SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vaspit 1 mg filmomhulde tabletten
Vaspit 2 mg filmomhulde tabletten
Vaspit 4 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains pitavastatin calcium equivalent to 1 mg, 2 mg or 4 mg pitavastatin.

Excipient with known effect: lactose.
Each [Product name] 1 mg film-coated tablet contains 60.855 mg lactose monohydrate.
Each [Product name] 2 mg film-coated tablet contains 121.71 mg lactose monohydrate.
Each [Product name] 4 mg film-coated tablet contains 243.42 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

[Product name] 1 mg film-coated tablets: White round, concave, film coated tablets, debossed with '10' on one side and plain on the other side, with diameter approximately 6mm.
[Product name] 2 mg film-coated tablets: Yellow round, concave, film coated tablets, debossed with '20' on one side and plain on the other side, with diameter approximately 8mm.
[Product name] 4 mg film-coated tablets: White round, concave, film coated tablets, debossed with 'MC' on one side and plain on the other side, with diameter approximately 10.3mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Patients should be on a cholesterol lowering diet before treatment. It is important that all patients continue dietary control during treatment.
The usual starting dose is 1 mg once daily. Adjustment of dose should be made at intervals of 4 weeks or more. Doses should be individualized according to LDL-C levels, the goal of therapy and patient response. The maximum daily dose is 4 mg.

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

Paediatric population

Children and adolescents aged 6 years and over
[Product name] use in children should only be carried out by physicians experienced in the treatment of hyperlipidaemia and progress should be regularly reviewed.
In children and adolescents with heterozygous familial hypercholesterolaemia the usual starting dose is 1 mg once daily. Adjustment of dose should be made at intervals of 4 weeks or more. Doses should be individualized according to LDL-C levels, the goal of therapy and patient response. In children 6 to 9 years of age the maximum daily dose is 2 mg. In children 10 years or older the maximum daily dose is 4 mg (see sections 4.8, 5.1 and 5.2).

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

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

Patients with mild to moderate impaired hepatic function
The 4 mg dose is not recommended in patients with mild to moderate impaired hepatic function. A maximum daily dose of 2 mg may be given with close monitoring (see section 4.4 and 5.2).

Method of administration
For oral use only and should be swallowed whole. [Product name] can be taken at any time of the day with or without food. It is desirable that the patient takes the tablet at the same time each day. Statin therapy is generally more effective in the evening due to the circadian rhythm of lipid metabolism.
If a child or adolescent is unable to swallow the tablet, where necessary, the tablet may be dispersed in a glass of water and taken immediately. To ensure accurate dosage a second volume of water should be used to rinse the glass and swallowed immediately. Tablets must not be dispersed in either acidic fruit juices or milk.

4.3 Contraindications

Hypersensitivity to the active substance, other statins or to any of the excipients listed in section 6.1.
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 childbearing 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.
There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Pitavastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of pitavastatin and fusidic acid should only be considered on a case-by-case basis and under close medical supervision.

Before treatment
In common with other statins, 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 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 pitavastatin may be considered at a dose of 1 mg and with close monitoring.

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). [Product name] should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-)administered have been reported.

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

Renal effects
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, 4 mg dose is not recommended (see section 4.2).

Diabetes mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk of hyperglycaemia (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m2, raised triglycerides, hypertension), should be monitored both clinically and biochemically according to national guidelines. However, there has been no confirmed signal of a diabetes risk for pitavastatin either in post-marketing safety surveillance studies or in prospective studies (see section 5.1)

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Paediatric population

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

Other effects

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

Erythromycin

Co-administration with pitavastatin resulted in a 2.8-fold increase in pitavastatin AUC. A temporary suspension of 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. Pitavastatin should be administered with caution when used concomitantly with fibrates (see section 4.4). In Pharmacokinetic studies co-administration of pitavastatin with gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC with fenofibrate AUC increased 1.2-fold.

Niacin

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

Fusidic acid

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

Glecaprevir and pibrentasvir

Concomitant administration of HMG-COA reductase inhibitors and glecaprevir/pibrentasvir may increase plasma concentrations of the HMG-COA reductase inhibitor. Pitavastatin has not been studied but it is likely that the same interaction will occur. The lowest pitavastatin dose is recommended at the start of treatment with glecaprevir/pibrentasvir and clinical monitoring of patients receiving this combination is recommended.

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

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors
Co-administration of lopinavir/ritonavir, darunavir/ritonavir, atazanavir, or efavirenz with pitavastatin at the same time may result in minor changes in pitavastatin AUC.

Ezetimibe
Ezetimibe and its glucuronide metabolite inhibit the absorption of dietary and biliary cholesterol. Co-administration of 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
Digoxin, a known P-gp substrate, did not interact with 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 pitavastatin 4 mg daily. However, as for other statins, patients receiving warfarin should have their prothrombin time or INR monitored when pitavastatin is added to their therapy.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Pitavastatin is contraindicated during pregnancy (see section 4.3). Women of childbearing potential must take appropriate contraceptive precautions during treatment with 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 pitavastatin, treatment must be discontinued immediately.

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

Fertility
No current data

4.7 Effects on ability to drive and use machines

There is no pattern of adverse events that suggests that patients taking 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 pitavastatin.

4.8 Undesirable effects

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

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

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
Not known: Myasthenia gravis

Eye disorders
Rare: Visual acuity reduced
Not known: Ocular myasthenia

Ear and labyrinth disorders
Uncommon: Tinnitus

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

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

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

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

Renal and urinary disorders
Uncommon: Pollakiuria

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

Elevated blood creatinine kinase of >3 times the upper limit of normal (ULN) occurred in 49 out of 2800 (1.8%) patients receiving 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 4 mg pitavastatin (0.04%) in the clinical trial programme.

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

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 1 mg or 2 mg pitavastatin and not 4 mg. 10.4% of patients reported adverse events for which a causal relationship to pitavastatin could not be ruled out and 7.4% of patients withdrew from therapy due to adverse events. The myalgia rate was 1.08%. The majority of adverse events were mild. Adverse event rates were higher over 2 years in patients with a history of drug allergy (20.4%), or hepatic or renal disease (13.5%).

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

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

Nervous system disorders
Uncommon: Hypoaesthesia

Gastrointestinal disorders
Rare: Abdominal discomfort

Skin and subcutaneous tissue disorders
Not known: Angioedema

Musculoskeletal, connective tissue and bone disorders
Not known: Lupus-like syndrome

Reproductive system and breast disorders
Rare: Gynecomastia

Statin class effects
The following adverse events have been reported with some statins:
- Sleep disturbances, including nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI >30 kg/m2, raised triglycerides, history of hypertension)

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10AA08.

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
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
1 mg	52	-33.3	-22.8	9.4	-14.8	-24.1	8.5
2 mg	49	-38.2	-26.1	9.0	-17.4	-30.4	5.6
4 mg	50	-46.5	-32.5	8.3	-21.2	-36.1	4.7

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
*unadjusted							

Clinical efficacy and safety

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), pitavastatin consistently reduced LDL-C, TC, non-HDL-C, TG and Apo-B concentrations and elevated HDL-C and Apo-A1 concentrations. TC/HDL-C and Apo-B/Apo-A1 ratios were reduced. LDL-C was reduced by 38 to 39% with pitavastatin 2 mg and 44 to 45% with pitavastatin 4 mg. The majority of patients taking 2 mg achieved the European Atherosclerosis Society (EAS) treatment target for LDL-C (<3 mmol/L).

In a controlled clinical trial in 942 patients aged ≥65 years (434 treated with pitavastatin 1 mg, 2 mg or 4 mg) 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 pitavastatin 4 mg) 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 4 mg were LDL-C reduction 42.9%, EAS target attainment 74%, HDL-C elevation 14.3%.

In an extension to the two year surveillance study conducted in Japan (LIVES-01, see section 4.8), 6582 patients with hypercholesterolaemia who had received treatment with pitavastatin 1, 2, or 4 mg for 2 years, were continued on treatment for a further 3 years (5 years total treatment). During this 5-year study, LDL-C reduction (-30.5%) was maintained from 3 months for the duration of the study, HDL-C values increased by 1.7% at 3 months to 5.7% at 5 years, with greater HDL-C increases seen in patients with lower baseline HDL-C values (<40 mg/dL), e.g. serum levels increased by 11.9% at 3 months to 28.9% after 5 years were observed.

Atherosclerosis

The JAPAN-ACS study compared the effects of 8 to 12 month's treatment with pitavastatin 4 mg or atorvastatin 20 mg on coronary plaque volume in 251 patients undergoing percutaneous coronary intervention for Acute Coronary Syndrome, guided by intravascular ultrasound. This study demonstrated approximately 17% reduction in plaque volume for both treatments (-16.9 ± 13.9% with pitavastatin and -18.1 ± 14.2% with atorvastatin). Non-inferiority was proven between pitavastatin and atorvastatin and vice versa. In both cases, plaque regression was associated with negative vessel remodelling (113.0 to 105.4 mm3). There was no significant correlation between LDL-C reduction and plaque regression in this study, in contrast to the findings in placebo-controlled studies.

The beneficial effects on mortality and morbidity have not yet been evaluated.

Diabetes mellitus

In an open-label prospective controlled study in 1269 Japanese patients with impaired glucose tolerance randomised to lifestyle modification with or without pitavastatin 1 mg or 2 mg daily, 45.7%

of patients in the control group developed diabetes in comparison to 39.9% of patients in the pitavastatin group over a 2.8-year period, hazard ratio 0.82 [95% CI 0.68-0.99].
A meta-analysis of 4815 non-diabetic patients included in randomised controlled double-blind studies of at least 12-weeks duration (weighted mean follow-up 17.3 weeks [SD 17.7 weeks]) demonstrated a neutral effect for pitavastatin on the risk of new-onset diabetes (0.98% of control patients and 0.50% of pitavastatin patients developed diabetes, relative risk 0.70 [95% CI 0.30-1.61]) whilst 6.5% (103/1579) of control patients were treated with placebo; the rest were treated with statins including atorvastatin, pravastatin and simvastatin.

HIV population
The efficacy of pitavastatin and other statins on LDL-C is reduced in patients with hypercholesterolaemia associated with HIV infection or its treatment compared to patients with primary hypercholesterolaemia and mixed dyslipidaemia without HIV.
In the INTREPID trial, a total of 252 HIV-infected patients with dyslipidaemia (n=126 per arm) entered a 4-week wash-out/dietary lead-in period, and then were randomized to a once daily dose of pitavastatin 4 mg or pravastatin 40 mg for 52 weeks. The primary efficacy endpoint was assessed at Week 12.
The fasting serum LDL-C decreased by 31% and 30% in the pitavastatin treatment group and 21% and 20% in the pravastatin treatment group over 12 and 52 weeks, respectively (LS mean treatment difference -9.8%, P <0.0001 at Week 12, and -8.4% P = 0.0007 at Week 52). There was a statistically significant treatment difference in the mean percent change from Baseline to Weeks 12 and 52 for the secondary efficacy endpoints of TC, non-HDL-C, and Apo B, with a greater decrease in the pitavastatin treatment group than in the pravastatin treatment group for each parameter. No new safety signals or adverse experiences with pitavastatin 4 mg were observed. At Week 52, virological failure (defined as an HIV-1 RNA viral load value >200 copies/mL and a >0.3-log increase from Baseline) was reported for 4 subjects (3.2%) in the pitavastatin group and 6 subjects (4.8%) in the pravastatin group, with no statistically significant differences between treatments.

Paediatric population
In a double-blind, randomized, multi-centre, placebo-controlled study (n=106; 48 male and 58 female) children and adolescent patients (≥6 years of age and <17 years of age) with high-risk hyperlipidaemia (fasting plasma LDL-C levels ≥160 mg/dL (4.1 mmol/L), or LDL-C ≥130 mg/dL (3.4 mmol/L) with additional risk factors) received pitavastatin 1 mg, 2 mg, 4 mg or placebo daily for 12 weeks. At study entry, the majority of the patients were diagnosed with heterozygous familial hypercholesterolaemia, approximately 41% of the patients were 6 to <10 years old and approximately 20%, 9%, 12%, and 9% were Tanner stage II, III, IV, and V, respectively. Mean LDL-C was reduced 23.5%, 30.1%, and 39.3% by pitavastatin 1, 2 and 4 mg, respectively, compared to 1.0% for placebo.
In a 52-week open-label extension and safety study (n=113, including 87 patients from the 12-week placebo-controlled study; 55 male and 58 female) children and adolescent patients (≥6 years of age and <17 years of age) with high-risk hyperlipidaemia received pitavastatin for 52 weeks. All patients started treatment with pitavastatin 1 mg daily, and the dose of pitavastatin may have been up-titrated to 2 mg and 4 mg to achieve an optimum LDL-C treatment target of <110 mg/dL (2.8 mmol/L) based on LDL-C values at Week 4 and Week 8. At study entry, approximately 37% of the patients were 6 to <10 years old and approximately 22%, 11%, 12%, and 13% were Tanner stage II, III, IV, and V, respectively. The majority of patients (n=103) were up-titrated to 4 mg pitavastatin daily. Mean LDL-C was reduced 37.8% at the Week 52 endpoint. In total, 47 patients (42.0%) achieved the AHA minimal LDL-C target of <130 mg/dL and 23 patients (20.5%) achieved the AHA ideal LDL-C target of <110 mg/dL at Week 52. The reduction in mean LDL-C at the Week 52 endpoint was 40.2% for patients ≥6 to <10 years of age (n=42), 36.7% for patients ≥10 to <16 years of age (n=61), and 34.5% for patients ≥16 to <17 years of age (n=9). Patient gender did not appear to have an effect on response. In addition, mean TC was decreased 29.5% and mean TG was decreased 7.6% at the Week 52 endpoint.

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

5.2 Pharmacokinetic properties

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

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.

Distribution
Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 133 L. Pitavastatin is actively transported into hepatocytes, the site of action and metabolism, by multiple hepatic transporters including OATP1B1 and OATP1B3. Plasma AUC is variable with an approximately 4-fold range between the highest and lowest values. Studies with SLCO1B1 (the gene which encodes OATP1B1) suggests that polymorphism of this gene could account for much of the variability in AUC. Pitavastatin is not a substrate for p-glycoprotein.

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

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

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

Renal insufficiency
For patients with moderate renal disease and those on haemodialysis increases in AUC values were 1.8-fold and 1.7-fold respectively (see section 4.2).

Hepatic insufficiency
For patients with mild (Child-Pugh A) hepatic impairment AUC was 1.6 times that in healthy subjects, while for patients with moderate (Child-Pugh B) hepatic impairment AUC was 3.9-fold higher. Dose restrictions are recommended in patients with mild and moderate hepatic impairment (see section 4.2). 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, carcinogenic potential, toxicity to reproduction. Indications of renal toxicity were seen in monkeys at exposures greater than those reached in adult humans administered the maximum daily dose of 4 mg 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 Hydroxypropyl Cellulose
Magnesium Aluminometasilicate
Hypromellose 2910
Magnesium Stearate

Film coating
Opadry white 03O580007
- Hypromellose
- Titanium dioxide (E171)
- Triethyl citrate (E1505)
- Colloidal anhydrous silica

Yellow iron oxide E172 (*2 mg tablets*)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Opaque blisters in cartons of 7, 28 or 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Medochemie Limited
1-10 Constantinoupoleos
3011 Limassol
Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

Vaspit 1 mg filmomhulde tabletten - RVG 129348
Vaspit 2 mg filmomhulde tabletten - RVG 129349
Vaspit 4 mg filmomhulde tabletten - RVG 129350

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 27 maart 2023

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8: 6 september 2023