

Public Assessment Report

Decentralised Procedure

Livazo 1mg, 2mg and 4mg film-coated tablets
Alipza 1mg, 2mg and 4mg film-coated tablets
Vezeptra 1mg, 2mg and 4mg film-coated tablets
Pitavastatin 1mg, 2mg and 4mg film-coated tablets
(pitavastatin)

Procedure Nos: UK/H/1555-8/001-3/DC
UK Licence Nos: PL 32363/0001-8 and PL 32363/0011-14

Kowa Pharmaceutical Europe Company Limited

LAY SUMMARY

On 12 August 2010, the MHRA granted Kowa Pharmaceutical Europe Company Limited Marketing Authorisations for the medicinal products containing the new active ingredient, pitavastatin.

The products are intended to be marketed under the following names: Livazo, Alipza, Vezepra and Pitavastatin Tablets.

The tablets are made available in a range of different strengths in order to help the selection of the most appropriate dose for each patient. The strengths approved are 1, 2 and 4mg tablets. The strength refers to the amount of pitavastatin in each tablet.

These medicines are only available on prescription from your doctor. The approved use of these medicines is to correct the levels of fat (lipid) in your blood. An imbalance of fats, particularly cholesterol, can sometimes lead to a heart attack or stroke. These products belong to a group of medicines called 'statins'.

Data supporting the quality, safety and efficacy of these products were assessed by MHRA, and it was judged that the benefits of using Livazo/Alipza/Vezepra/Pitavastatin 1mg, 2mg and 4mg tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Names	Livazo 1mg, 2mg and 4mg film-coated tablets Alipza 1mg, 2mg and 4mg film-coated tablets Vezepra 1mg, 2mg and 4mg film-coated tablets Pitavastatin 1mg, 2mg and 4mg film-coated tablets
Type of Application	Full dossier, Article 8.3
Active Substance	Pitavastatin
Pharmacotherapeutic classification (ATC code)	HMG CoA reductase inhibitors (C10A A08)
Form	Film-coated tablets
Strength	1mg, 2mg and 4mg
MA Holder	Kowa Pharmaceutical Europe Co Ltd, Winnersh Triangle, Wokingham, RG41 5RB, UK
Reference Member State (RMS)	UK
Concerned Member States (CMS)	UK/H/1555/001-3/DC: Austria, Belgium, Cyprus, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden UK/H/1556/001 and 003/DC: Cyprus, France, Ireland, Greece, Italy, Portugal and Spain UK/H/1556/002/DC: Cyprus, France, Ireland, Greece, Italy, Portugal, Spain,,Austria, Germany, Poland and Sweden UK/H/1557/001-03/DC: Austria, Belgium, Finland, The Netherlands, Norway, Poland and Sweden UK/H/1558/0-03/DC: France, Greece, Italy, Portugal and Spain
Procedure Number	UK/H/1555-8/001-3/DC
Timetable	Day 210 – 13 July 2010

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Livazo ▼ 1mg film-coated tablets.
 Alipza ▼ 1mg film-coated tablets
 Vezeptra ▼ 1mg film-coated tablets
 Pitavastatin ▼ 1mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains pitavastatin calcium equivalent to 1mg pitavastatin.
 Excipient(s) include 63.085mg 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 '1' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Livazo/Alipza/Vezeptra/Pitavastatin is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adult patients 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

For oral use only and should be swallowed whole. Livazo/Alipza/Vezeptra/Pitavastatin 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 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. Most patients will require a 2mg dose (see Section 5.1). The maximum daily dose is 4mg.
Elderly:	No dosage adjustment is required (see Sections 5.1 and 5.2).
Paediatric use:	Pitavastatin 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:	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 Sections 4.4 and 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 Sections 4.4 and 5.2).

4.3 Contraindications

Livazo/Alipza/Vezeptra/Pitavastatin 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

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.

Before Treatment

In common with other statins, Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin may be considered at a dose of 1mg and with close monitoring.

Liver Effects

In common with other statins, Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin and then periodically during treatment. Livazo/Alipza/Vezepra/Pitavastatin treatment should be discontinued in patients who have a persistent increase in serum transaminases (ALT and AST) exceeding 3x ULN.

Renal Effects

Livazo/Alipza/Vezepra/Pitavastatin 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).

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.

Other effects

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

Erythromycin: Co-administration with Livazo/Alipza/Vezepra/Pitavastatin resulted in a 2.8-fold increase in pitavastatin AUC. A temporary suspension of Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin should be administered with caution when used concomitantly with fibrates (see Section 4.4). In Pharmacokinetic studies co-administration of Livazo/Alipza/Vezepra/Pitavastatin with Gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC with Fenofibrate AUC increased 1.2-fold.

Niacin: Interaction studies with Livazo/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin should be administered with caution when used concomitantly with niacin.

Fusidic acid: There have been reports of severe muscle problems such as rhabdomyolysis attributed to interactions between fusidic acid and statins. A temporary suspension of Livazo/Alipza/Vezepra/Pitavastatin is recommended for the duration of treatment with fusidic acid (see section 4.4).

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

Protease inhibitors: Co-administration with Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin. 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/Alipza/Vezepra/Pitavastatin 4mg daily. However, as for other statins, patients receiving warfarin should have their prothrombin time or INR monitored when Livazo/Alipza/Vezepra/Pitavastatin is added to their therapy.

4.6 Pregnancy and lactation

Pregnancy

Livazo/Alipza/Vezepra/Pitavastatin is contraindicated during pregnancy (see Section 4.3). Women of childbearing potential must take appropriate contraceptive precautions during treatment with Livazo/Alipza/Vezepra/Pitavastatin. 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/Alipza/Vezepra/Pitavastatin, treatment must be discontinued immediately.

Lactation

Livazo/Alipza/Vezepra/Pitavastatin is contraindicated during lactation (see Section 4.3). Pitavastatin is excreted in rat milk. It is not known whether it is excreted in human milk.

4.7 Effects on ability to drive and use machines

There is no pattern of adverse events that suggests that patients taking Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin.

4.8 Undesirable effects

Summary of the safety profile

In controlled clinical trials, at the recommended doses, less than 4% of Livazo/Alipza/Vezepra/Pitavastatin 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 ($\geq 1/10$), common ($\geq 1/100$, to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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

Renal and urinary disorders*Uncommon:* PollakiuriaGeneral 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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin (0.04%) in the clinical trial programme.

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 disorderMusculoskeletal, 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/Alipza/Vezepra/Pitavastatin treated patients 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 (see Section 4.4)

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 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/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/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 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/Alipza/Vezeptra/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%, 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/Alipza/Vezeptra/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 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%.

A beneficial effect of pitavastatin on cardiovascular morbidity and mortality has not been demonstrated as no outcome studies were included in the clinical programme.

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.

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.

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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin 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: Pharmacokinetic data in the paediatric population are not available.

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/Alipza/Vezepra/Pitavastatin is contraindicated in patients with severe hepatic impairment.

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 and carcinogenic potential. 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

3 years.

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

Kowa Pharmaceutical Europe Co. Ltd.,
Winnersh Triangle
Wokingham
RG41 5RB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 32363/0011
PL 32363/0012
PL 32363/0013
PL 32363/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2010

10 DATE OF REVISION OF THE TEXT

12/08/2010

1 NAME OF THE MEDICINAL PRODUCT

Livazo ▼ 2mg film-coated tablets.
 Alipza ▼ 2mg film-coated tablets
 Vezeptra ▼ 2mg film-coated tablets
 Pitavastatin ▼ 2mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains pitavastatin calcium equivalent to 2mg pitavastatin.
 Excipient(s) include 126.17mg 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 '2' on the reverse.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Livazo/Alipza/Vezeptra/Pitavastatin is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adult patients 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

For oral use only and should be swallowed whole. Livazo/Alipza/Vezeptra/Pitavastatin 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 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. Most patients will require a 2mg dose (see Section 5.1). The maximum daily dose is 4mg.
Elderly:	No dosage adjustment is required (see Sections 5.1 and 5.2).
Paediatric use:	Pitavastatin 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:	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 Sections 4.4 and 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 Sections 4.4 and 5.2).

4.3 Contraindications

Livazo/Alipza/Vezeptra/Pitavastatin 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

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.

Before Treatment

In common with other statins, Livazo/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/Pitavastatin 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 $\leq 5x$ ULN. If symptoms resolve and CK levels return to normal, then re-introduction of Livazo/Alipza/Vezeptra/Pitavastatin may be considered at a dose of 1mg and with close monitoring.

Liver Effects

In common with other statins, Livazo/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/Pitavastatin and then periodically during treatment. Livazo/Alipza/Vezeptra/Pitavastatin treatment should be discontinued in patients who have a persistent increase in serum transaminases (ALT and AST) exceeding $3x$ ULN.

Renal Effects

Livazo/Alipza/Vezeptra/Pitavastatin 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).

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.

Other effects

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

Erythromycin: Co-administration with Livazo/Alipza/Vezeptra/Pitavastatin resulted in a 2.8-fold increase in pitavastatin AUC. A temporary suspension of Livazo/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/Pitavastatin should be administered with caution when used concomitantly with fibrates (see Section 4.4). In Pharmacokinetic studies co-administration of Livazo/Alipza/Vezeptra/Pitavastatin with Gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC with Fenofibrate AUC increased 1.2-fold.

Niacin: Interaction studies with Livazo/Alipza/Vezeptra/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 Livazo/Alipza/Vezeptra/Pitavastatin should be administered with caution when used concomitantly with niacin.

Fusidic acid: There have been reports of severe muscle problems such as rhabdomyolysis attributed to interactions between fusidic acid and statins. A temporary suspension of Livazo/Alipza/Vezeptra/Pitavastatin is recommended for the duration of treatment with fusidic acid (see section 4.4).

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

Protease inhibitors: Co-administration with Livazo/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/Pitavastatin. 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/Alipza/Vezeptra/Pitavastatin 4mg daily. However, as for other statins, patients receiving warfarin should have their prothrombin time or INR monitored when Livazo/Alipza/Vezeptra/Pitavastatin is added to their therapy.

4.6 Pregnancy and lactation

Pregnancy

Livazo/Alipza/Vezeptra/Pitavastatin is contraindicated during pregnancy (see Section 4.3). Women of childbearing potential must take appropriate contraceptive precautions during treatment with Livazo/Alipza/Vezeptra/Pitavastatin. 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/Alipza/Vezepra/Pitavastatin, treatment must be discontinued immediately.

Lactation

Livazo/Alipza/Vezepra/Pitavastatin is contraindicated during lactation (see Section 4.3). Pitavastatin is excreted in rat milk. It is not known whether it is excreted in human milk.

4.7 Effects on ability to drive and use machines

There is no pattern of adverse events that suggests that patients taking Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin.

4.8 Undesirable effects

Summary of the safety profile

In controlled clinical trials, at the recommended doses, less than 4% of Livazo/Alipza/Vezepra/Pitavastatin 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 ($\geq 1/10$), common ($\geq 1/100$, to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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

Renal and urinary disorders*Uncommon:* PollakiuriaGeneral 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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin (0.04%) in the clinical trial programme.

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 disorderMusculoskeletal, 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/Alipza/Vezepra/Pitavastatin treated patients 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 (see Section 4.4)

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 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/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin 2mg and 44 to 45% with Livazo/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/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%, 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/Alipza/Vezepra/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 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%.

A beneficial effect of pitavastatin on cardiovascular morbidity and mortality has not been demonstrated as no outcome studies were included in the clinical programme.

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.

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.

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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin 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: Pharmacokinetic data in the paediatric population are not available.

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/Alipza/Vezepra/Pitavastatin is contraindicated in patients with severe hepatic impairment.

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 and carcinogenic potential. 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

3 years.

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, 30 or 100 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

Kowa Pharmaceutical Europe Co. Ltd.,
Winnersh Triangle
Wokingham
RG41 5RB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 32363/0001
PL 32363/0003
PL 32363/0005
PL 32363/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2010

10 DATE OF REVISION OF THE TEXT

12/08/2010

1 NAME OF THE MEDICINAL PRODUCT

Livazo/Alipza/Vezepza/Pitavastatin ▼ 4mg film-coated tablets.
 Alipza ▼ 4mg film-coated tablets
 Vezepza ▼ 4mg film-coated tablets
 Pitavastatin ▼ 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/Alipza/Vezepza/Pitavastatin is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adult patients 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

For oral use only and should be swallowed whole. Livazo/Alipza/Vezepza/Pitavastatin 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 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. Most patients will require a 2mg dose (see Section 5.1). The maximum daily dose is 4mg.

Elderly: No dosage adjustment is required (see Sections 5.1 and 5.2).

Paediatric use: Pitavastatin 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: 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 Sections 4.4 and 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 Sections 4.4 and 5.2).

4.3 Contraindications

Livazo/Alipza/Vezepza/Pitavastatin 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

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.

Before Treatment

In common with other statins, Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin 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 $\leq 5x$ ULN. If symptoms resolve and CK levels return to normal, then re-introduction of Livazo/Alipza/Vezepra/Pitavastatin may be considered at a dose of 1mg and with close monitoring.

Liver Effects

In common with other statins, Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin and then periodically during treatment. Livazo/Alipza/Vezepra/Pitavastatin treatment should be discontinued in patients who have a persistent increase in serum transaminases (ALT and AST) exceeding $3x$ ULN.

Renal Effects

Livazo/Alipza/Vezepra/Pitavastatin 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).

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.

Other effects

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

Erythromycin: Co-administration with Livazo/Alipza/Vezepra/Pitavastatin resulted in a 2.8-fold increase in pitavastatin AUC. A temporary suspension of Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin should be administered with caution when used concomitantly with fibrates (see Section 4.4). In Pharmacokinetic studies co-administration of Livazo/Alipza/Vezepra/Pitavastatin with Gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC with Fenofibrate AUC increased 1.2-fold.

Niacin: Interaction studies with Livazo/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin should be administered with caution when used concomitantly with niacin.

Fusidic acid: There have been reports of severe muscle problems such as rhabdomyolysis attributed to interactions between fusidic acid and statins. A temporary suspension of Livazo/Alipza/Vezepra/Pitavastatin is recommended for the duration of treatment with fusidic acid (see section 4.4).

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

Protease inhibitors: Co-administration with Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin. 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/Alipza/Vezepra/Pitavastatin 4mg daily. However, as for other statins, patients receiving warfarin should have their prothrombin time or INR monitored when Livazo/Alipza/Vezepra/Pitavastatin is added to their therapy.

4.6 Pregnancy and lactation

Pregnancy

Livazo/Alipza/Vezepra/Pitavastatin is contraindicated during pregnancy (see Section 4.3). Women of childbearing potential must take appropriate contraceptive precautions during treatment with Livazo/Alipza/Vezepra/Pitavastatin. 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/Alipza/Vezepra/Pitavastatin, treatment must be discontinued immediately.

Lactation

Livazo/Alipza/Vezepra/Pitavastatin is contraindicated during lactation (see Section 4.3). Pitavastatin is excreted in rat milk. It is not known whether it is excreted in human milk.

4.7 Effects on ability to drive and use machines

There is no pattern of adverse events that suggests that patients taking Livazo/Alipza/Vezepra/Pitavastatin 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/Alipza/Vezepra/Pitavastatin.

4.8 Undesirable effects

Summary of the safety profile

In controlled clinical trials, at the recommended doses, less than 4% of Livazo/Alipza/Vezepra/Pitavastatin 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 ($\geq 1/10$), common ($\geq 1/100$, to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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

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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin (0.04%) in the clinical trial programme.

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/Alipza/Vezepra/Pitavastatin treated patients 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 (see Section 4.4)

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 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/Alipza/Vezeptra/Pitavastatin 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/Alipza/Vezeptra/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 Livazo/Alipza/Vezeptra/Pitavastatin 2mg and 44 to 45% with Livazo/Alipza/Vezeptra/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 Livazo/Alipza/Vezeptra/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%, 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/Alipza/Vezeptra/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 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%.

A beneficial effect of pitavastatin on cardiovascular morbidity and mortality has not been demonstrated as no outcome studies were included in the clinical programme.

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.

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.

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/Alipza/Vezepra/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 Livazo/Alipza/Vezepra/Pitavastatin 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: Pharmacokinetic data in the paediatric population are not available.

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/Alipza/Vezepra/Pitavastatin is contraindicated in patients with severe hepatic impairment.

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 and carcinogenic potential. 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

3 years.

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

Kowa Pharmaceutical Europe Co. Ltd.

Winnersh Triangle

Wokingham

RG41 5RB

UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 32363/0002

PL 32363/0004

PL 32363/0006

PL 32363/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2010

10 DATE OF REVISION OF THE TEXT

12/08/2010

Module 3

Patient Information Leaflet

Please note that a representative Patient Information Leaflet (PIL) for Livazo 1mg, 2mg and 4mg film-coated tablets (PL 32363/00011 and PL 32363/001-2) is shown below. The PIL details for Alipza, Vezepra and Pitavastatin 1mg, 2mg and 4mg film-coated tablets are consistent this PIL, with the exception of the product name and product licence number.



C4 XXXX

Package Leaflet: Information for the user

Livazo 1mg, 2mg and 4mg film-coated tablets

pitavastatin

Read all of this information carefully before you start taking Livazo film-coated tablets.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

- 1 What Livazo film-coated tablets are and what they are used for
- 2 Before you take Livazo film-coated tablets
- 3 How to take Livazo film-coated tablets
- 4 Possible side effects
- 5 How to store Livazo film-coated tablets
- 6 Further information

1 What Livazo film-coated tablets are and what they are used for

Livazo film-coated tablets contain a medicine called pitavastatin. This belongs to a group of medicines called 'statins'. Livazo film-coated tablets are used to correct the levels of fat (lipid) in your blood. An imbalance of fats particularly cholesterol can sometimes lead to a heart attack or stroke.

You have been given Livazo film-coated tablets because you have an imbalance of fats and changing your diet and making lifestyle changes have not been enough to correct this. You should continue with your cholesterol-lowering diet and lifestyle changes while you are taking Livazo film-coated tablets.

2 Before you take Livazo film-coated tablets

Do not take Livazo film-coated tablets if:

- you are allergic (hypersensitive) to pitavastatin, any other statin or the other ingredients of Livazo film-coated tablets (listed in 6. 'Further information')
- you are pregnant or breast-feeding
- you are a woman able to have children and you are not using a reliable contraceptive method (see 'Pregnancy and breast-feeding')
- you currently have liver problems
- you take ciclosporin - used after an organ transplant
- you have repeated or unexplained muscle aches or pains.

If you are not sure, talk to your doctor or pharmacist before taking Livazo film-coated tablets.

Take special care with Livazo film-coated tablets

Check with your doctor or pharmacist before taking your medicine if:

- you have severe respiratory failure (severe breathing problems).
- you have ever had problems with your kidneys.

- you have previously had liver problems. 'Statins' can affect the liver in a small number of people. Your doctor will usually carry out a blood test (liver function test) before and during treatment with Livazo film-coated tablets.
- you have ever had problems with your thyroid gland.
- you or any member of your family have a history of muscle problems.
- you have had a previous history of muscle problems when taking other cholesterol-lowering medicines (e.g. statins or fibrates).
- you drink excessive amounts of alcohol.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Livazo film-coated tablets.

Taking other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines. This includes any medicines obtained without a prescription and herbal remedies. Some medicines can stop each other from working properly.

In particular tell your doctor or pharmacist if you are taking any of the following:

- other medicines called fibrates - such as gemfibrozil and fenofibrate.
- erythromycin, fusidic acid or rifampicin - types of antibiotics used for infections.
- warfarin or any other medicine used to thin the blood.
- medicines for HIV called 'protease inhibitors'.
- niacin (vitamin B3).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Livazo film-coated tablets.

Pregnancy and breast-feeding

Do not take Livazo film-coated tablets if you are pregnant or breast-feeding. If you are trying to become pregnant, talk to your doctor before taking Livazo film-coated tablets.

If you are a woman who is able to have children, you must use a reliable contraceptive method, while taking Livazo film-coated tablets. Stop taking Livazo film-coated tablets and see a doctor straight away if you become pregnant while taking Livazo film-coated tablets.

Ask your doctor or pharmacist for advice before taking any medicine, if you are pregnant or breast-feeding.

Taking Livazo film-coated tablets with food and drink

Livazo film-coated tablets can be taken with or without food.

Driving and using machines

Livazo film-coated tablets are not expected to interfere with your ability to drive or operate machinery. However, if you feel dizzy or sleepy whilst taking Livazo film-coated tablets do not drive, use any machinery or tools.

Important information about some of the ingredients of Livazo film-coated tablets

Livazo film-coated tablets contain lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

3 How to take Livazo film-coated tablets

Always take Livazo film-coated tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine

Swallow the tablet whole with a drink of water, with or without food. You can take it at any time of day. However, try to take your tablet at the same time every day.

How much to take

- The usual starting dose is 1mg once a day. After a few weeks your doctor may decide to increase your dose. The maximum dose is 4mg each day.
- If you have problems with your liver you should not take more than 2mg a day.

Children

Livazo film-coated tablets are not recommended for use in children aged below 18 years.

Other things you need to know whilst taking Livazo film-coated tablets

- If you go into hospital or receive treatment for another problem, tell the medical staff that you are taking Livazo film-coated tablets.
- Your doctor may do regular cholesterol checks.
- Do not stop taking Livazo film-coated tablets without talking to your doctor first. Your cholesterol levels might increase.

If you take more Livazo film-coated tablets than you should

If you take more Livazo film-coated tablets than you should, talk to a doctor or go to hospital straight away. Take the medicine pack with you.

If you forget to take a dose

Do not worry, just take your next dose at the correct time. Do not take a double dose to make up for the one you have missed.

4 Possible side effects

Like all medicines, Livazo film-coated tablets can cause side effects, although not everybody will have them. The following side effects may happen with this medicine:

Stop taking Livazo film-coated tablets and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:

- allergic reaction - the signs may include: difficulty breathing, swelling of the face, lips, tongue or throat, problems swallowing, severe itching of the skin (with raised lumps)
- unexplained muscle pain or weakness, especially if you feel unwell, have a fever or have reddish brown urine. Livazo film-coated tablets can rarely (less than 1 in 1,000 people) cause unpleasant muscle effects. If not investigated they can lead to serious problems such as abnormal muscle breakdown (rhabdomyolysis), which can lead to kidney problems.
- breathing problems including persistent cough and/or shortness or breath or fever.

Most other side effects are usually mild and disappear after a short time, these include:

Common (affects less than 1 in 10 people)

- joint pain, muscle ache
- constipation, diarrhoea, indigestion, feeling sick
- headache.

Uncommon (affects less than 1 in 100 people)

- muscle spasms
- feeling weak, weary or unwell
- swelling of the ankles, feet or fingers
- stomach pain, dry mouth, being sick, loss of appetite, altered taste
- pale skin and feeling weak or breathless (anaemia)
- itching or rash
- ringing in the ears
- feeling dizzy or sleepy, insomnia (other sleep disturbances including nightmares)
- increased need to go to the toilet (urinary frequency).

Rare (affects less than 1 in 1,000 people)

- liver problems which may cause yellowing of the skin and eyes (jaundice)
- pancreatitis (severe pain in the abdomen and back)
- redness of the skin, raised red itchy skin
- deteriorating eye sight
- pain in the tongue.

Other possible side effects

- memory loss
- sexual difficulties
- depression.

If any of the side effects becomes troublesome, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store Livazo film-coated tablets

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

The blisters and carton have an expiry date printed on them, do not take these tablets if this date has passed. Keep your tablets in a safe place out of the reach and sight of children. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

Livazo film-coated tablets contain pitavastatin calcium equal to 1mg, 2mg or 4mg of pitavastatin. Your tablets also contain lactose monohydrate, LS-hydroxypropylcellulose, hypromellose (E464), titanium dioxide (171), triethyl citrate (E1505), magnesium aluminometasilicate, magnesium stearate, colloidal anhydrous silica.

What Livazo film-coated tablets look like and contents of the pack

Livazo film-coated tablets are supplied in packs of 7, 28, 30 or 100. Not every pack is available in the market for each strength. The tablets are round, white and marked on one side with the letters 'KC'. To help identify the different strengths, they are each a different size and marked with either '1', '2' or '4' on the other side.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Kowa Pharmaceutical Europe Co Ltd,
Winnersh Triangle, Wokingham, RG41 5RB UK

Manufacturer:
Pierre Fabre Médicament Production*,
Rue du Lycée, 45502 Gien Cedex, FRANCE

Or
Recordati Industria chimica Farmaceutica SpA*,
Via M Civitali 1, 20148 Milan, ITALY

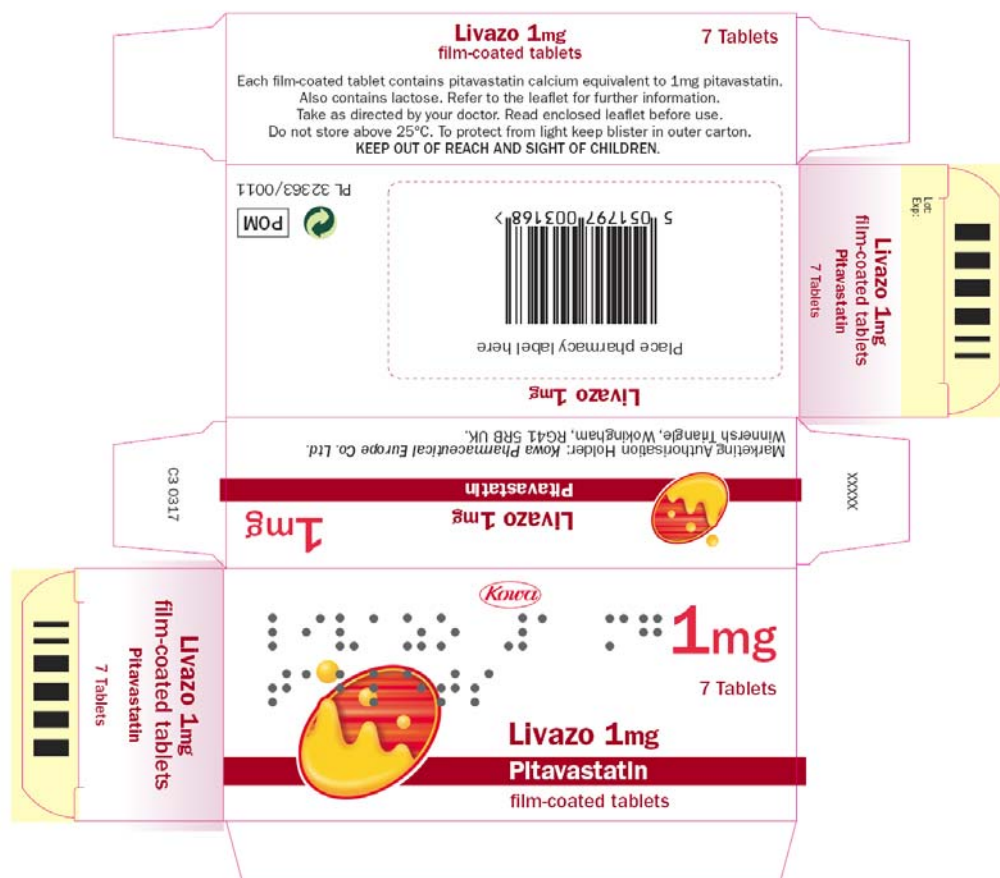
This leaflet was approved in 13-07-2010.

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* Only the manufacture site responsible for product release into an individual market will be named on the leaflet in that particular market.

Module 4 Labelling

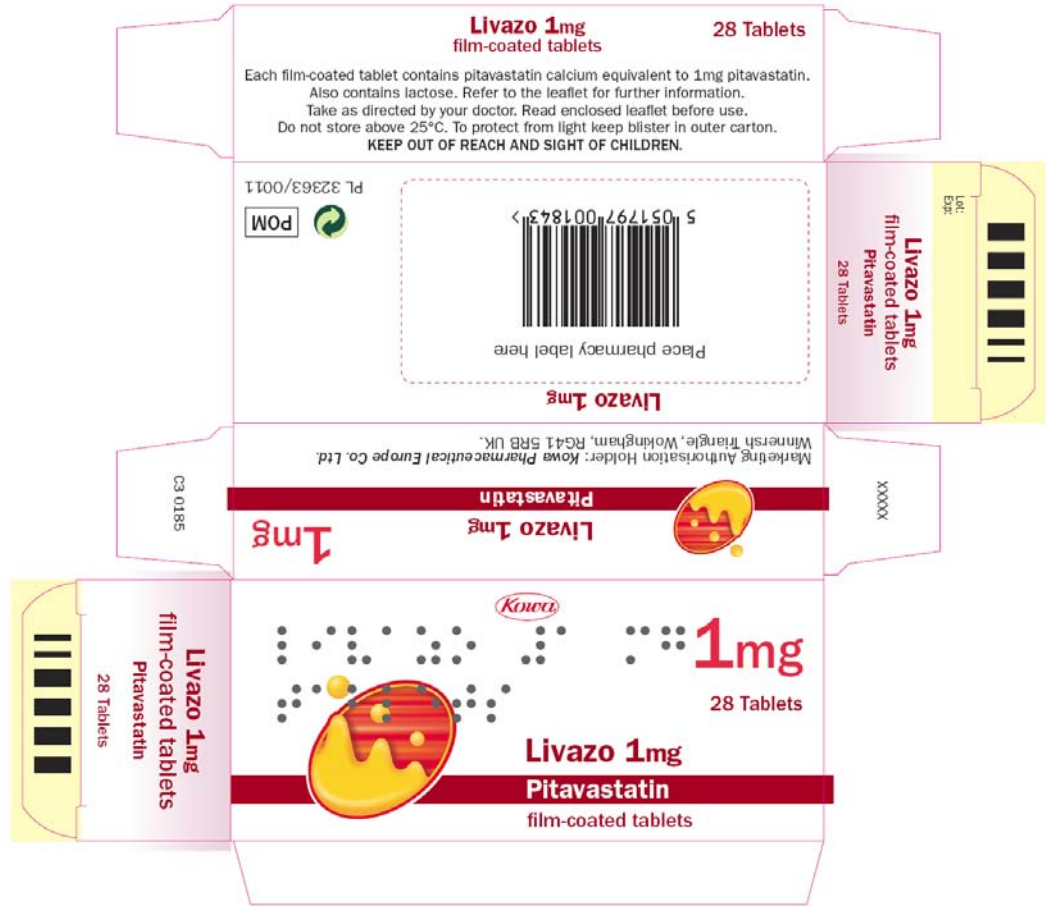
Please note that representative labelling for Livazo 1mg, 2mg and 4mg film-coated tablets (PL 32363/00011 and PL 32363/001-2) are shown below. The labelling details for Alipza, Vezepra and Pitavastatin 1mg, 2mg and 4mg film-coated tablets are consistent these labels, with the exception of the product name and product licence number.



Pack size: 7
Quantity: 7 x 1

97 x 42 mm

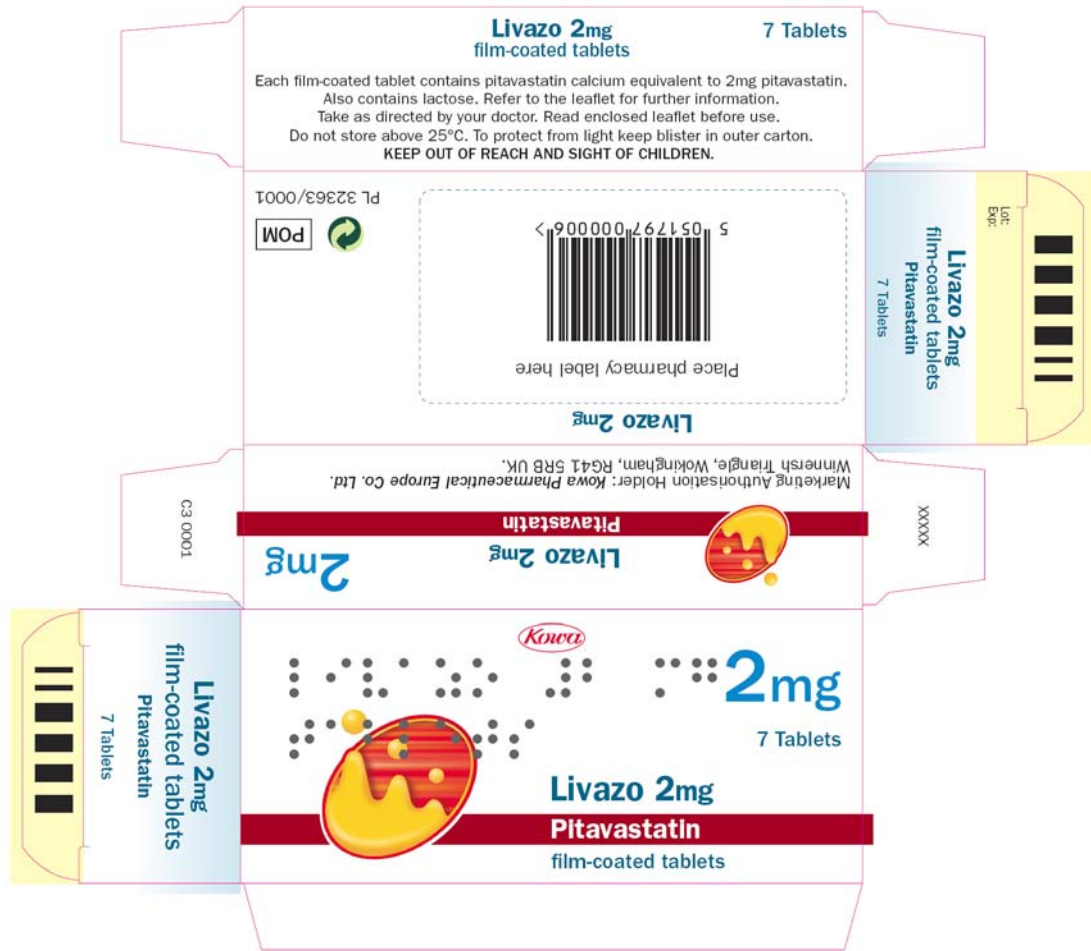




Pack size: 28
Quantity: 14 x 2

97 x 42 mm





Pack size: 7
Quantity: 7

97 x 42 mm

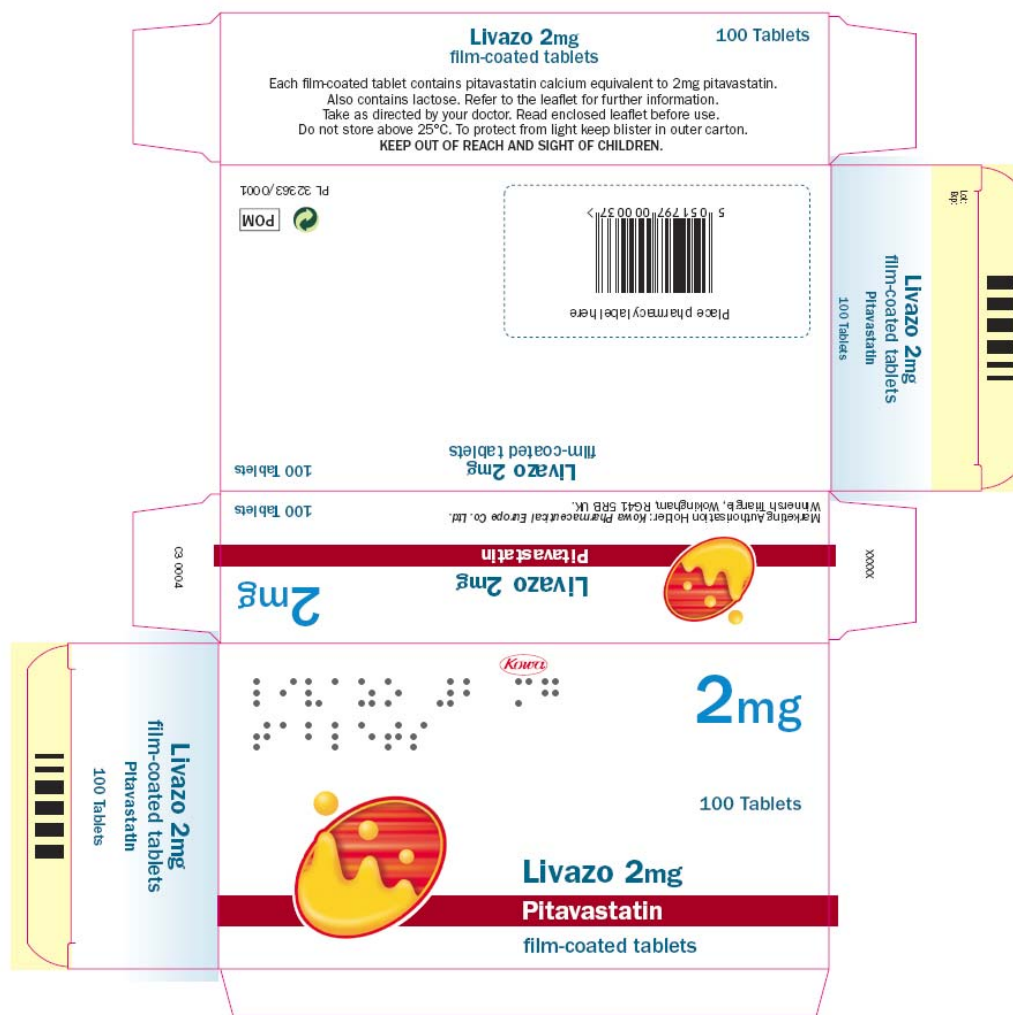




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Quantity: 14 x 2

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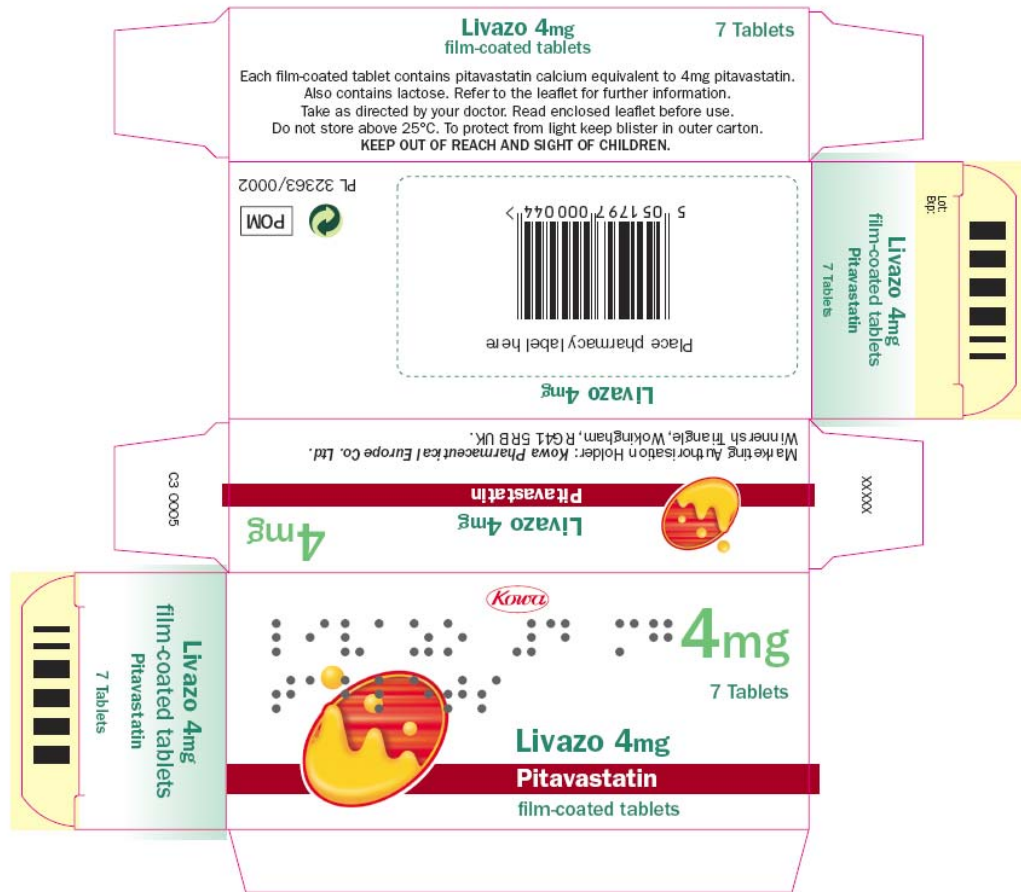




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Quantity: 20 x 5

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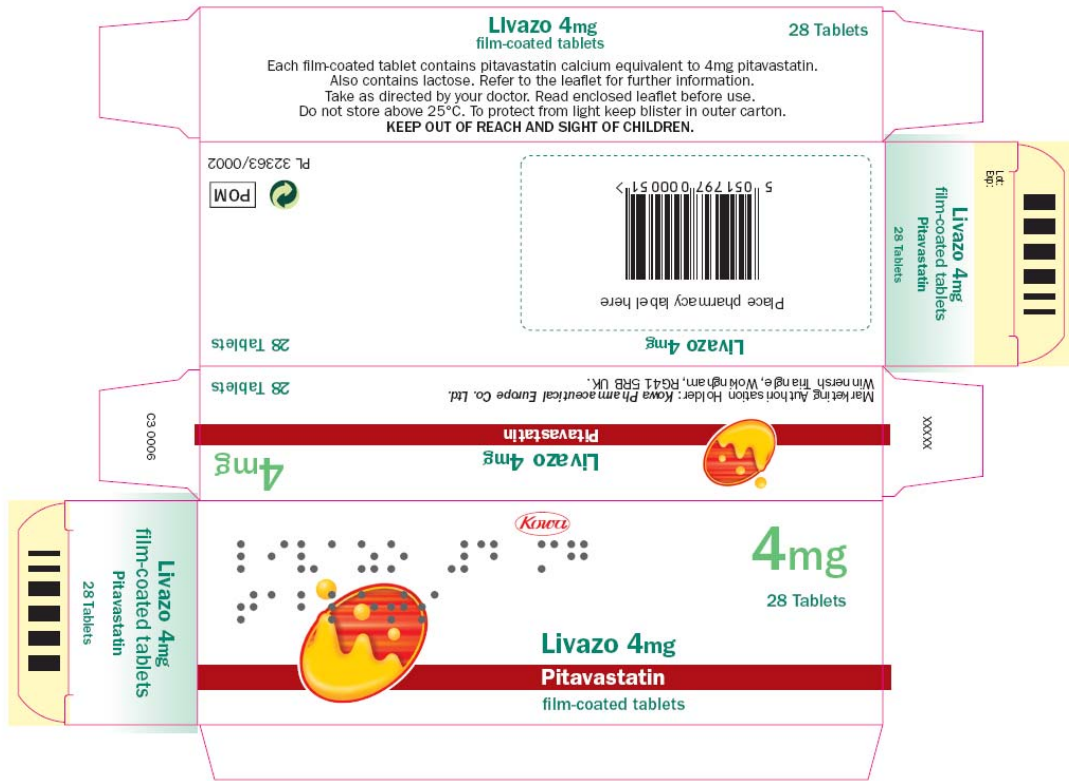




Pack size: 7
Quantity: 7

97 x 42 mm





Pack size: 28
 Quantity: 14 x 2
132 x 45 mm



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Livazo/Alipza/Vezepra/Pitavastatin 1mg, 2mg and 4mg film-coated tablets (PL 32363/0001-8 and PL 32363/0011-4; UK/H/1555-8/001-3/DC) could be approved. The products are prescription-only medicines (POM) indicated for the reduction of elevated total cholesterol (TC) and LDL cholesterol (LDL-C) in adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia and combined (mixed) dyslipidaemia, when response to diet and other non-pharmacological measures is inadequate.

These full dossier applications for a new chemical entity (NCE), pitavastatin, were submitted via the decentralised procedure, in accordance with Article 8.3 of 2001/83/EC, as amended. The UK acted as Reference Member State (RMS) and Austria, Belgium, Cyprus, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain and Sweden were Concerned Member States (CMS). Pitavastatin has been licensed as tablets by Kowa Company Limited in Japan since 2003, South Korea since 2005 and Thailand since 2007. The formulation used in the current applications is based on the Japanese formulation.

Pitavastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (HMGR) or 'statin'. It was selected for development on the basis that it had the potential to correct lipid abnormalities in patients with primary hypercholesterolaemia and combined (mixed) dyslipidaemia, who have not responded adequately to dietary control. The primary pharmacology of a HMGR is reduction of lipid parameters, especially LDL-cholesterol.

The applicant sought scientific advice from the Committee of Medicinal Products for Human Use (CHMP) in November 2004 with follow up scientific advice in July 2005. The CHMP accepted the overall development programme, but had specific comments on certain aspects:

1. Although the placebo and active comparator studies were considered suitable with the 6% margin of non-inferiority, it was recommended that the duration should be up to a period of at least 1 year.
2. Generation of data should be at the highest recommended dose,
3. Assessment of safety should be in relation to liver and kidney impairment and muscle toxicity.
4. Concerns were raised regarding the doses of comparators and achieving target LDL-C reductions.
5. Additional interaction studies were requested (UGT inhibitors and inducers, and OATP substrates).
6. Further investigation of the reasons for the 4-fold increase in exposure in those with Child-Pugh B (moderate hepatic impairment).

The applicant has stated that they have complied with the CHMP's advice, except in the last instance of hepatic impairment (where the reasons were presumed to be related to hepatic uptake similar to atorvastatin). Furthermore, the development programme is considered to be in line with the *Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders* (CPMP/EWP/3020/03), the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), and the National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP-III) guidelines.

Within the development programme, special populations (such as the elderly, women and ethnic groups) have been included, albeit in small numbers. In some areas, the paucity of numbers does impact on the data and the inferences, although no specific issues have been identified that suggests a different conclusion. For example, dosing in elderly should have been discussed better with pharmacodynamic studies in the elderly population; similarly, gender and ethnicity study suffers from very few elderly black women (only 1 subject). Studies in those with renal and hepatic impairment have been included and the conclusions would be applicable overall.

In accordance with Article 25 (5) of Regulation (EC) No 1901/2006 of the European Parliament on medicinal products for paediatric use, a Paediatric Investigation Plan has been agreed with the European Medicines Agency's Paediatric Committee.

The majority of the safety, pharmacology and pivotal toxicity studies were conducted in compliance with Good Laboratory Practice (GLP). Two early safety pharmacology studies were not conducted under GLP conditions, but appear to have been carried out in a scientifically valid manner and subsequent, GLP-compliant studies have corroborated the results of these studies. Much of the information on pharmacokinetics was provided as published papers (from the applicant's laboratories). These studies were not GLP-compliant, but again this does not detract from the scientific validity of the studies. Generally, the safety studies that should be conducted in compliance in-line with GLP have been, with the exception of two non-GLP toxicokinetic studies that were associated with repeated-dose toxicity studies.

The clinical studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the applications could be approved, with the end of procedure (Day 210) on 13 July 2010. After a subsequent national phase, licences were granted in the UK to Kowa Pharmaceutical Europe Company Limited, Winnersh Triangle, Wokingham, RG41 5RB, UK, on 12 August 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Livazo 1mg, 2mg and 4mg film-coated tablets Alipza 1mg, 2mg and 4mg film-coated tablets Vezepra 1mg, 2mg and 4mg film-coated tablets Pitavastatin 1mg, 2mg and 4mg film-coated tablets
Name(s) of the active substance(s) (INN)	Pitavastatin
Pharmacotherapeutic classification (ATC code)	HMG-Co-A reductase inhibitors (ATC code C10A A08)
Pharmaceutical form and strength(s)	Film-coated Tablets; 1mg, 2mg and 4mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1555/001-3/DC UK/H/1556/001-3/DC UK/H/1557/001-3/DC UK/H/1558/001-3/DC
Reference Member State (RMS)	United Kingdom
Concerned Member States (CMS)	UK/H/1555/001-3/DC: Austria, Belgium, Cyprus, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain & Sweden UK/H/1556/001 and 003/DC: Cyprus, France, Ireland, Greece, Italy, Portugal and Spain UK/H/1556/002/DC: Cyprus, France, Ireland, Greece, Italy, Portugal, Spain, Austria, Germany, Poland and Sweden UK/H/1557/001-03/DC: Austria, Belgium, Finland, The Netherlands, Norway, Poland and Sweden UK/H/1558/0-03/DC: France, Greece, Italy, Portugal and Spain
Marketing Authorisation Number(s)	Livazo 1mg, 2mg and 4mg film-coated tablets: PL 32363/0011 and PL 32363/0001-2 Alipza 1mg, 2mg and 4mg film-coated tablets: PL 32363/0012 and PL 32363/0003-4 Vezepra 1mg, 2mg and 4mg film-coated tablets: PL 32363/0013 and PL 32363/0005-6 Pitavastatin 1mg, 2mg and 4mg film-coated tablets: PL 32363/0014 and PL 32363/0007-8
Name and address of the authorisation holder	Kowa Pharmaceutical Europe Company Limited, Winnersh Triangle, Wokingham, RG41 5RB, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

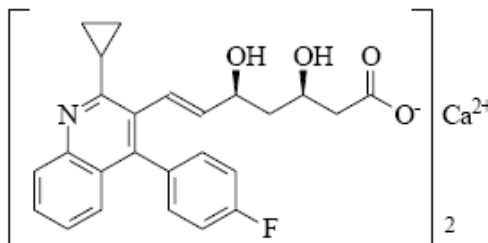
ACTIVE SUBSTANCE

INN: Pitavastatin

JAN Pitavastatin calcium

Chemical name: (+)-Monocalcium bis {(3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinoly]-3,5-dihydroxy-6-heptenoate}

Structure:



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

Molecular weight: 880.98

Appearance: A white to pale yellow hygroscopic crystalline powder, which is very slightly soluble in water. It contains two asymmetric carbons at the 3- and 5-positions in the 3,5-dihydroxy-6-heptenoic acid side chain, giving rise to four stereoisomers, the 3*S*-epimer, the 5*R*-epimer, Pitavastatin and its enantiomer (3*S*,5*R*). Pitavastatin calcium is used as a single enantiomer with the 3*R*,5*S*-configuration. The structure of the 3*R*,5*S*-dihydroxy-6-heptenoic acid side chain gives the specific rotation, $[\alpha]_D^{20}$ of $+22.8^\circ$ (1.0 w/v%) in a mixture of acetonitrile and water (1:1). Several potential polymorphs have been confirmed, however, this product only uses polymorph A.

Pitavastatin calcium is not the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications and certificates of analysis have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning plastic containers and closures for pharmaceutical use, and with legislation relating to contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose (E464), magnesium aluminometasilicate and magnesium stearate (making up the tablet core), and hypromellose (E464), titanium dioxide (E171), triethyl citrate (E1505) and colloidal anhydrous silica (making up the film-coating).

Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of low-substituted hydroxypropylcellulose and magnesium aluminometasilicate (which both comply with their respective US Pharmacopoeia monographs), all the excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis are provided for each excipient showing compliance with their respective monograph.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to develop immediate-release, linear, film-coated tablets containing pitavastatin, which were efficacious and well-tolerated.

Comparative dissolution and batch analysis data have been provided for the European formulation of the 2mg product (Livazo/Alipza/Vezepra/Pitavastatin 2mg film-coated tablets) and the Japanese formulation of the 2mg product (Livalo 2mg film-coated tablets). Furthermore, a bioequivalence study has been performed comparing the European versus the Japanese 2mg formulations, showing that the two are bioequivalent and, therefore, interchangeable. These data show that the clinical studies performed on the Japanese formulation can be used interchangeably with those for the European formulation, as they can be considered to be the same product.

A further bioequivalence study was performed comparing the European versus Japanese formulations of the 4mg product. Again, these studies showed that these products were bioequivalent and support the extrapolation of data from studies conducted with the Japanese formulation.

Details of these bioequivalence studies are provided in the Section III.3 (Clinical Aspects).

Manufacturing Process

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. Suitable validation data have been submitted and are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The tablets are packaged in white polyvinylidene chloride/polyvinylchloride/aluminium blister strips. These are packed in cardboard cartons with patient information leaflets in pack sizes of 7, 28 or 30 tablets. An additional pack size of 100 tablets is available for the 2mg strength.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size of the products.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with food.

Stability of the product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data support a shelf-life of 3 years, with the storage conditions 'Store below 25°C'. Keep blisters in the outer carton to protect from light.'

Summaries of Product Characteristics (SPCs), Patient Information Leaflets (PILs) and Labelling

The SPCs, PILs and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms

The MAA forms are satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

There are no objections to the grant of marketing authorisations on quality grounds.

III.2 NON-CLINICAL ASPECTS

Pharmacology

Pitavastatin calcium is a 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitor. In *in vitro* studies, pitavastatin competitively inhibited the enzyme in rat liver microsomes with a median (50%) inhibitory concentration (IC₅₀) of 6.8nM and inhibitory affinity constant (K_i) of 1.7nM, and it was 2.4 times more potent than simvastatin and 6.8 times more potent than pravastatin in this system.

Pitavastatin has two assymetrical carbon atoms and consequently four optical isomers. The epimers and enantiomer are at least 100 times less potent than pitavastatin and, therefore, one stereospecific configuration is required for the exhibition of enzyme inhibitory activity. The 8-hydroxy metabolite of pitavastatin has a similar IC₅₀ to the parent drug in rat liver microsomes.

Pitavastatin inhibited cholesterol synthesis in human hepatoma cells (HepG2), skeletal muscle cells and hepatocytes with IC₅₀s of 5.8, 3.4 and 24.5nM, respectively.

In vivo, pitavastatin showed a preference for the liver in rats, with effective doses (E₅₀s) for inhibition of sterol synthesis in the liver, skeletal muscle and ileum being 0.17, 0.39 and 0.6mg/kg, respectively, and ≥3mg/kg in spleen, adrenal and testis. In a similar study, pitavastatin, pravastatin and simvastatin were administered to rats as a single oral dose and inhibition of sterol synthesis in tissues was evaluated. The greatest effect was again seen in the liver, with ED₅₀s of 0.13, 2.4 and 0.36 mg/kg for pitavastatin, pravastatin and simvastatin, respectively.

In guinea pigs, the ED₅₀s for inhibition of sterol synthesis in the liver were 0.33mg/kg for pitavastatin and 5.1mg/kg for simvastatin. Pitavastatin showed a more sustained effect.

Repeated oral dosing of pitavastatin in guinea pigs dose-dependently decreased plasma total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels; reductions were significant at ≥ 0.3 mg/kg. At ≥ 1mg/kg, plasma triglycerides (TG) also decreased significantly, and at 3mg/kg, very low-density lipoproteins (VLDL), including VLDL-cholesterol (VLDL-C), VLDL-TG and VLDL-phospholipid (VLDL-PL), as well as VLDL-apoprotein B (VLDL-apoB). Pravastatin, fluvastatin, cerivastatin and atorvastatin all significantly reduced LDL-C concentrations, but apart from pitavastatin, only atorvastatin significantly decreased TG and VLDL-C in this series of studies.

In dogs, pitavastatin significantly reduced plasma cholesterol from doses of 0.1mg/kg, and to a lesser extent, plasma phospholipids. In another dog study, twice daily dosing of pitavastatin for 14 days (0.28 mg/kg/day) significantly decreased plasma TC, PL and TG concentrations, with 0.25 mg/kg/day of the lactone having similar activity. The effect of the lactone was a result of conversion back to pitavastatin *in vivo*.

In animal models of hyperlipidaemia, pitavastatin at 1mg/kg/day for 2 weeks lowered TG in male kwl:Zucker rats and in hyperlipidaemic guinea pigs, it reduced plasma TC and LDL-C and increased clearance of LDL.

In Watanabe heritable hyperlipidaemic (WHHL) rabbits, pitavastatin (administered for 6 months in the drinking water at 0.5mg/kg/day) lowered plasma cholesterol (by 7 to 20%), triglyceride (by 16 to 39%) and phospholipid (by 7 to 26%), although the reductions were not significant at all time points. After 26 weeks, pitavastatin had significantly reduced

concentrations of VLDL-C and intermediate density lipoprotein (IDL)-C, by 61.8% and 48.8%, respectively.

Mechanism-of-action studies demonstrated that the effects on plasma lipids resulted from pitavastatin-induced increases in the expression of LDL receptors via suppression of cholesterol synthesis in the liver and, in consequence, enhanced LDL internalisation into the liver and LDL clearance, with a resultant decrease in plasma LDL-C and TC concentrations.

Additional studies *in vitro* and *in vivo* in rabbits showed pitavastatin to have an anti-atherosclerotic effect. It reduced cholesteryl ester in an LDL-loaded mouse peritoneal macrophage cell line, suppressed intimal thickening in the balloon-endothelisation model of carotid artery in rabbits and suppressed the progression of aortic atherosclerosis and stabilised the atherosclerotic plaque in WHHL rabbits

Pitavastatin did not affect biliary lipids or lithogenic index in guinea pigs or hamsters, and had no effect on plasma steroid hormone levels in rats and guinea pigs.

In safety pharmacology studies, the only statistically significant findings were:

- inhibition of writhing frequency in mice at single oral doses of 10 and 30mg/kg
- decreased urinary excretion of electrolytes in rats at 10 mg/kg p.o. and decrease in urinary excretion of electrolytes and urine volume at 30 mg/kg
- increase in heart rate at 3 and 6 hours after 10 mg/kg p.o. in dogs (C_{max} was 44 to 110 times higher than that seen following the clinical dose of 4 mg)

Pitavastatin has no significant effect on the lactone-suppressed human *Ether-à-go-go* Related Gene (hERG) current in hERG-transfected HEK293 cells at 1 μ mol/L (about 1000-fold the estimated clinical plasma protein-free concentration of lactone).

A pharmacodynamics interaction with warfarin appears unlikely.

Overall, the pharmacology studies were conducted appropriately and raise no particular concerns for use of the product in the proposed indication.

Pharmacokinetics

Pitavastatin was absorbed relatively rapidly after an oral dose in rats ($T_{max} < 1$ hour), but more slowly in dogs, rabbits and monkeys. In rodents, exposure was higher in females than in males. There was no obvious accumulation on repeated dosing, although in rats dosed for 9 days exposure did increase compared with the first dose, with steady state being reached after about 4 days. The main sites of absorption of pitavastatin in the rat were the duodenum and large intestine.

Kinetics appeared to be tri-exponential in rats, rabbits, dogs and monkeys, with terminal elimination half-lives of about 4 to 6 hours for pitavastatin and of more than 40 hours for radioactivity after administration of 14 C-pitavastatin.

Bioavailability of an oral dose was high in rats, rabbits and dogs (80-100%), but lower in monkeys (18%), suggesting greater metabolism in this species. In humans, bioavailability is reportedly 51%. In a rat model of liver dysfunction, exposure to pitavastatin (area under the curve [AUC]) increased about 3 times after a single oral dose compared with rats with normal liver function.

Pitavastatin was highly bound to plasma proteins in all species studied, with limited transfer into blood.

Distribution of radioactivity after an oral dose of ^{14}C -pitavastatin in rats showed highest levels in the liver, with significant levels in heart, skeletal muscle, lung and kidney. Radioactivity was cleared more slowly from the heart, skeletal muscle and abdominal fat than from other tissues and was present at levels higher than those in plasma at 24 hours post dose. Repeated dosing increased tissue levels compared with those after a single dose. Comparison with distribution in Lister Hooded rats demonstrated that pitavastatin had no particular affinity for melanin, as radioactivity in eyes and pigmented skin was not significantly greater than in albino rats.

In monkeys, highest levels of radioactivity were found in the bile following a single oral dose of ^{14}C -pitavastatin. Levels in the liver were 60-fold those in plasma with lesser amounts in kidney.

Pitavastatin was a substrate for human hepatic organic anion transporting polypeptide 1B1 (hOATP1B1), and uptake by this transporter is saturable. It is not a substrate for P-glycoprotein (P-gp).

Pitavastatin showed limited placental transfer in rats, but was distributed into milk, reaching a higher concentration than in maternal plasma.

Pitavastatin appears to be extracted efficiently by the liver, but was metabolised to only a limited extent by cytochrome P450 (CYP) isozymes. The main metabolic pathways are the formation of the lactone (and its conversion back to pitavastatin), hydroxylation of the quinoline ring (particularly 8-hydroxylation), β -hydroxylation of the side chain and the formation of glucuronic acid and taurine conjugates.

The lactone is formed via an ester-type pitavastatin glucuronide conjugate by UDPGT1A3 and 2B7, and is converted back to pitavastatin in the presence of CYP isozymes.

The metabolic profile is qualitatively similar across species, although there are quantitative differences. However, there are no unique human metabolites and the species used in the toxicology studies are, therefore, appropriate to investigate the toxicity of pitavastatin and its metabolites.

Faecal excretion of radioactivity predominated after oral dosing in rats, guinea pigs, dogs and monkeys, as it does in man, but urinary excretion predominated in rabbits. In rats and dogs, approximately 50% of the administered dose was excreted as unchanged pitavastatin, but the fraction was much lower in monkeys, indicating a much higher rate of metabolism in this species. In man, unchanged pitavastatin accounted for most of the radioactivity in faeces.

Enterohepatic circulation occurs in all species investigated (rat, guinea pig, dog and monkey), and contributes to the prolonged half-life (>40 hours) of radioactivity in these species. Pitavastatin was not a substrate for canalicular membrane organic anion transporter (cMOAT).

Pharmacokinetic interaction studies showed that there are unlikely to be interactions as a result of displacement of other compounds from their protein binding sites or through effects on CYP isoenzymes. However, pitavastatin is actively taken up into liver through Organic anion transporting polypeptide 1B1 (OATP1B1) and competition for, or inhibition of, this

transporter by other drugs may lead to interactions with pitavastatin. Pharmacokinetic drug interactions have also been investigated clinically and section 4.5 of the proposed SPC reflects the available information adequately.

Toxicology

In single-dose toxicity studies, the target organs were the gastrointestinal tract and liver. There were no findings in the monkey following single doses up to 50mg/kg. At the 10mg/kg dose, exposure to pitavastatin was 8-times that in man following an 8mg dose.

The findings seen in the repeated-dose toxicity studies have generally been reported previously with other HMG-CoA reductase inhibitors. Target organs were the forestomach in rats and mice, the kidney in monkeys and rabbits, the eyes, lung and liver in dogs, and the liver, thyroid and muscle in rodents. A number of studies were conducted to investigate the possible mechanisms behind these toxicities.

The forestomach effects in rodents are alleviated by co-administration of mevalonate and are a recognised class effect of statins. The findings are not considered to be clinically relevant.

Pulmonary lesions seen in the 3- and 12-month dog studies, mainly consisted of foam cells and inflammatory cells. Similar findings were not seen in other species, and co-administration of mevalonate for 3 months in a separate study in dogs suppressed these findings. The increase in liver enzymes induced by pitavastatin was also suppressed by co-administration of mevalonate in this dog study, demonstrating that both lung and liver findings were related to the pharmacological activity of pitavastatin.

The dog appears particularly sensitive to effects on the eye, with pitavastatin accumulating in the lens and only slowly clearing (with a half-life of about 2 weeks). Levels of pitavastatin (and lactone) in the lens of other species were much lower than those in the dog and no corneal opacity was seen in the 26-week study in cynomolgus monkeys, although systemic exposure reached levels producing such findings in dogs. The lens findings in the dog may be considered a class effect, and it likely that humans are at relatively low risk of developing cataracts as a result of treatment with pitavastatin.

The kidney findings in the monkey (necrosis and regeneration of the renal proximal tubular epithelium in the 4-week study and swelling of the renal proximal tubular epithelium in the 26-week study) were considered to be of little toxicological significance as they were mild, reversible and generally not associated with blood chemistry changes, and renal function was not affected. However, a mechanistic study was conducted in rats with 8-hydroxy pitavastatin to investigate whether this compound may contribute to renal toxicity. The study failed to elucidate whether or not this metabolite may contribute to the findings in the kidney seen in the repeated dose monkey studies, as all animals died or were sacrificed early and it was not possible to say whether the slight renal changes seen were secondary to the poor condition of the animals. There were also some renal findings in rabbits dosed with pitavastatin and this species excretes pitavastatin-related material predominantly via the urine. Although the monkey excretes pitavastatin mainly in the faeces, the proportion eliminated via the urine is higher than in rats and dogs. The risk management plan has been updated to include renal disorders as potential risks.

Degeneration and necrosis of skeletal muscle was seen in a 4-week rat study at 50 mg/kg/day and higher, and in a 13-week rat study also at 50 mg/kg/day. There were no muscle effects in the 26-week rat study, where the high dose was 10 mg/kg/day. The exposure (AUC) at this dose was 10527 and 6740 ng.h/ml in males and females, respectively, which is 69 and 44

times the AUC of 153 ng.h/ml in humans receiving the therapeutic dose of 4 mg and, therefore, provides a good safety margin. In the carcinogenicity studies, skeletal muscle atrophy was seen in both mice (from 12mg/kg/day in males and 1mg/kg/day in females) and rats (at 25 mg/kg/day in males). In a 2-week dog study, there were no skeletal muscle findings although CK was elevated at 50 mg/kg/day. In the 4-week monkey study, a high dose (15 mg/kg/day) female had a number of findings that were possibly related to poor nutritional status, but did include atrophy of skeletal muscle and elevation of CK. Therefore, the findings in muscle are not necessarily restricted to rodents.

Skeletal muscle effects in animals have been described for other statins, and have also been reported clinically; cerivastatin was withdrawn due to the high level of rhabdomyolysis. The IC₅₀ for the inhibition of cholesterol synthesis in human skeletal muscle for cerivastatin was 0.3nM, and for pitavastatin, 3.4nM. Simvastatin, atorvastatin and fluvastatin were similar to pitavastatin (4.1 to 4.8nM), but pravastatin had a weaker effect, with an IC₅₀ of 164.4nM.

If this were to reflect a rank order of likelihood of causing muscle damage, then pitavastatin would be ranked with simvastatin, atorvastatin and fluvastatin, rather than with cerivastatin. Nevertheless, rhabdomyolysis has been reported in the clinical trials with pitavastatin, albeit at the higher dose of 8mg, and consequently patients should be monitored for potential myopathy. The identified risk of rhabdomyolysis in the risk management plan has been extended to include myalgia and renal disorders and an appropriate warning statement is included in the SPC.

Toxicokinetic analyses conducted in support of the toxicity studies revealed exposures in the animals at the no-observed-adverse-event-level (NOAEL) in the repeated-dose studies ranged from about 2- (in the 12-month dog study) to 7.5-fold (in the 3-month dog study) that in humans following a dose of 4mg/day for 2 weeks.

A battery of genotoxicity studies suggests that pitavastatin does not have genotoxic potential.

In carcinogenicity studies, target organs were the forestomach in mice and rats, and the thyroid in rats. The development of papillomas and carcinomas in the forestomach can be considered a natural progression over time of the changes in the forestomach seen in the repeated-dose studies. Forestomach papillomas have also been reported for fluvastatin, lovastatin, pravastatin and simvastatin in the mouse, and for fluvastatin in the rat, and are not considered to be a cause for concern at clinical doses of pitavastatin.

A mechanistic study in rats using a tumour promoter (DHPN) and pitavastatin with and without T₄ supplementation suggested that reduced T₄ levels are involved in the production of thyroid tumours by pitavastatin in rats, by way of a feedback increase in thyroid stimulating hormone (TSH) levels and consequent chronic stimulation of the thyroid tissue, leading to hypertrophy, hyperplasia and neoplasia.

Pitavastatin did not induce tumorigenesis, nor did it promote that of urethane or influence tumour growth in Tg-RasH2 mice, and was not carcinogenic in a 26-week study in CB6F1-Tg rasH2 transgenic mice.

Overall these studies suggest that there is no risk of carcinogenicity from use of pitavastatin.

The reproductive toxicity studies show similar effects to other HMG-CoA reductase inhibitors when administered during late pregnancy and lactation, with effects on the viability and development of offspring as well as maternal toxicity. The effects are due to the

pharmacological activity of pitavastatin, as they are suppressed by the administration of mevalonate. The applicant has contraindicated the product during pregnancy, lactation, and in women of childbearing potential who are not using effective contraception, which is appropriate and in-line with other statins.

Pitavastatin does not appear to have any antigenic potential.

Single-dose and 4-week repeated-dose oral toxicity studies conducted with the main lactone metabolite and related substances (3- and 5-epimers and the enantiomer) of pitavastatin showed a lower toxicity in comparison to the parent compound. In addition, a single-dose study in mice was conducted with the 5-ketone metabolite (M-3), which is also a degradant, and showed similar toxicity to pitavastatin.

The lactone was not mutagenic or clastogenic in *in vitro* studies. The epimers and enantiomer of pitavastatin produced equivocal/positive findings in a chromosomal aberration assay in Chinese hamster lung cells, but bacterial reverse mutation assays and mouse micronucleus tests were negative. Overall these impurities are not considered to be genotoxic. On the basis of these studies, the proposed shelf-life limit of 0.6% for the lactone in the drug product specification, and of not more than 1.0% for the enantiomer and not more than 0.5% for the epimers in the drug substance specification, are acceptable.

Appropriate studies have been conducted to investigate the potential risk to the environment from use of pitavastatin. It was concluded that pitavastatin does not pose a risk to surface water, micro-organisms, sediment dwelling organisms or to the terrestrial compartment.

Expert report

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Environmental Risk Assessment

The Marketing Authorisation Holder has provided an adequate Environmental Risk Assessment. Appropriate studies have been conducted to investigate the potential risk to the environment from use of pitavastatin. It was concluded that pitavastatin does not pose a risk to surface water, micro-organisms, sediment dwelling organisms or to the terrestrial compartment.

Conclusion

The toxicity of pitavastatin has been shown to be similar to that of other HMG-CoA reductase inhibitors. The non-clinical points raised for consideration following the original assessment have been addressed adequately. There are no objections to the authorisation of these products on non-clinical grounds.

III.3 CLINICAL ASPECTS

PHARMACOKINETICS

The dossier includes a number of pharmacokinetic and bioequivalence studies in healthy volunteers. The clinical pharmacokinetics of pitavastatin have been characterised using various immediate-release oral formulations. Pitavastatin is an orally bioavailable, potent inhibitor of HMG-CoA reductase, with a long duration of action and its pharmacology (and pharmacokinetics) have been studied in a number of *in vitro* and *in vivo* test systems. The *in vitro* studies use human biomaterials, investigated plasma protein binding, hepatic metabolism, potential drug interactions and pharmacological action of pitavastatin. *In vitro* pharmacology studies were performed in cells derived from human hepatoma (HepG2 cells), which are widely used in the study of lipid metabolism. In human-derived cellular transporter studies, organic anion transporting polypeptide 2 (OATP1B1, also known as liver-specific Na⁺-independent organic anion transporter LST-1, OATP-C or OATP2), was principally responsible for the uptake into human liver of pitavastatin.

The clinical pharmacokinetic studies focused on identifying the pharmacokinetic profile of pitavastatin and its lactone metabolite in plasma and urine in healthy volunteers; volunteers with hepatic or renal impairment; in Japanese, Korean, Chinese, Black (African-American) and Caucasian races; in males and females; and in the elderly. The analytical methods adopted are in-line with the standard techniques and testing systems. The hepatic metabolism studies included various test systems, such as human liver microsomes, transgenic oocytes (*Xenopus laevis*) or other human microsomal expression systems.

The involvement of the transporters OATP1B1 and OATP1B3 in the hepatic uptake of pitavastatin was evaluated using stably transfected HEK293 cells expressing human OATP1B1 and OATP1B3 and in human cryopreserved hepatocytes. For pitavastatin, the observed uptake clearance in human hepatocytes was almost completely accounted for by OATP1B1 and OATP1B3 and ~70 % of the total hepatic clearance was accounted for by OATP1B1 and the rest by other similar transporters of the same class. The pharmacokinetic data analysis followed the conventional plans with the following primary parameters: maximum concentration (C_{max}), area under the curve (AUC), area under the curve to timepoint (AUC_t), area under the curve to infinity ($AUC_{0-\infty}$), and used the standard 80-125% 90% confidence intervals for all the relevant parameters and, where appropriate, wider margins were adopted.

The test systems, testing methods and analytical methodology appear appropriate. Standard pharmacokinetic parameters have been utilised in defining the pharmacokinetics, and these included primary and secondary parameters. Conventional methods and designs were used for bioequivalence and food-effect studies.

Studies NK-104V.1.02EU and NKS104A2115 investigated the bioavailability of Pitavastatin using single doses of the immediate-release formulation. The absolute oral bioavailability of NK-104 (Pitavastatin) has been shown to be 51% and that the predominant absorption occurs in the proximal parts of the jejunum. The observed characteristics of NKS104 in this study, indicates that for optimal absorption, the majority of the drug should be released from a given formulation in the first 4 meters of the small intestine. ¹⁴C-NK-104 (SNY 419/013926) study evaluated the absorption, metabolism and excretion of 32 mg dose of radiolabelled

¹⁴C-Pitavastatin delivering no more than 2.5MBq/70μCi in six healthy male volunteers. The absorption is rapid as seen in ¹⁴C study (30-45 minutes post dose). The mean terminal half-life of ¹⁴C pitavastatin was ~70 hours, with radioactivity detected even at 168 hours in three subjects. The half-life of pitavastatin was 14.3 hours. The ENTERION capsule

technique is an acceptable method of evaluation of site of absorption. This, however, is not crucial in the long-term as there are no indicators of great dependency on the site or pH for absorption. The mean plasma clearance (CL/F) of 183 mL/min was low compared to the average cardiac (3L/min), liver (ca 800 mL/min) and kidney (ca 700 mL/min) plasma flow rates.

Studies NK-104-1 in Japanese subjects; PKH/NKN98389N/NK-104.1.01 and HPC/NKN 00435N/NK-104.1.19 and NK-104-1.21US (in Caucasians) with the EU Phase III formulation, investigated the effect of food on the bioavailability of NK-104 (pitavastatin). The pharmacokinetics of pitavastatin is only marginally affected by food, especially high-fat food. The differences in conclusions of each study notwithstanding, it is clear that food delays absorption to a variable extent. As the composition of food in the first three studies listed has not been specified and, therefore, it is possible that meal composition may influence the impact on the parameters, the worst case being high-fat meal reducing the C_{max} by about ~40%. However, as the AUC remained relatively unchanged, and the exposure remains consistent, this finding will have little impact on dosing strategy or administration of pitavastatin.

Pitavastatin was highly bound to plasma protein with an unbound fraction (fp) of 0.4% to 0.5% in human plasma. Pitavastatin is predominantly excreted unchanged (>50%) with about 10-15% undergoing the main metabolic pathway of lactonisation studies (studies C-NK-104, NK-104-10, PKH/NKN 98389N/NK-104.1.01, and HPC/NKN 00435N/NK-104.1.19). The main biotransformation pathways of pitavastatin in healthy subjects appeared to be lactonisation of the dihydroxyheptenoic acid side chain, glucuronidation, aromatic hydroxylation and aryldihydrodiol formation. Overall, only small quantities of pitavastatin lactone are generated through the uridine diphosphate-glucuronosyltransferase (UGT) pathway. Involvement of CYP450 enzyme pathways appears to be proportionally less and, although some metabolism mediated by CYP2C9 and CYP2C8 is noted, the applicant claims that these are small. As pitavastatin glucuronide is one of the main metabolites and gemfibrozil affects this pathway, there may be potential for interaction here that has not been detailed. Studies [PKH/NKN 98389N/NK-104.1.01] and [HPC/NKN 00435N/NK-104.1.19] both found urinary excretion of pitavastatin and pitavastatin lactone to be very low (<3%) and independent of dose. Study [NK-104-01] in Japanese subjects showed excretion into urine to be limited for both pitavastatin and lactone with less than 2% of total dose recovered in urine.

There is potential for interconversion of pitavastatin lactone to the acid and for stereoisomeric interconversion. As the lactone resulting from metabolism is only a small fraction of the dose, and impurity level is 0.1%, the overall impact on interconversion is deemed to be extremely small. No specific genetic polymorphism relevant to metabolism has been identified in this dossier that could be of clinical impact in terms of dosing, either for efficacy or safety. The applicant was asked to discuss the possible role of SLCO1b1 gene polymorphisms on the transport of pitavastatin and any impact on safety. However, as the polymorphism has not been evaluated either in clinical trials or in post marketing studies, the applicant has pleaded inability to provide this information, but has argued that this polymorphism is likely to affect response to any statin by altering the pharmacokinetics (AUC and C_{max} mainly). The applicant has made attempts to demonstrate that varying pharmacokinetic parameters is unlikely to affect either efficacy or safety of pitavastatin and so by corollary, polymorphisms of SLCO1B1 are unlikely to affect efficacy or safety. This supposition remains hypothetical and the applicant should study this aspect in the post marketing observational studies requested in Europe.

In the bioequivalence studies, the pharmacokinetic parameters of the both formulations (Japanese and EU formulations) in European subjects were similar and fulfilled the standard acceptance criteria for bioequivalence, *Note for Guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98). The study report accepts that for primary comparison of pitavastatin, the results do not fulfil the standard criteria for equivalence, but do so for the lactone. It is unclear how these comparisons are useful in determining whether the two formulations are similar. The applicant has confirmed that the study conducted was a four-way crossover study providing “within study comparison”. The EU formulation contains 5% more of the active ingredient, but as is evident, this did not impact significantly on the pharmacokinetic parameters in the European subjects.

Two studies (PKH/NKN98389N/NK-104.1.01 and HPC/NKN00435N/NK-104.0.19) investigated the dose and pharmacokinetic relationship of pitavastatin in Caucasians. The NK-104.101 study used doses of 1, 2, 4, 8, 16 and 24 mg of pitavastatin while the NK-104.1.19 used doses of 24, 32, 48, and 64 mg. These have been previously described under the section on food effect. The pharmacokinetics of pitavastatin and the lactone were linear over the range of 1 to 24 mg, although the increase in steady state AUC between 2-4 mg was 2.7 fold. A significant degree of inter-subject variation was noted, with ratios between highest and lowest AUC values varying up to 4-fold within the therapeutic dose range. In study NK-104-1.23US, no specific time dependency was noted either for pharmacokinetics or pharmacodynamics of pitavastatin. Although conventionally cholesterol synthesis is deemed to be maximal at night, with evening dose of statin achieving the highest reduction in LDL-C, a number of studies have shown that there is no relevant difference between morning or evening dose of a statin (for example, fluvastatin and now pitavastatin). Therefore, time-dependency is not a significant factor for pitavastatin dosing.

Special populations

Renal impairment: Study NK-104-1.24 investigated the pitavastatin pharmacokinetics in those with renal impairment of various severities (n=31; 3 grps- normal, CRF requiring dialysis and GFR 30-50ml/min). C_{max} was ~40% higher in the haemodialysis group and about 60% higher in the moderate renal impairment group compared to healthy controls. The AUC values were 73 and 80% higher, respectively. The findings of this study are slightly surprising and the mechanism of increase in AUC is unclear, although historically such phenomena have been recognised in patients with renal impairment. This may relate to dependence on transporters (OATP). The applicant has pursued this argument further to suggest that, as the variation is high within the so-called normal population, any increase in pitavastatin AUC in renal impairment is unlikely to be of consequence to safety. This might only be applicable to the 1 and 2 mg doses, and as data in severe renal impairment with 4mg are virtually non-existent, it has been recommended not to administer the 4mg dose in patients with severe renal impairment. This proposal has a significant disadvantage in that a number of subjects with high cardiovascular risk (diabetes, hypertension, etc) will have mild or moderate renal impairment, but will also need a statin that achieves considerable reduction in lipid levels at lower doses. Dose per dose, pitavastatin has one of the best dose-response curves; it would stand to reason that this might be a better choice for treatment of such subjects. It is also crucial to note that at the time of assessment, although there are limited data with 4mg in severe renal impairment, there is no clear safety signal. A contraindication is, therefore, a disproportionate step in the absence of clear evidence of harm. Thus, although the 4mg dose is not recommended for use in those with severe renal impairment, in those with other grades of impairment it may be used with caution after careful consideration and only when there is poor response to lower doses.

Hepatic impairment: Studies NK-104-16 and NK-104-HK investigated the pharmacokinetics of pitavastatin in those with varied degrees of hepatic impairment. A significant increase of the C_{max} and AUC_t of NK-104 related with the severity of the hepatic impairment was noted. The NK-104 lactone results were, however, lower in those with hepatic impairment - C_{max} and AUC of NK-104 Lactone were 0.90 and 0.84-fold smaller in Child-Pugh Grade A, and 0.48 and 0.67-fold smaller in Child-Pugh Grade B, respectively. Overall, as expected hepatic impairment increases the plasma concentrations of NK-104 considerably and the elevations relate to the severity of impairment. This will have implications for dosing strategies in larger clinical trials and in practice, although the effect of multiple doses or chronic administration can not be inferred based on this study. It has been accepted that the 4mg dose should be contraindicated in those with severe hepatic impairment as AUC increases ~4 fold in these patients. This is scientific and appropriate.

Gender and Race: Female subjects had higher peak concentrations of pitavastatin and greater $AUC_{0-\infty}$ compared to male subjects. The clearance of pitavastatin was lower in females than in males and the half-life was longer. The maximum concentrations of pitavastatin appear to be about 20% lower in Black or African-American subjects than in Caucasian subjects, but the AUC values are comparable. While the study has limited value for dose recommendation due to small numbers studied, especially for the racial comparisons, the increased exposure in females (combined with the data from post marketing studies in Japan showing evidence of muscle toxicity with 1 and 2mg doses) raises safety concerns. These were raised as questions and explanations sought. The applicant has confirmed that gender bias was small but in favour of women especially for muscle adverse drug reactions (myopathy/rhabdomyolysis SMQ), while in the spontaneously and post marketing study LIVS-01 there appeared to be a predominance of women. Overall it is agreed that there is little gender bias and if anything is it is favour of women, but this is too preliminary to state in the SPC or product info.

Elderly: Some differences between elderly and non-elderly are noted, but the same limitations described above for gender and race differences apply here. The numbers are small, although they are better than the racial group comparisons. Of note, within this grouping, it should be noted that gender differences could not be determined and there was one single elderly non-Caucasian, female subject. Further efficacy data in the elderly are discussed in the efficacy sections.

Interactions

The interactions have been studied with medicinal products that are commonly used with a statin. Moreover, potential interactions based on the metabolic pathways have also been included. The crucial interactions to be considered are with ciclosporin, erythromycin, rifampicin, warfarin, fibrates and gemfibrozil.

Of these, ciclosporin, erythromycin and gemfibrozil showed interactions that could be clinically relevant. Of interest, the interaction with ciclosporin was studied only after 1-2 doses of ciclosporin. Whilst the hypothesis that single dose of ciclosporin is adequate to inhibit both transporters and CYP3A4, CYP2C9 appears to be the main enzyme involved in pitavastatin metabolism and, therefore, the magnitude of interaction remains unexplained, but may be related to degrees of OATP inhibition. This may have an impact if steady state was achieved with both agents after multiple dosing and the magnitude of interaction can not be commented up on with any certainty given the current design adopted. It might be prudent to follow the two possible course of action;

- restriction in the SPC (limit the dose of pitavastatin in those receiving ciclosporin to the lowest possible dose such as 1mg or contraindicate concomitant use altogether), and

- provide a steady state study that evaluates and confirms that there are no tolerance issues including that there is no accumulation of pitavastatin.

The applicant has been unable to provide further data on this issue regarding ciclosporin (4.6 fold increase in pitavastatin AUC with 2mg/kg of ciclosporin single dose) and has analysed the data from PM study LIVS-01 for concomitant use of erythromycin, but these numbers are small and few definitive conclusions can be drawn.

The applicant has taken on board the suggestions and contraindicated use of ciclosporin with pitavastatin and erythromycin (macrolides- temporary suspension of pitavastatin use).

Table-1: Summary of Pharmacokinetic effects of the drug-drug interactions.

Concomitant drug	Metabolic path(s) investigated	Pitavastatin Fold change		Pitavastatin lactone Fold change		Concomitant drug		Result of pharmacodynamic drug interaction
		C _{max}	AUC _{0-t}	C _{max}	AUC _{0-t}	C _{max}	AUC _{0-t}	
Ciclosporin	CYP3A4, MRP2, MDR1 & OATP1B1 inhibition	6.60	4.60*	1.07	1.10*	ND	ND	
Erythromycin	CYP3A4 Inhibition	3.62	2.82	1.08	0.87	ND	ND	
Atazanavir	UGT inhibition	1.60	1.31‡	1.10	0.95‡	1.13	1.06‡	
Rifampicin	OATP1B1 Inhibition & UGT1A3, CYP3A4 induction	2.00	1.29‡	0.83	0.42‡	0.82	0.85‡	
Gemfibrozil	OATP1B1 & CYP2C8 inhibition	1.31	1.45*	0.72	0.85*	ND	ND	
Bezafibrate	Fibrate interaction	0.96	1.08	0.97	0.98	ND	ND	
Fenofibrate	Fibrate interaction	1.11	1.18*	1.09	1.14*	ND	ND	
R-Warfarin	Protein binding	ND	ND	ND	ND	1.03	1.07‡	INR not affected
S-Warfarin	Protein Binding & CYP2C9	ND	ND	ND	ND	1.03	1.06‡	INR not affected
Digoxin	OATP1B3 and P-glycoprotein substrate	0.91	1.04‡	0.98	1.01‡	0.96	0.97‡	
Enalapril	OATP1B1 substrate	0.93	1.06‡	1.02	0.99‡	1.12	1.12‡	
Itraconazole	CYP3A4 Inhibition	0.78	0.77‡	0.81	0.91‡	ND	ND	
Grapefruit juice	CYP3A4 & P-glycoprotein transport	0.88	1.15	0.87	1.16	ND	ND	
Ezetimibe	Co prescription with statins	1.00*	0.98*	ND	ND	1.02*	1.09*	

* AUC₀₋₂₄ as AUC_{0-t} not supplied in report. ‡ AUC_{0-t} as AUC_{0-t} not supplied in report.

As with other statins, a cautionary note is needed for concomitant use of pitavastatin with fibrates, especially gemfibrozil (increased risk of rhabdomyolysis; gemfibrozil increases relative risk by 5.5-fold compared to statin monotherapy and co-administration of fibrates and statin is associated with 12-fold increase in rhabdomyolysis). The SPC has been updated regarding the contraindications.

PHARMACODYNAMICS

The pharmacodynamic actions of pitavastatin were evaluated in various *in vitro* systems and these included the following: cholesterol synthesis inhibition in hepG2 cells compared with simvastatin and atorvastatin; in human skeletal muscle cells and hepatocytes; LDL-receptor activity in HepG2 cells; LDL-receptor mRNA expression in HepG2 cells and finally effects on apolipoproteins. Studies NK-104-02 in Japanese subjects and NK-104-1.23US in the American populations delineate the pharmacodynamics directly in humans *in vivo*. The placebo-controlled studies further substantiate the pharmacodynamics and efficacy aspects. The primary pharmacology of a HMG-CoA reductase inhibitor is the effect on cholesterol/lipid parameters (LDL-C, total cholesterol, Apo-A etc).

Primary pharmacology of a HMG-CoA reductase inhibitor is reduction of lipid parameters, especially LDL-cholesterol. The dossier evaluates this in several stages, from a mechanism of action (as detailed below) to the *in vivo* placebo and active comparators in clinical studies. LDL-cholesterol and total cholesterol decreased from day 2, with a decrease in urinary mevalonic acid (suggestive of inhibition of HMG-CoA reductase). Study NK-104-1.23US evaluated the potential differences between morning and evening doses in healthy male and female volunteers in a crossover study. From a pharmacodynamic perspective, the two dosing regimes were considered equivalent if 90% confidence intervals of the difference lay between -6 to +6%. There was no difference in relative bioavailability of pitavastatin between the dosing schedules or total exposure, but equivalence as defined was not fully established.

Secondary pharmacology; A number of pleiotropic effects have been attributed to statins that are on the market and may provide explanations for the significant cardiovascular benefit, but these have not been studied in detail in this dossier. The only relevant secondary pharmacology relate to the thorough QT study that has been performed. There was no evidence of any effect on QT interval, even at the suprathreshold dose of 16 mg. Furthermore, there was little to no relationship between the difference from time-matched baseline in the QTc and plasma concentration for either pitavastatin or pitavastatin lactone.

Unsurprisingly, the primary pharmacology of LDL-C reduction is very clear. Conventionally statins have been advocated to be administered in the evening. This is based on the rationale that endogenous cholesterol synthesis is maximal at night, i.e. HMG-CoA activity is expected to be maximal. In this instance, the morning dosing was not equivalent by set criteria, although the difference was not clinically relevant. There is no secondary pharmacology of relevance to comment in this dossier, as pleiotropic effects are not explored in the dossier and, therefore, are beyond the scope of this report. The relationship between pharmacokinetics and pharmacodynamics has not been studied in patients and, therefore, it is difficult to determine whether the magnitude of the differences in serum concentrations of pitavastatin correlates with the effects on lipid profiles. However, a dose-response relationship was evident for LDL-C reduction after seven days of treatment at doses up to 8 mg.

The predominant interaction expected is with other lipid-lowering therapies, such as fibrates and cholesterol absorption inhibitors (e.g., ezetimibe). For details see the pharmacokinetic interaction section in the clinical assessment report. A certain level of pharmacodynamic interaction, in terms of reduction of lipid parameters, is expected with a combination of pitavastatin and fibrates (or ezetimibe). The actual clinical relevance of this long-term has not been assessed and based on the ENHANCE and SEAS studies (with simvastatin and Ezetimibe, NEJM 2008 Apr, and NEJM 2008, Sep) this is questionable. Therefore, the warning in section 4.4 of the SPC is considered appropriate. Whilst there are no specific studies in this dossier regarding differences in pharmacodynamic responses arising out of genetic polymorphisms, the comments regarding SLCO1b1 variant alleles and other transporters variants as discussed in the pharmacokinetic section apply here.

The applicant has provided reasoned arguments for not conducting further studies for interactions, but has amended several parts of the SPC and extrapolation of these seem reasonable. We consider that this is appropriate, especially with the product literature amendments.

CLINICAL EFFICACY

Efficacy studies included both placebo and active comparator studies, with simvastatin, atorvastatin and pravastatin (in the elderly) used as comparators. Both placebo and active comparator studies were double-blind with extension phases. Of note is the fact that some of the placebo-controlled studies also acted as dose-response or pharmacodynamic studies. Attempts were made to include crucial relevant populations, such as those at high risk of coronary heart disease and diabetics.

The universal inclusion criterion for all studies was primary hypercholesterolemia and mixed dyslipidemia, unless specifically stated. Specific populations were studied in the following: NK-104-305 was in Type II diabetes and mixed dyslipidemia, NK-104-306 was age-specific (>65 years), and NK-104-09 was in heterozygous familial hypercholesterolemia with primary hypercholesterolemia. Interestingly, in all studies the inclusion/ exclusion criteria were preset and this excluded at-risk or target populations, especially where a statin is likely to be used most frequently or readily. For example, the common exclusion criteria were: *hypertension, circulatory diseases, cancers and diabetes, patients with endocrine, metabolic or depressive disorders, patients with HIV, elderly (>75 years), patients treated with immunosuppressive drugs (e.g. organ transplant patients)*. The data set, therefore, provides utility of pitavastatin in a rather clean population of those with hypercholesterolemia. Whilst this is not expected to affect efficacy significantly, safety issues may arise in these groups that affect the risk: benefit balance.

Table-3; Summary of Clinical studies with pitavastatin.

Double-blind placebo-controlled	Long-term studies
Phase II HEC/NK98402N/NK-104.2.02	
Phase II HEC/NKN98403N/NK-104.2.03	
Phase II NK-104-209 (open atorvastatin), terminated	
Phase II NKS104A2204 (open atorvastatin), terminated	NKS104A2204E1, terminated, safety data only
Phase II NK-104-210 (open atorvastatin), terminated	NK-104-211, terminated, safety data only
Double-blind active-controlled	
Phase III NK-104-301 (atorvastatin)	NK-104-307
Phase III NK-104-302 (simvastatin)	
Phase III NK-104-304 (simvastatin), high risk of CHD	NK-104-309
Phase III NK-104-305 (atorvastatin), diabetes	NK-104-310
Phase III NK-104-306 (pravastatin), elderly	NK-104-308
	NK-104-09, heterozygous FH

CHD = coronary heart disease, FH = familial hypercholesterolaemia

The dose-response studies and pharmacodynamic studies are common in the sense that they demonstrated a pharmacodynamic effect in comparison to placebo at different doses of pitavastatin. Dose-response was also evaluated in the main comparator studies with atorvastatin and simvastatin. These active, controlled studies function both as dose-response studies and main efficacy studies. In a proportion of the studies, the dose escalation between 2 and 4 mg of Pitavastatin were enforced as per protocol design. Higher doses of pitavastatin were not enforced in this development programme. Some of the long-term studies also adopted the same dosing strategy; low dose escalated to higher dose if target response (ATP-III or NCEP criteria) were not attained at a pre-specified interval. A certain level of dose-response starting from 1mg upwards has been demonstrated and the difference from placebo is clear for all parameters (LDL-C, TC, HDL-C, TG, Apo-B and Apo-A1). The

LDL-C reduction was 33% for 1mg, 38.2% for 2mg, 46.5% for 4mg and 54.5% for 8 mg. The reductions for total cholesterol (TC) were along the same proportions. Higher doses achieve better reductions in LDL-C and TC. The dose response for triglycerides and Apo-B are less pronounced. Crucially, HDL-C demonstrates no dose response with increasing doses of pitavastatin (9.4% for 1mg, 9% for 2 mg, 8.3% for 4mg and 7.6% at 8mg dose; placebo effect was 2.5%). Based on these and the fact that even 1 mg achieves ~30% reduction in LDL-C in these patients, a starting dose of 1mg would be considered appropriate especially in the special populations where exposure increases many fold; for example, elderly, those with renal impairment, those with propensity for adverse events. The applicant has now accepted this and proposed a starting dose of 1mg universally, with up-titration recommended to achieve the National Cholesterol Program/European Atherosclerosis Society (NCEP/EAS) target lipid reduction (but on an individual basis). This change has been instituted in the SPCs and the applicant has provided the 1mg strength tablet in order to facilitate this.

All short-term studies included a dietary lead-in phase of between 4 and 8 weeks to ensure adequate washout of prior therapy, where applicable, and stable baseline lipid values. Assessment of efficacy was primarily after 12 weeks of study treatment, although one dose-ranging study used 8 weeks for the primary comparison [NK-104-209]. Seven long-term studies of up to 104 weeks' duration were used to determine efficacy over the longer term, but two of these were terminated prematurely due to adverse events and reported only safety data [NKS104A2204E1] and [NK-104-211]. The efficacy of pitavastatin has been compared with placebo in the Phase II studies and with three established marketed products: atorvastatin, simvastatin and pravastatin in Phase II and III studies. Pravastatin was chosen as the comparator in the elderly study for its favourable efficacy and safety characteristics.

In all five active, controlled, double-blind studies, pitavastatin was force-titrated (2mg for 4 weeks and 4mg for subsequent 8 weeks) and it is of interest that three studies (NK-104-301, 302 and 306) also included fixed dose arms of 2mg pitavastatin (and 1mg in NK-104-306). The comparators were either fixed dose (atorvastatin 10mg or 20mg simvastatin) or forced titration (10-20 mg for atorvastatin or 20-40mg for simvastatin). Pravastatin followed a similar pattern. Whilst at first glance the dosing strategies adopted appear reasonable, with forced titration of dose upwards if target LDL-C is not achieved both in active, controlled and long-term efficacy/safety studies. However, based on the results from placebo-controlled studies and dose response, it would have been appropriate to test 1mg dose in the long-term efficacy studies especially as a large number of subjects achieved target levels (nearly 85% compared to 75% for simvastatin). The outcomes/endpoints were the standard lipid parameters as detailed above, although there were minor differences between studies. Some studies had the essential lipid parameters, while others had extended endpoints.

The primary endpoint in all short-term studies was percent change from baseline in LDL-C at week 12 (using last observation carried forward [LOCF]), except for NK-104-209 where 8-week LOCF was used. As Friedewald method is less reliable with increasing TG concentrations, a limit on TG concentration was used in the inclusion /exclusion criteria. The secondary endpoints for short-term studies included other lipid and lipoprotein fractions (TC, TG, HDL-C and apolipoproteins [Apo-B, Apo-A1, etc]). Some studies included non-HDL-C, high sensitivity CRP (hs-CRP), oxidised LDL and ratios of various lipid parameters. In all studies, percent changes from baseline were used to analyse LDL-C, TC, HDL-C, non-HDL-C, TG, Apo-A1, Apo-B and Lp(a), except in Study NK-104-09 where HDL-C was summarised using change from baseline rather than percent change from baseline. The endpoints are considered appropriate for a lipid-lowering agent. Statins have an established role with major effect on LDL-C and variable effect on HDL-C. There have been hypotheses

about pleiotropic effects of statins, especially in relation to their mortality /morbidity effects (such as the proposed anti-inflammatory action). However, the above endpoints, even when inclusive of CRP, are of limited use in supporting these hypotheses. As both the European Atherosclerosis Society and National Cholesterol Education Program (NCEP) targets are well-accepted in clinical practice as assessment tools or endpoints. The duration of the short-term studies is in accordance with the most clinical and regulatory guidelines for assessment of change in lipid parameters, i.e. 12 week studies. The 8-week LOCF approach in NK-104-209 could be a limitation, especially if the LOCF is well-short of the 8-week endpoint in a significant proportion of cases.

The predominant outcomes reviewed relate to LDL-C, TC and HDL-C, and these are discussed as a pooled analysis. There is a dose-dependent change from baseline for pitavastatin versus placebo; 1mg (mean decrease of 33.3% and an adjusted mean decrease of 27.0% versus 4.0% and 1.6% on placebo in two studies), 2mg (38.2 and 31.4% in two studies versus 4.0 and 1.6% for placebo) and 4mg (46.5%, 41.5% and 42.1% in three studies versus 4.0%, 1.6% and 2.4% for placebo). The 8mg dose showed similar changes of larger magnitude, although this did not include a statistical comparison (with adjusted mean decreases of 54.5% and 46.2% for pitavastatin 8 mg versus 4.0% and 1.6% for placebo). It should be noted that 8mg arm was terminated early in the longer term follow-up.

Table 4 below details the results from active-comparator studies. The design of the studies comparing pitavastatin with reference therapy is appropriate as placebo-controlled studies are no longer considered acceptable in this indication (see CPMP/EWP/3020/03, *Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders*). The methods used to achieve blinding, including use of the double-dummy technique, are considered appropriate.

Table-4; Effect of Pitavastatin (& comparators) at different doses

Treatment (FAS)	LDL-C (mg/dL)						Percent change		
	Baseline			Week 12 Endpoint			Week 12 Endpoint		
	N	Mean	SD	N	Mean	SD	N	%	SD
Pita 1 mg	309	173.4	28.8	308	119.4	27.4	308	-30.8	12.3
Pita 2 mg	945	179.3	21.5	945	111.1	28.5	945	-38.0	14.1
Pita 4 mg	1533	171.5	27.2	1532	97.0	28.6	1532	-43.2	15.3
Ator 10 mg	118	180.8	17.6	118	112.3	27.1	118	-37.7	14.8
Ator 20 mg	238	161.4	29.2	237	91.1	30.6	237	-43.4	16.2
Simv 20 mg	107	184.1	17.2	107	119.1	27.6	107	-35.0	15.5
Simv 40 mg	228	175.1	21.8	228	98.8	26.6	228	-43.3	15.1
Prav 10 mg	103	163.6	22.3	103	126.7	28.6	103	-22.4	14.1
Prav 20 mg	96	163.7	19.3	96	116.2	20.9	96	-28.8	11.1
Prav 40 mg	102	166.6	21.9	102	109.5	25.3	102	-34.0	14.3
Placebo	154	189.6	29.7	154	184.3	34.7	154	-2.4	13.0

The details of the analysis of the primary variable to address the non-inferiority of pitavastatin to the comparators are acceptable. All important subgroups were pre-defined as specified in the *Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorder* (CPMP/EWP/3020/03). The justification of the non-inferiority margin is considered adequate. As pitavastatin would be considered non-inferior to the comparator only if both doses were shown to be non-inferior, adjustment for multiplicity was not required. The analysis of the primary efficacy endpoint for the full-analysis and per-protocol populations demonstrated the non-inferiority of pitavastatin at both the low and high dose to the corresponding doses of atorvastatin. Furthermore, pitavastatin 2mg was statistically superior to simvastatin 20mg, although the clinical importance of the estimated difference was not discussed in the report. The three studies in special populations indeed offer little to the already established data. In the secondary prevention population, pitavastatin is no different to simvastatin and in the elderly it is non-inferior to pravastatin.

This comparison does not suggest that pitavastatin offers better control of LDL-C at lower doses. Similarly, in diabetics, non-inferiority was not proven. The applicant has now provided further analysis of these studies in diabetics, including the results of the extension studies. It is argued that the inability to show non-inferiority appeared to be more a statistical issue as the effect size for LDL-C reduction was similar based on dose comparisons and the reanalysis has not been able to provide any other clues for this result. This appears reasonable and could be accepted. As this has little implication for clinical use, it is considered that this issue is one of academic curiosity rather than a clinically important consideration and no further points are raised. Overall, there is little to choose between pitavastatin over other comparators at this stage.

The long-term efficacy studies have very little contribution other than attainment of the National Cholesterol Education Program (NCEP) targets or maintaining targets. The rates of withdrawals from these studies do not appear to offer any advantage for pitavastatin. Importantly, clinical event reduction has not been studied for pitavastatin or comparators, and this is a considerable drawback. Recent discussions regarding intense statin therapy with a number of agents have failed to confirm benefits over and above the conventional doses. In that context, based on the data here, the applicant's claim of anticipated superiority over other agents has not been confirmed. No data on long-term clinical event reduction has been generated. As the claim is predominantly treatment of familial hypercholesterolemia, (with implied benefit in terms of reduction of cardiovascular events all through the discussions), and this is in line with the current CHMP note for guidance, this might be acceptable with explicit statement in the SPC that no mortality data have been generated. The applicant should be encouraged to generate clinical event data as part of the post marketing commitment. From a regulatory perspective, this seems a reasonable option given that the mechanism of benefit for statins has been well-established. It is considered that the applicant should be encouraged to generate long-term morbidity/mortality data for pitavastatin, especially in high-risk situations as this may offer some advantages over high doses of other agents currently available purely from a safety perspective.

CLINICAL SAFETY

The formulation for which marketing authorisation is sought in Europe is based on the immediate-release product (as sold in Japan), with some modification. Pitavastatin has been evaluated in 77 studies (40 healthy volunteer studies and 37 studies in patients with primary hypercholesterolaemia, combined [mixed] dyslipidaemia and familial hypercholesterolemia), of which the EU/US programme has contributed 26 healthy volunteer studies and 18 patient studies. The majority of the clinical studies presented in this dossier, on which claims of clinical pharmacology, clinical efficacy and clinical safety are made, were conducted in Europe, the US and Canada. Some of the Phase III European studies had sites in Russia, India, and Israel. The total data set for the European Union (EU) filing based on the Phase II and Phase III comparative clinical studies consists of a total safety population of approximately 3,500 patients who received pitavastatin. Data from a post-marketing surveillance study [LIVS-01], which recruited more than 20,000 patients in Japan are presented to support the safety profile. The post-marketing exposure to pitavastatin, based on sales of tablets in Japan, is estimated to be about 1.8 million patient-years as of January 2008. LIVS-01 study was aimed at identifying rare adverse drug reactions (ADRs), evaluating the incidence and pattern of adverse drug reactions under actual use conditions, and identify clinical factors that might affect the safety and efficacy of pitavastatin. The surveillance was started in December 2003, and patient registration was completed in March 2005. The patient exposure as detailed in the safety summary is rather inadequate. Time-related exposure should have been detailed further. The majority of the patients were exposed for upto 12 weeks overall at all doses and in some studies the exposure was for 8 weeks only. Whilst

some information about longer exposures has been cited, the exact number exposed for durations of more than 26 weeks or 52 weeks is difficult to glean from the summary. This is especially true of the EU population. Based on post marketing study in Japan, a claim has been made that nearly 19,000 subjects were exposed to doses of pitavastatin. The follow-up data from LIVS-01 study has been updated up to mid 2009 and these are now included in the calculation of safety events. This has improved the overall strength of the data from the post marketing study.

Standard definitions for events, and the severity or relationship to the product, have apparently been used. All events were defined in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the table below provides a summary of events based on System Organ Class (SOC) >1.0% incidence in any group.

Table-5: Summary of Adverse events in the pitavastatin development programme

MedDRA System Organ Class No. (%) of Subjects	Placebo (N=208)	Pita Overall† (N=3448)	Ator Overall# (N=505)	Simv Overall‡ (N=336)	Prava Overall§ (N=301)
No. (%) of Subjects with any TEAE	113 (54.3)	1432 (41.5)	188 (37.2)	128 (38.1)	159 (52.8)
Cardiac Disorders	4 (1.9)	50 (1.5)	8 (1.6)	8 (2.4)	3 (1.0)
Ear & Labyrinth Disorders	5 (2.4)	26 (0.8)	5 (1.0)	3 (0.9)	2 (0.7)
Eye Disorders	3 (1.4)	25 (0.7)	5 (1.0)	4 (1.2)	6 (2.0)
Gastrointestinal Disorders	31 (14.9)	394 (11.4)	59 (11.7)	34 (10.1)	42 (14.0)
Gen. Disorders & Admin. Site Cond.	11 (5.3)	130 (3.8)	25 (5.0)	7 (2.1)	10 (3.3)
Immune System Disorders	3 (1.4)	12 (0.3)	0	4 (1.2)	0
Infections and Infestations	47 (22.6)	437 (12.7)	54 (10.7)	30 (8.9)	62 (20.6)
Injury, Poisoning & Proced. Comp.	4 (1.9)	66 (1.9)	12 (2.4)	4 (1.2)	6 (2.0)
Investigations	10 (4.8)	147 (4.3)	19 (3.8)	8 (2.4)	6 (2.0)
Metabolism & Nutrition Disorders	0	32 (0.9)	6 (1.2)	2 (0.6)	3 (1.0)
Musculoskeletal & Connective Tissue Disorders	28 (13.5)	364 (10.6)	46 (9.1)	39 (11.6)	32 (10.6)
Neoplasms	2 (1.0)	2 (0.1)	1 (0.2)	0	3 (1.0)
Nervous System Disorders	25 (12.0)	221 (6.4)	25 (5.0)	23 (6.8)	25 (8.3)
Psychiatric Disorders	9 (4.3)	60 (1.7)	6 (1.2)	8 (2.4)	8 (2.7)
Renal & Urinary Disorders	3 (1.4)	44 (1.3)	6 (1.2)	6 (1.8)	2 (0.7)
Reproductive System & Breast Disorders	1 (0.5)	28 (0.8)	3 (0.6)	2 (0.6)	5 (1.7)
Respiratory, Thoracic & Mediastinal Disorders	9 (4.3)	91 (2.6)	10 (2.0)	9 (2.7)	15 (5.0)
Skin & Subcut. Tissue Disorders	4 (1.9)	98 (2.8)	6 (1.2)	9 (2.7)	23 (7.6)
Surgical & Medical Procedures	3 (1.4)	9 (0.3)	0	0	0
Vascular Disorders	4 (1.9)	54 (1.6)	8 (1.6)	1 (0.3)	10 (3.3)

In the double-blind comparative studies with doses up to 64 mg of pitavastatin, a dose-related increase in overall adverse event rates were noted. Similar pattern was seen with treatment-emergent adverse events (TEAEs). Severe TEAEs were also higher with increasing doses in this (NK-104-209) study; 26.2%, 33.0%, 35.3% and 63.6% for 8, 16, 32 and 64 mg, respectively; compared to Atorvastatin 80 mg that had 31.3% severe TEAEs. In the same study, serious TEAEs were 1.0, 8.8 and 9.1% for 16, 32 and 64mg pitavastatin. More than 5% adverse events were noted in the following systems overall; infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders and nervous system disorders.

The adverse drug reactions are anticipated and there are very little surprises in terms of systems involved. The muscle effects predominate the off-target effects. Cardiac disorders, including myocardial infarctions, dominated as the most common side effects, but in the population studied this is unsurprising. It is heartening to note that the frequency of these is not high and appears to conform to other similar studies. In the absence of long-term event-reduction data, no clear decisions can be made based on this information. It will only

be possible to state that there does not appear to be a safety signal as regards cardiac event rates with use of pitavastatin (ischaemic events or QT events).

The special systems of interest remain musculoskeletal system and, as expected, these effects occur with a certain frequency. They appear to be dose-related, but comparable, frequency to standard doses of atorvastatin. A total of 283 and 321 subjects receiving 2mg (11.0%) and 4mg pitavastatin (13.3%), respectively, reported TEAEs in “musculoskeletal and connective tissue disorders” in the analysis of the Phase II and III core and extension patient studies in the EU/US. At the highest dose (80mg), atorvastatin had more muscle effects. In general, musculoskeletal disorders were slightly more common long-term (group-3 analysis) than short-term (groups 1 & 2 analysis); 11.1 versus 8.6% for 2mg, and 13.3% versus 8.0% for 4mg with increases in arthralgia more obvious than myalgia (4.1 versus 3.1%).

There were few deaths in the overall clinical development programme; two patients in the Phase II core short-term studies, five in the extension studies. The causes of deaths detailed in the clinical assessment report were mostly unrelated to the agent and could be attributable clearly to other critical events, such as pre-existing disease (coronary heart disease) and malignancy. One additional death in the extended-release formulation (not progressed further) was due to subarachnoid haemorrhage. In the post marketing studies, three deaths are reported in relation to rhabdomyolysis and these will be discussed later.

There were few serious adverse events in the short-term core studies - 68 in all and 45 related to pitavastatin of all doses (1.3% of 3448 subjects), compared to 0.5% for placebo, 1.6% for atorvastatin, 2.9% for simvastatin and 1.3% for pravastatin. As would be expected, these increased with increasing doses. These belonged to the same SOCs in both short- and long-term studies and included cardiac disorders, investigations, musculoskeletal/ connective tissue and nervous system disorders (all less than 1.0%). In the Group 3 analysis (Phase II and III core and extension-patient studies) in EU/US development programme, 172 subjects experienced serious TEAEs. Serious TEAEs were reported at similar frequency with 2 mg and 4 mg pitavastatin (66 subjects, 2.6%; and 73 subjects, 3.0%, respectively). Based on the limited long-term information, the incidence of adverse events did not increase disproportionately compared to short-term exposure and this is somewhat reassuring, although this is again limited by the number studied.

The withdrawals were dose-related, with the frequency increasing hugely after 8mg dose. In the clinical dosing range proposed, the withdrawals were of similar frequency. The frequency is comparable to that of other statins.

Rhabdomyolysis/ muscle effects: This serious TEAE has not been reported with 2 and 4mg of pitavastatin, although at 8mg and above there is a significant incidence within the clinical trial programme. The most common serious TEAEs were **rhabdomyolysis** (eight subjects: two on 8 mg pitavastatin [0.4%]; three on 32 mg pitavastatin [8.8%] and three on 64 mg pitavastatin [9.1%]), and **myalgia** (two subjects: one on 32 mg pitavastatin [2.9%], one on 64 mg pitavastatin [3.0%]). Rhabdomyolysis was considered to be related to pitavastatin treatment in all eight subjects. The absence of rhabdomyolysis within the clinical trials at 2 and 4 mg is heartening, but may not be conclusive as the number exposed is not large and based on proportionality, larger exposure might still detect it at lower doses. Another limitation of this dataset is the fact that different definitions were used in different studies for rhabdomyolysis and this complicates interpretations. The studies were carried out by a number of different sponsors as well as the applicant. Analysis of details of the reporting of this type of adverse event (using MedDRA terminology inclusive of rhabdomyolysis/myopathy) together with the incidence per patient-year of exposure was

made. With 2mg and 4mg pitavastatin, the incidence per patient-year was 0.136 and 0.112, respectively. In general, the incidence for these doses tended to be lower or comparable to equivalent doses of the comparators, except for the 2mg dose where the incidence was 0.136 patients per patient-year compared to 0.061 for 10mg atorvastatin. The applicant has made an attempt to provide a summary of events and classify the diagnosis of rhabdomyolysis using various criteria (NCEP/ATP-III, study protocol definitions, American Heart Association definitions, etc). Had a consistent definition that captured all serious cases been used, it is possible that we would be discussing a different set of numbers. From 4 mg to 8mg, there is a sizeable jump in frequency, and beyond that dose (8mg) the increase is of such magnitude that the risk is completely unacceptable. It is important to remember that the numbers of patients treated at each dose was variable, especially for the Group 1 dataset, thus percentages were based on differing levels of information. For example, 1540 patients were treated at the 4mg dose with only 102 at 16mg in the Group 1 dataset. This makes comparison problematic between doses where the numbers of patients treated were very different. Although it is accepted that there were no cases of clinically significant rhabdomyolysis or hospitalisation due to myopathy at doses below 32mg of pitavastatin in the clinical programme, this is probably because too few patients were studied to judge the frequency of this rare event (estimated to be approximately 1 in 20,000 patient-years exposure for all statins). As recommended, the standard MedDRA query for rhabdomyolysis/myopathy was used to address the concern over the variety of definitions used throughout the clinical programme. This provides a more conservative definition of muscular adverse events, although it is accepted that this will probably over-estimate the incidence of rhabdomyolysis. The results in terms of incidence per patient-year of exposure, based on the Group 3 studies (including extension studies), suggest that the rate per patient-year exposure was similar for the three doses of pitavastatin (notwithstanding the differences in exposure).

It is also important to establish the relative safety of pitavastatin in the context of other available statins (see Table-6). It appears that the risk of muscle events overall was highest with atorvastatin 20 or 40mg (relative rate) and these doses are commonly used in clinical practice. As pitavastatin risk appears lower than this, with similar efficacy in LDL-lowering, the applicant has argued that the benefit/risk ratio has to be favourable.

TABLE-6. TEAEs in the Rhabdomyolysis/myopathy SMQ by Number of Subjects (Rate per Patient-Year Exposure) and by Dose in Phase II/III Core and Extension Studies (Group 3)

	No. of Weeks of Exposure (Mean)	Total Patient-Years of Exposure	TEAEs in the rhabdomyolysis/myopathy SMQ		
			Number of Subjects	Incidence per Patient-year exposure	Relative rate
Pitavastatin 1 mg (N=309)	11.56	68.68	9	0.131	1
Pitavastatin 2 mg (N=2562)	16.71	823.47	112	0.136	1.04
Pitavastatin 4 mg (N=2406)	37.36	1728.64	194	0.112	0.85
Atorvastatin 10 mg (N=394)	6.54	49.53	3	0.061	1
Atorvastatin 20 mg (N=264)	11.59	58.87	6	0.102	1.67
Atorvastatin 40 mg (N=54)	7.39	7.68	1	0.130	2.1
Simvastatin 20 mg (N=336)	6.57	42.44	11	0.259	1
Simvastatin 40 mg (N=219)	17.69	74.48	11	0.148	0.57

Source: Module 2.7.4 Tables 2.7.4.58 and 2.7.4.65

The question that remains to be addressed is whether the risk of rhabdomyolysis with 4mg has been adequately assessed in this small safety data set. The solution to this may lie in evaluating the risk at 1 and 2 mg including obtaining clarity on the disparity between the clinical trial data and postmarketing data from Japan and also tailoring the RISK MINIMISATION STEPS. Risk management plan will need to be amended to include an

observational/PASS study in the EU population with careful monitoring of use of the 4mg dose. The applicant has agreed to this and committed to providing the PASS study.

In the post marketing studies, there were several reports of rhabdomyolysis. It is interesting to note that, while in the controlled clinical trial programme, no cases of rhabdomyolysis were reported below the 4mg dose. In the post marketing setting, a greater number of cases (suspected or proven) are reported; 51 cases, of which 34 were considered serious and 17 were non-serious [of note there are 47 cases listed in the table-8]. These, however, have the same limitations; use of different definitions (American College of Cardiology/American Heart Association/National Lipid Association), in addition to the distinct possibility of under-reporting as muscle effects are expected with statins. Notwithstanding the probable underreporting, the difference between trial programme and the post marketing cases of rhabdomyolysis with 1 and 2mg doses could be due to multiple reasons, including that in the trial programme those at risk were excluded, varied definitions of rhabdomyolysis, relatively smaller size of the study population and potentially other confounding factors. It is crucial to note that in the LIVS-01 study, certain features were identified as risk factors for myopathy/rhabdomyolysis: in the factorial analysis gender, liver disease, renal disease, hypertension or drug allergy and use of biguanides were identified; and in the cox regression analysis: renal disease, drug allergy, male gender and biguanide therapy were noted as independent factors. It is now clarified that inclusion of biguanides was not always in diabetics and, hence, this regression model is not perfect. The other risk factors have been addressed in the risk minimisation strategies.

TABLE-7: Serious and Non-serious ADRs in the Rhabdomyolysis/Myopathy SMO from LIVS-01 Study 2 Year Data

Population	Estimated Patient-years of Exposure	Serious and Non-serious ADRs Rhabdomyolysis/myopathy SMO			Serious and non-serious Rhabdomyolysis ADR (%)
		Patients with ADR	% Patients with ADR	Incidence per Patient-Year Exposure	
Dose 1 mg (7224 patients)	11454	321	4.4%	0.028	2 (0.01%)
Dose 2 mg* (10979 patients)	17336	416	3.8%	0.024	1 (0.01%)
Dose 4 mg** at any time (247 patients)	398 ⁺	11	4.5%	0.028 ⁺	0

TABLE-8: Rate per 100,000 Prescriptions, and estimated patient exposure from prescriptions, of Rhabdomyolysis ADRs (Serious and Non-serious) from Spontaneous Reports and LIVS-01 from the International Birth Date (17 July 2003) to 16 July 2009

Post-marketing reports of rhabdomyolysis	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg
Total prescriptions 2004 to mid 2009*	25,214,240	33,912,855	628,913
Number of patients reporting ADR (rate per 100,000 prescriptions)			
Serious	14 (0.06)	17 (0.05)	3 (0.48)
Non-serious**	4 (0.02)	9 (0.03)	0
Serious and non-serious	18 (0.07)	26 (0.08)	3 (0.48)
ADR rate per 10,000 Patient-years***			
Serious	0.14	0.12	1.16
Non-serious**	0.04	0.06	0
Serious and non-serious	0.17	0.19	1.16

The applicant subsequently provided an updated estimate of myopathy/rhabdomyolysis from the postmarketing studies, prescription evaluation and a comparative estimate of these events (myopathy/rhabdomyolysis). It is recognised that the spontaneous reports suffer from a

number of limitations and the applicant has argued that in these cases the definitions varied, with a number of reports not fulfilling the required criteria. Notwithstanding these limitations, the tables above provide an estimate of annual rate of muscle events for pitavastatin. Information from the Japanese market from both spontaneous reports and post marketing studies suggest that no excessive reporting of rhabdomyolysis or similar conditions was seen for patients treated with pitavastatin at doses of 1mg and 2mg, compared to other statins. These provide some reassurance that at doses clinically recommended, the muscle events with pitavastatin are not too onerous or different from other statins on the market.

Creatinine kinase (CK) elevations were also dose dependent. The 1mg dose had little CK elevation and at higher dose there was considerable elevation of CK in significant number of subjects. However, this is likely a super selective representation as CK elevation was of interest in the trial programme and actively sought. In standard clinical practice, CK monitoring is not recommended by most scientific societies or recommendations. The predictability of rhabdomyolysis needed to be established based on CK elevations and the applicant has clarified that within the development programme/postmarketing studies this was not consistent and is unlikely to be of significant use as a biomarker. While the liver enzyme elevation has been point of debate with statins, in this dataset, pitavastatin exhibited no greater increase in enzyme elevation or alteration of liver function than other statins. Therefore, no special reference other than the class warning is considered necessary at this stage.

In general, safety aspects in special groups showed some trends; elderly overall experienced higher frequency of adverse drug reactions and this was largely at lower doses. The ethnic distribution is skewed towards majority being Caucasians and hence a true comparison between racial groups is not possible to obtain. In the initial analysis, women had higher incidence of adverse drug reactions at lower doses, especially muscle-related effects, and this appears to follow the findings in the elderly. Reanalysis has not confirmed this and indeed raised the possibility that the gender bias in adverse drug reactions, especially muscle adverse drug reactions, in favour of women. The difference between genders is, however, small and not consistent for all muscle effects as, although adverse drug reactions were less frequent in women in the rhabdomyolysis group, there was slight preponderance of women. The gender difference in adverse events does not appear to relate clearly to the plasma pharmacokinetics parameters (C_{max} and AUC) that are 1.6-fold higher in women and the applicant has argued that plasma levels are not the main determinant of adverse drug reactions. The reanalysis presented appears to support this concept. The only safety finding of significance from special groups is that it reinforces the need to have lower starting doses of 1mg in the elderly; the 1mg starting dose has been applied universally.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applicant has submitted a Risk Management Plan in accordance with the EU pharmaceutical legislation. This has been the subject of a detailed assessment. The approved Risk Management Plan is satisfactory and is suitable for monitoring the adverse drug reactions observed with this type of product.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labels

The SPCs, PILs and labels are medically acceptable. The SPCs and PILs are in compliance with current guidelines and in line with other products of this therapeutic class. The labels are in-line with current requirements.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

There are no objections to the grant of marketing authorisations on clinical grounds.

IV OVERALL CONCLUSION AND BENEFIT:RISK ASSESSMENT QUALITY

The important quality characteristics of Livazo/Alipza/Vezepra/Pitavastatin 1mg, 2mg and 4mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative effect on the benefit:risk balance.

NON-CLINICAL

The toxicity of pitavastatin has been shown to be similar to that of other HMG-CoA reductase inhibitors. All non-clinical points raised for consideration have been addressed adequately. There are no objections to the authorisation of these products on non-clinical grounds.

EFFICACY

The dossier for pitavastatin has been compiled reasonably well and includes an adequate number of pharmacology studies, and efficacy studies. The clinical pharmacology studies are comprehensive and evaluate the mechanism of action, the pharmacokinetics and pharmacodynamics.

The dose finding suggested a significant effect of 1mg pitavastatin on lipid parameters (31% reduction in LDL-C) and this has been recommended as a starting dose universally. Pitavastatin has been shown to reduce LDL-cholesterol, as expected for a statin, and there are reductions in total cholesterol, TG and APO-B.

Placebo comparator studies confirm the pharmacodynamic effect and the active comparator trials show that pitavastatin dose per dose could be considered marginally superior to pravastatin, and non-inferior to simvastatin and atorvastatin in the familial hypercholesterolemic population. The effects on other lipid parameters (secondary endpoints) are also similar for the doses tested.

The interactions with ciclosporin and alteration in pharmacokinetics in those with renal failure are considered to be of sufficient concern that the applicant has contraindicated concomitant use of ciclosporin with pitavastatin. The possibility that genetic polymorphisms could alter tolerability considerably has not been addressed, but it has been argued that tolerability is not dependent on pharmacokinetics. While the absence of information on genetic polymorphism is a limitation of the dataset, this is not primary hurdle for the MA grant and has been addressed in the RMP.

SAFETY

In general, the safety of pitavastatin appears to be similar to other statins that were used in the development programme, such as simvastatin, atorvastatin and pravastatin at clinical doses. The safety in special populations has been discussed, and in the elderly it appears that there may be slightly higher incidence of adverse drug reactions. Gender differences are in favour of women in the reanalysis, including the post-marketing study results (i.e. lower frequency of adverse drug reactions in women, especially muscle events), although slightly more women had reported rhabdomyolysis events. The differences are small and not sufficient for inclusion in the product literature.

The issue of myopathy and rhabdomyolysis, where a certain level of discrepancy was noted in the reporting of these within the trial programme and the post marketing surveillance, has now been discussed and clarified. In the controlled trial programme that excluded 'at risk' subjects, rhabdomyolysis was only noted at doses 8mg or greater although the dataset is

limited. In the post marketing surveillance, while there appear to be some cases of rhabdomyolysis, the overall incidence has been shown to be similar for all doses of pitavastatin and the relative rate per year of patient use is similar. Moreover, the updated data analysis provides some assurance that these events with pitavastatin are similar to that reported for other statins on the market, notably simvastatin and atorvastatin. Indeed, by the applicant's estimates, it appears that risk with pitavastatin (all doses) is lower than 20 or 40 mg of atorvastatin. As higher dose of atorvastatin and simvastatin are already approved, restriction of pitavastatin 4mg does not stand to reason, in the absence of a very clear signal of risk. However, a risk can not be excluded completely and, therefore, a containment strategy has been adopted. This includes risk minimisation procedures (lower starting dose, restriction of use in at risk population, adequate contraindications, clear description of risks in the SPC) and a robust risk management plan.

PRODUCT LITERATURE

The approved SPCs and PILs are satisfactory and in-line with those for products of this type. The final labelling is satisfactory and in-line with current guidelines.

BENEFIT:RISK ASSESSMENT

The quality of the products is acceptable. A positive benefit:risk is concluded in the patient population studied for a symptomatic indication.

A robust risk management plan will need to be implemented in order to identify and characterise uncommon serious adverse events, in particular psychiatric morbidity and other CNS effects. The applicant has provided a detailed assessment of safety concerns with post marketing commitments to carry out studies.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome