SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil 5 mg/1000 mg, zachte capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 5 mg rosuvastatin (as rosuvastatin calcium) and 1000 mg omega-3-acid ethyl esters 90 (comprising 460 mg eicosapentaenoic acid (EPA), 380 mg docosahexaenoic acid (DHA) and 4 mg alpha tocopherol).

Excipient with known effect:
The anti-oxidant alpha tocopherol is derived from soy beans. The soft capsule may therefore contain traces of soybean oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft (capsule)

White, film-coated, oblong-shaped soft capsules, 23.5±2.0 mm x 9,5±1.0 mm in size, filled with light yellow oil.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is indicated as substitution therapy for the treatment of mixed hyperlipidaemia (type IIb) in adult patients adequately controlled with rosuvastatin and omega-3-acid ethyl esters 90 given concurrently at the same dose level.

4.2 Posology and method of administration

Posology

The recommended dose is 4 capsules daily.

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil should not be used for initiating treatment of mixed hyperlipidaemia (type IIb). Patients should be adequately controlled with each component given concurrently before initiating treatment with Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil.

In order to avoid gastrointestinal disturbances, administer capsules with food.

Elderly population
There is limited clinical data regarding the use of omega-3-acid ethyl esters 90 in elderly patients over 70 years of age (see section 4.4).

Patients with renal insufficiency
No dose adjustment is necessary for rosuvastatin in patients with mild to moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).
There is limited clinical data regarding the use of omega-3-acid ethyl esters 90 in patients with renal impairment (see section 4.4).

Patients with hepatic impairment
There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see section 5.2). In these patients an assessment of renal function should be considered (see section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Rosuvastatin is contraindicated in patients with active liver disease (see section 4.3).
There is no information regarding the use of omega-3-acid ethyl esters 90 in patients with hepatic impairment (see section 4.4).

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see sections 4.4 and 4.5). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing rosuvastatin therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered (see section 4.5).

Method of administration

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is for oral use. Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil may be given at any time of the day, preferably with food to avoid gastrointestinal disturbances.

4.3 Contraindications

Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is contraindicated in:
- Hypersensitivity to the active substances, to soya or to any of the excipients listed in section 6.1. Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil may contain traces of soybean oil. If you are allergic to peanut or soya, do not use this medicinal product.
- Patients with active liver disease, including unexplained persistent serum transaminase elevations or serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- Patients with myopathy.
- Patients receiving concomitant ciclosporin.
- Patients with severe renal insufficiency (creatinine clearance < 30 ml/min)).
- Pregnant and lactating women and women who do not use appropriate methods of contraception.

4.4 Special warnings and precautions for use

For rosuvastatin

Skeletal muscle effects
Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see section 4.5) and caution should be exercised with their combined use. There have been reports of an immune-mediated

necrotizing myopathy during or after treatment with rosuvastatin. Immune-mediated myopathy is clinically characterized by proximal muscle weakness and elevated serum creatinine kinase, which persist despite discontinuation of statin treatment.

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Creatine kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (> 5 x ULN) a confirmatory test should be carried out within 5–7 days. If the repeat test confirms a baseline CK > 5 x ULN, treatment should not be started.

Before Treatment
Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age > 70 years
- situations where an increase in plasma levels may occur (see section 5.2)
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x ULN) treatment should not be started.

Whilst on Treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (> 5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, cyclosporine, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

Rosuvastatin 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). Patients 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 rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Rosuvastatin should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appears, Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil should be discontinued immediately and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil, treatment with Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil must not be restarted in this patient at any time.

Hepatic effects
As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

Race
Pharmacokinetic studies show an increase in exposure to rosuvastatin in Asian subjects compared with Caucasians (see section 5.2).

Protease inhibitors
Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted (see sections 4.2 and 4.5).

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.

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 (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Paediatric population
In the absence of efficacy and safety data, use of this medication in children is not recommended.

For omega-3-acid ethyl esters

Systematic reviews and meta-analyses of randomized controlled clinical trials highlighted a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl esters compared to placebo. The observed risk is highest with a dose of 4 g/daily (see section 4.8). If atrial fibrillation develops, treatment should be permanently discontinued.

Sensitivity to fish
Omega-3-acid ethyl esters 90 should be used with caution in patients with known sensitivity or allergy to fish.

Anticoagulation
Because of the moderate increase in bleeding time caused by omega-3-acid ethyl esters 90 (with the high dosage, i.e. 4 capsules), patients receiving anticoagulant therapy must be monitored and the dosage of anticoagulant adjusted if necessary (see section 4.5). Use of this medication does not eliminate the need for the surveillance usually required for patients of this type.
Make allowance for the increased bleeding time in patients at high risk of haemorrhage (because of severe trauma, surgery, etc).

During treatment with omega-3-acid ethyl esters 90, there is a fall in thromboxane A2 production. No significant effect has been observed on the other coagulation factors. Some studies with omega-3-acids demonstrated a prolongation of bleeding time, but the bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes.

Renal and hepatic effects
Only limited information regarding the use in patients with renal impairment is available.
In some patients a small but significant increase (within normal values) in ASAT and ALAT was reported, but there are no data indicating an increased risk for patients with hepatic impairment.

ALAT and ASAT levels should be monitored in patients with any signs of liver damage (in particular with the high dosage, i.e. 4 capsules).

Exogenous hypertriglyceridaemia
Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is not indicated in exogenous hypertriglyceridaemia (type 1 hyperchylomicronaemia). There is only limited experience in secondary endogenous hypertriglyceridaemia (especially uncontrolled diabetes). There is no experience regarding hypertriglyceridaemia in combination with fibrates.

4.5 Interaction with other medicinal products and other forms of interaction

No studies have been conducted on drug interactions between Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil and other drugs. The following shows drug interaction data of the individual components, rosuvastatin and omega-3-acid ethyl esters 90.

For rosuvastatin

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of

rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4 and 4.5, Table 1).

*Ciclosporin***:** During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C_{max} respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4 and 4.5, Table 1).

Gemfibrozil and other lipid-lowering products: Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4).

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone.

Ezetimibe: Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out (see section 4.4).

Antacid: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50 %. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of rosuvastatin and erythromycin resulted in a 20 % decrease in AUC and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher.

Table 1: Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20 % ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47 % ↓
*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑", no change as "↔", decrease as "↓". **Several interaction studies have been performed at different Crestor dosages, the table shows the most significant ratio OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily		

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Omega-3-acid ethyl esters 90 have been given in conjunction with warfarin without haemorrhagic complications. However, the prothrombin time must be checked when omega-3-acid ethyl esters 90 are combined with warfarin or when treatment with omega-3-acid ethyl esters 90 is stopped.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26 % and 34 %, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Ticagrelor: Ticagrelor can cause renal insufficiency and may affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. In some cases, co-administered ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis. Renal function and CPK control is recommended while using ticagrelor and rosuvastatin concomitantly.

Other medicinal products:
Digoxin: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Fusidic acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. 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, Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4

For omega-3-acid ethyl esters

Oral anticoagulants: See section 4.4.

Omega-3-acid ethyl esters has been given in conjunction with warfarin without haemorrhagic complications. However, the prothrombin time must be checked when omega-3-acid ethyl esters is combined with warfarin or when treatment with omega-3-acid ethyl esters is stopped.

4.6 Fertility, pregnancy and lactation

The safety of rosuvastatin in pregnancy and lactation has not been established and therefore Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil is contraindicated during pregnancy and lactation (see section 4.3). Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy
Rosuvastatin
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity of rosuvastatin (see section 5.3). If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Omega-3-acid ethyl esters 90
There are no adequate data from the use of omega-3-acid ethyl esters 90 in pregnant women. Studies in animals have not shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown and therefore omega-3-acid ethyl esters 90 should not be used during pregnancy unless clearly necessary.

Breastfeeding
Rosuvastatin
Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans. Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the suckling child, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during breastfeeding (see section 4.3).

Omega-3-acid ethyl esters 90
There are no data on the excretion of omega-3-acid ethyl esters 90 in animal and human milk.

Fertility

Rosuvastatin

No clinical data are available on the effects of rosuvastatin on human fertility. Rosuvastatin had no effect on the fertility of male or female rats.

Omega-3-acid ethyl esters 90

No data are available on the effects of rosuvastatin on animal and human fertility.

4.7 Effects on ability to drive and use machines

Studies to determine the effect of rosuvastatin or omega-3-acid ethyl esters 90 on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, rosuvastatin is unlikely to affect this ability and omega-3-acid ethyl esters 90 is expected to have no or negligible influence on the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Rosuvastatin

The adverse reactions seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4 % of rosuvastatin-treated patients were withdrawn due to adverse reactions.

Tabulated list of adverse reactions

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

The frequencies of adverse reactions are ranked according to the following convention: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2. Adverse reactions based on data from clinical studies and post-marketing experience

System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia		
Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus[1]				
Psychiatric disorders					Depression
Nervous system disorders	Headache, dizziness			Polyneuropathy, memory loss	Peripheral neuropathy, sleep disturbances (including insomnia and nightmares),

					myasthenia gravis
Eye disorders					Ocular myasthenia
Respiratory, thoracic and mediastinal disorders					Cough, dyspnoea
Gastrointestinal disorders	Constipation, nausea, abdominal pain		Pancreatitis		Diarrhoea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice, hepatitis	
Skin and subcutaneous tissue disorders		Pruritis, rash, urticaria			Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Myalgia		Myopathy (including myositis), rhabdomyolysis	Arthralgia	Immune-mediated necrotising myopathy, tendon disorders, sometimes complicated by rupture
Renal and urinary disorders				Haematuria	
Reproductive system and breast disorders				Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension).					

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in < 1 % of patients at some time during treatment with 10 and 20 mg, and in approximately 3 % of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy.

Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg.
A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (> 5 x ULN), treatment should be discontinued (see section 4.4).

Liver effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

The following adverse events have been reported with some statins:
- Sexual dysfunction.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at a 40 mg dose.

Omega-3-acid ethyl esters 90

The frequencies of adverse reactions are ranked according to the following convention: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3. Adverse reactions based on data from clinical studies and post-marketing experience

System organ class	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders			Hypersensitivity		
Metabolism and nutrition disorders		Hyperglycaemia, gout			
Nervous system disorders		Dizziness, dysgeusia, headache			
Cardiac disorders	Atrial fibrillation				
Vascular disorders		Hypotension			
Respiratory, thoracic and mediastinal disorders		Epistaxis			
Gastrointestinal disorders	Gastrointestinal disorders (including abdominal distension, abdominal pain, constipation,	Gastrointestinal haemorrhage			

	diarrhoea, dyspepsia, flatulence, eructation, gastro-oesophageal reflux disease, nausea or vomiting)				
Hepatobiliary disorders			Liver disorders (including transaminases increased, alanine aminotransferase increased and aspartate aminotransferase increased)		
Skin and subcutaneous tissue disorders		Rash	Urticaria		Pruritus

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. 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: Rosuvastatin and omega-3 fatty acids, ATC code: C10BA07

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

The omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids. Omega-3-acid ethyl esters 90 are active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low-density lipoprotein), and omega-3-acid ethyl esters 90 are also active on haemostasis and blood pressure.

Pharmacodynamic effects

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

A therapeutic effect is obtained within 1 week following treatment initiation and 90 % of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Omega-3-acid ethyl esters 90 reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and they inhibit esterification of other fatty acids. The increase in peroxisomes of β-oxidation of fatty acids in the liver also contributes to the fall in triglycerides, by reducing the quantity of free fatty acids available for their synthesis. The inhibition of this synthesis lowers VLDL.

Omega-3-acid ethyl esters 90 increase LDL-cholesterol in some patients with hypertriglyceridaemia. A rise in HDL-cholesterol is only small, significantly smaller than seen after administration of fibrates, and not consistent. The long-term lipid-lowering effect (after more than one year) is not known. Otherwise there is no strong evidence that lowering triglycerides reduces the risk of ischaemic heart disease. During treatment with omega-3-acid ethyl esters 90, there is a fall in thromboxane A2 production and a slight increase in bleeding time. No significant effect has been observed on the other coagulation factors.

Clinical efficacy and safety
Combination of rosuvastatin and omega-3-acid ethyl esters 90

A multicenter, randomized, double-blind, and parallel-group trial was conducted for the safety and efficacy of Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil in Korean patients at high risk for coronary heart disease who are not adequately controlled for triglyceride levels.

In this trial, patients underwent a 4-week run-in period with 20 mg of rosuvastatin per day prior to randomization, and LDL-cholesterol was adequately controlled (< 1.2 mmol/l). Patients were randomly assigned to the test group (4 capsules of Rosuvastatine/Omega-3 vetzuren ethylesters 90 Kuhnil) or a control group (20 mg rosuvastatin alone). Compared with the control group, the decrease rate of non-HDL-cholesterol was significantly greater in the test group compared with the control group.

The changes in the major lipid levels at 8 weeks were as follows.
Table 5: Lipid values and percent change in therapeutic validation clinical trials (%)

	Test group (N=97)			Control group (N=104)			p-value
	Baseline	8 weeks	Percent change (%)	Baseline	8 weeks	Percent change (%)	
non-HDL-C	99.08±23.65	86.02±25.36	-10.69±28.68	96.72±21.95	94.09±30.72	-2.21±25.22	0.0009
TG	284.00±68.62	205.91±91.43	-26.30±30.69	279.56±64.16	241.74±97.68	-11.44±34.55	0.0002
TC	141.22±24.53	128.34±27.15	-8.12±18.30	139.35±23.96	137.18±31.87	-1.17±17.45	0.0003
HDL-C	42.14±7.52	42.32±8.79	0.94±14.27	42.63±10.09	43.10±8.91	2.83±15.90	0.3772
LDL-C	61.90±19.62	61.46±22.16	1.83±29.99	62.53±18.39	64.71±25.48	4.34±29.68	0.3347
VLDL-C	37.18±16.43	24.55±15.12	-28.53±43.29	34.19±13.41	29.37±19.48	-12.16±50.17	0.0039
Apo-B	75.38±20.45	71.12±18.32	-3.36±24.25	75.70±16.51	75.31±20.37	0.28±20.41	0.0495
Apo-A1	140.06±23.04	133.75±24.49	-1.48±40.67	139.87±23.80	138.00±22.74	-0.53±12.48	0.0085
Percent Change: Average ± Standard Deviation, p-value: Wilcoxon's rank sum test							

Rosuvastatin

Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

Omega-3-acid ethyl esters 90
The omega-3 series polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids.
Omega-3-acid ethyl esters 90 are active on the plasma lipids by lowering triglyceride levels as a result of a fall in VLDL (very low density lipoprotein), and the substance is also active on haemostasis and blood pressure.

5.2 Pharmacokinetic properties

Rosuvastatin
Absorption
Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20 %.

Distribution
Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90 % of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation
Rosuvastatin undergoes limited metabolism (approximately 10 %). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50 % less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90 % of the circulating HMG-CoA reductase inhibitor activity.

Elimination
Approximately 90 % of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5 % is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7 %). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity
Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations
Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults.
Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and C_{max}. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration

and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50 % greater compared to healthy volunteers.

Hepatic insufficiency: In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

Omega-3-acid ethyl esters 90

During and after absorption, there are three main pathways for the metabolism of the omega-3 fatty acids:
- the fatty acids are first transported to the liver where they are incorporated into various categories of lipoproteins and then channelled to the peripheral lipid stores.
- the cell membrane phospholipids are replaced by lipoprotein phospholipids and the fatty acids can then act as precursors for various eicosanoids.
- the majority is oxidised to meet energy requirements.

The concentration of omega-3 fatty acids, EPA and DHA, in the plasma phospholipids corresponds to the EPA and DHA incorporated into the cell membranes.

Animal pharmacokinetic studies have shown that there is a complete hydrolysis of the ethyl ester accompanied by satisfactory absorption and incorporation of EPA and DHA into the plasma phospholipids and cholesterol esters.

5.3 Preclinical safety data

Rosuvastatin
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

Omega-3-acid ethyl esters 90
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In addition, non-clinical literature data on safety pharmacology are indicating that there is no hazard for humans.

Combination of rosuvastatin and omega-3-acid ethyl esters 90

In a repeat-dose toxicity study in rats, no new toxicity has been observed in dosing the combination of rosuvastatin and omega-3-acid ethyl esters 90 compared to the same doses of the separate compounds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soft capsule core
Gelatin
Glycerol (E422)

Capsule coating
Hypromellose 2910
Amino Methacrylate Copolymer (=Eudragit® E PO)
Magnesium oxide (E530)
Triethyl citrate (E1505)
May contain traces of soybean oil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25 °C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

oPA/Al/PVC – Al blisters in a cardboard carton: 28 or 32 soft capsules.
PVC/Al blisters in a pillow bag and a cardboard carton: 28 or 30 soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Oy Medfiles Ltd
Volttikatu 5
FI-70700 Kuopio
Finland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 26 februari 2020
Datum van laatste verlenging: 15 januari 2025

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 20 juni 2024