Ear and labyrinth disorders
*Uncommon:* Tinnitus

Gastrointestinal disorders
*Common:* Constipation, Diarrhoea, Dyspepsia, Nausea
*Uncommon:* Abdominal Pain, Dry Mouth, Vomiting
*Rare:* Glossodynia, pancreatitis acute

Hepato-biliary disorders
*Uncommon:* Transaminases (aspartate aminotransferase, alanine aminotransferase) increased
*Rare:* Jaundice cholestatic

Skin and subcutaneous tissue disorders
*Uncommon:* Pruritus, Rash
*Rare:* Urticaria, Erythema

Musculoskeletal, connective tissue and bone disorders
*Common:* Myalgia, Arthralgia
*Uncommon:* Muscle spasms
*Frequency unknown:* Immune-mediated necrotising myopathy (see section 4.4)

Renal and urinary disorders
*Uncommon:* Pollakiuria

General disorders and administration site conditions
*Uncommon:* Asthenia, Malaise, Fatigue, Peripheral Oedema

Elevated blood creatinine kinase of >3 times the upper limit of normal (ULN) occurred in 49 out of 2800 (1.8%) patients receiving Livazo 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 Livazo (0.04%) in the clinical trial programme.

**Paediatric population**
The clinical safety database includes safety data for 142 paediatric patients who received pitavastatin among which 87 patients were in the age range of 6 to 11, and 55 patients were in the age range of 12 to 17. In total, 91 patients received pitavastatin for 1 year with 12 patients receiving pitavastatin for 2.5 years and 2 patients for 3 years. Less than 3% of pitavastatin treated patients were withdrawn due to adverse events. The most commonly reported pitavastatin related adverse reactions in the clinical programme were headache (4.9%), myalgia (2.1%) and abdominal pain (4.9%). Based on the data available, the frequency, type and severity of adverse reactions are expected to be similar in children and adolescents to adults.

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**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 Livazo 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)
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI >30 kg/m$^2$, raised triglycerides, history of hypertension)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 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.

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# 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 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.

**Pharmacodynamic Effects**

Livazo reduces elevated LDL-C, total cholesterol and triglycerides and increases HDL-cholesterol (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 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 1687 patients with primary hypercholesterolaemia and mixed dyslipidaemia, including 1239 patients treated at the therapeutic doses (mean baseline LDL-C about 4.8 mmol/L), Livazo 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 Livazo 2mg and 44 to 45% with Livazo 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 Livazo 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%, 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 Livazo 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.

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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 1346 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 (LIVES-01, see section 4.8), 6582 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 month's 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 1269 Japanese patients with impaired glucose tolerance randomised to lifestyle modification with or without Livazo 1mg or 2mg daily, 45.7% of patients in the control group developed diabetes in comparison to 39.9% of patients in the Livazo group over a 2.8 year period, hazard ratio 0.82 [95% CI 0.68-0.99].

A meta-analysis of 4815 non-diabetic patients included in randomised controlled double-blind studies of at least 12-weeks duration (weighted mean follow-up 17.3 weeks [SD 17.7 weeks]) demonstrated a neutral effect for Livazo on the risk of new-onset diabetes (0.98% of control patients and 0.50% of Livazo 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 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.

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The European Medicines Agency Paediatric Committee has waived the obligation to submit the results of studies in children under the age of 6 years and in the treatment of children of all ages with homozygous familial hypercholesterolaemia.

## 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 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 Livazo 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 Livazo 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 population:** There are limited pharmacokinetic data in children and adolescents. In study NK-104-4.01EU (see section 5.1) sparse sampling revealed a dose-dependent effect on pitavastatin plasma concentrations at 1 hour post dose. There was also indication that concentration at 1 hour post dose were (inversely) related to body weight and may be higher in children than adults.

**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 (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. Dose restrictions are recommended in patients with mild and moderate hepatic impairment (see section 4.2). Livazo is contraindicated in patients with severe hepatic impairment.

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Applicant / Date 19.03.19

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on results from conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. Indications of renal toxicity were seen in monkeys at exposures greater than those reached in adult humans administered the maximum daily dose of 4mg and urinary excretion plays a far greater role in the monkey than in other animal species. In vitro studies with liver microsomes indicate that a monkey-specific metabolite may be implicated. The renal effects observed in monkeys are unlikely to have clinical relevance for humans, however the potential for renal adverse reactions cannot be completely excluded.

Pitavastatin had no effect on fertility or reproductive performance and there was no evidence of teratogenic potential. However, maternal toxicity was observed at high doses. A study in rats indicated maternal mortality at or near term accompanied by fetal and neonatal deaths at doses of 1 mg/kg/day (approximately 4 fold greater than the highest dose in humans on an AUC basis). No studies have been conducted in juvenile animals.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Tablet core**
Lactose monohydrate
Low substituted hydroxypropylcellulose
Hypromellose (E464)
Magnesium Aluminometasilicate
Magnesium stearate
**Film coating**
Hypromellose (E464)
Titanium dioxide (E171)
Triethyl citrate (E1505)
Colloidal anhydrous silica

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

4 years.

APPROVED BY SCDMTE JSC
Expert / Date 13 02 19
Applicant / Date 18/02/19

### 6.4 Special precautions for storage

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

### 6.5 Nature and contents of container

White PVdC coated PVC/AL blisters in cartons of 7, 28 or 30 tablets.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

To protect the environment, do not dispose of via waste water or household waste.

## 7. MARKETING AUTHORISATION HOLDER

Recordati Ireland Ltd.
Raheens East, Ringaskiddy, Co. Cork, Ireland




## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2010

## 10. DATE OF REVISION OF THE TEXT

10/12/2018

12