SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

~~<Product name> 5 mg/10 mg hard capsules~~
<Product name> 10 mg/10 mg hard capsules
<Product name> 20 mg/10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

~~<Product name> 5 mg/10 mg hard capsules~~
~~Each capsule contains 5 mg of rosuvastatin (as rosuvastatin zinc) and 10 mg of ezetimibe.~~

<Product name> 10 mg/10 mg hard capsules
Each capsule contains 10 mg of rosuvastatin (as rosuvastatin zinc) and 10 mg of ezetimibe.

<Product name> 20 mg/10 mg hard capsules
Each capsule contains 20 mg of rosuvastatin (as rosuvastatin zinc) and 10 mg of ezetimibe.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

~~<Product name> 5 mg/10 mg hard capsules: Unmarked self-closing Coni Snap type, size 0, hard gelatin capsule with yellow coloured cap and white coloured body filled with two tablets. The length of the capsule is about 21.7 mm (± 0.5 mm).~~

<Product name> 10 mg/10 mg hard capsules: Unmarked self-closing Coni Snap type, size 0, hard gelatin capsule with yellow coloured cap and yellow coloured body filled with two tablets. The length of the capsule is about 21.7 mm (± 0.5 mm).

<Product name> 20 mg/10 mg hard capsules: Unmarked self-closing Coni Snap type, size 0, hard gelatin capsule with caramel coloured cap and yellow coloured body filled with two tablets. The length of the capsule is about 21.7 mm (± 0.5 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name> is indicated as adjunct to diet for treatment of primary hypercholesterolemia as substitution therapy in adult patients adequately controlled with the individual substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

4.2 Posology and method of administration

Posology

<Product name> is indicated in adult patients whose hypercholesterolemia is adequately controlled with separately administered monocomponent preparations of the same doses as the recommended combination.
The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with <Product name>.

The recommended daily dose is one capsule of the given strength with or without food.

<Product name> are not suitable for initial therapy. Treatment initiation or dose adjustment if necessary, should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.
<Product name> ~~5 mg/10 mg,~~ 10 mg/10 mg and 20 mg/10 mg hard capsules are not suitable for the treatment of patients requiring 40 mg dose of rosuvastatin.

<Product name> should be taken either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

Paediatric population
The safety and efficacy of <Product name> in children below the age of 18 years have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly
A start dose of 5 mg rosuvastatin is recommended in patients > 70 years (see section 4.4).
The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary, should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment.
The recommended start dose is rosuvastatin 5 mg in patients with moderate renal impairment (creatinine clearance < 60 ml/min). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.
The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6).
Treatment with <Product name> is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction (see sections 4.4 and 5.2.). <Product name> is contraindicated in patients with active liver disease (see section 4.3).

Race
Increased systemic exposure of rosuvastatin has been seen in Asian subjects (see sections 4.4 and 5.2).
The recommended start dose is rosuvastatin 5 mg for patients of Asian ancestry. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see section 5.2). For patients who are known to have such specific types of polymorphisms, a lower daily dose of <Product name> is recommended.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is rosuvastatin 5 mg in patients with predisposing factors to myopathy (see section 4.4). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose.

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when <Product name> are 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 <Product name> therapy. In situations where co-administration of these medicinal products with <Product name> 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
For oral use.
<Product name> should be taken each day once at the same time of the day with or without food.
The capsule should be swallowed whole with a drink of water.

4.3 Contraindications

<Product name> is contraindicated:

- in patients with hypersensitivity to the active substances (rosuvastatin, ezetimibe) or to any of the excipients listed in section 6.1.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- during pregnancy and breast-feeding and in women of childbearing potential not using appropriate contraceptive measures.
- in patients with severe renal impairment (creatinine clearance < 30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).
- in patients receiving concomitant ciclosporin.

(See sections 4.4, 4.5 and 5.2.)

4.4 Special warnings and precautions for use

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, <Product name> 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 <Product name>, treatment with <Product name> must not be restarted in this patient at any time.

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.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine kinase level, ezetimibe, any statin, and any of these agents known to be associated with increased risk of rhabdomyolysis, that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

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 results.

If CK levels are significantly elevated at baseline (> 5 × ULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK> 5 × ULN, treatment should not be started.

Before treatment

<Product name>, as 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 × 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 × ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 × ULN). 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 characterized 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, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolid antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of <Product name> and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of <Product name> with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

<Product name> 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).

Fusidic acid
<Product name> 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 <Product name> and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Liver effects
In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥ 3 times the upper limit of normal [ULN]) have been observed.
It is recommended that liver functions tests be carried out prior to, and 3 months following the initiation of rosuvastatin 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 <Product name>.
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, <Product name> is not recommended (see section 5.2).

Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see section 4.8).

Race
Rosuvastatin pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2 and 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 <Product name> in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of <Product name> 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.
In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established.
If cholelithiasis is suspected in a patient receiving <Product name> and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Anticoagulants
If <Product name> is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Ciclosporin
See sections 4.3 and 4.5.

Paediatric population
The safety and efficacy of <Product name> in children below the age of 18 years have not yet been established therefore, its use is not recommended in this age group.

Liver disease and alcohol
<Product name> should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

<Product name>contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications
Ciclosporin: During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.
Co-administration of <Product name> with ciclosporin is contraindicated (see section 4.3).
In a study of eight post-renal transplant patients with creatinine clearance of > 50 ml/min on a stable dose of ciclosporin, a single 10 mg dose of ezetimibe resulted in a 3.4-fold (range 2.3 to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n = 17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted.

Not-recommended combinations

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see section 4.5 Table). 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). The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary, should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

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

Gemfibrozil and other lipid-lowering medicines: 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. ~~These patients should also start with the 5 mg rosuvastatin dose.~~

In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8). If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8). Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively). Co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile, but not all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

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 treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4.**

Other interactions

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.
Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Erythromycin: Concomitant use of rosuvastatin and eryhtromycin resulted in a 20% decrease in AUC_{0-t} 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).
In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

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.
Concomitant administration of ezetimibe (10 mg once daily) had no effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If <Product name> are added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and 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.
In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Colestyramine: Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to colestyramine may be lessened by this interaction (see section 4.2).

Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

Other medicinal products: Based on data from specific interaction studies no clinically relevant interaction between rosuvastatin and digoxin is expected.
In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Interactions requiring rosuvastatin dose adjustments (see also Table 1 below): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses 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. The maximum daily dose should be adjusted so that

the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of rosuvastatin with combination atazanavir/ritonavir (3.1-fold increase).

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20 mg.

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

2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting medicine dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg, single dose	7.4 -fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2-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 ↑
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 ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting medicine dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
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 ↑**
Decrease in AUC of rosuvastatin		
Interacting medicine dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
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 "↑", decrease as "↓".
**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio.
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily.

The following medical product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration:
Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200 mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary, should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

4.6 Fertility, pregnancy and lactation

<Product name> is contraindicated in pregnancy and breast-feeding.
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 (see section 5.3). If a patient becomes pregnant during use of <Product name>, treatment should be discontinued immediately.
Ezetimibe:
No clinical data are available on the use of ezetimibe during pregnancy.
Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development (see section 5.3).

Breast-feeding
Rosuvastatin:
Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion of rosuvastatin in milk in humans (see section 4.3).
Ezetimibe:
Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility
No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

<Product name> has no or negligible influence on the ability to drive and use machines. Studies to determine the effect of rosuvastatin and/or ezetimibe on the ability to drive and use machines have not

been conducted. However, when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

Summary of the safety profile
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.

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2 396 patients, or with a statin in 11 308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

According to available data 1 200 patients took rosuvastatin and ezetimibe combination in clinical studies. As reported in the published literature, the most frequent common adverse events related to rosuvastatin-ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases, gastrointestinal problems and muscle pain. These are known undesirable effects of the active substances. However, a pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out (see section 5.2).

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following: 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 (frequency cannot be estimated from the available data).

MedDRA system organ class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			thrombocytopenia[2]		thrombocytopenia[3]
Immune system disorders			hypersensitivity reactions including angioedema[2]		hypersensitivity, including rash, urticaria, anaphylaxis and angioedema[3]
Endocrine disorders	diabetes mellitus[1,2]				
Metabolism and nutrition disorders		decreased appetite[3]			
Psychiatric disorders					depression[2,3]
Nervous system disorders	headache[2,3], dizziness[2]	paraesthesia[3]		polyneuropathy[2], memory loss[2]	peripheral neuropathy[2], sleep disturbances (including

					insomnia and nightmares)[2], dizziness[3]
Vascular disorders		hot flush[3], hypertension[3]			
Respiratory, thoracic and mediastinal disorders		cough[3]			cough[2], dyspnoea[2,3]
Gastrointestinal disorders	constipation[2], nausea[2], abdominal pain[2,3], diarrhoea[3], flatulence[3]	dyspepsia[3], gastrooesophageal reflux disease[3], nausea[3], dry mouth[3], gastritis[3]	pancreatitis[2]		diarrhoea[2], pancreatitis[3], constipation[3]
Hepatobiliary disorders			increased hepatic transaminases[2]	jaundice[2], hepatitis[2]	hepatitis[3], cholelithiasis[3], cholecystitis[3]
Skin and subcutaneous tissue disorders		pruritus[2,3], rash[2,3], urticaria[2,3]			Stevens-Johnson syndrome[2], drug reaction with eosinophilia and systemic symptoms (DRESS)[2], erythema multiforme[3]
Musculoskeletal and connective tissue disorders	myalgia[2,3]	arthralgia[3], muscle spasms[3], neck pain[3], back pain[3], muscular weakness[3], pain in extremity[3]	myopathy (including myositis)[2], rhabdomyolysis[2], lupus-like syndrome[2], muscle rupture[2]	arthralgia[2]	immune-mediated necrotising myopathy[2], tendon disorders, sometimes complicated by rupture[2], myopathy/rhabdomyolysis[3] (see section 4.4)
Renal and urinary disorders				haematuria[2]	
Reproductive system and breast disorders				gynecomastia[2]	
General disorders and administration site conditions	asthenia[2], fatigue[3]	chest pain[3], pain[3], asthenia[3], oedema peripheral[3]			oedema[2]
Investigations	ALT and/or AST	blood CPK increased[3],			

	increased[3]	gamma-glutamyltransferase increased[3], liver function test abnormal[3]			

[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) – for rosuvastatin.
[2]Adverse reaction profile for rosuvastatin based on data from clinical studies and extensive post-marketing experience.
[3]Adverse reactions observed in clinical studies of ezetimibe (as a monotherapy or co-administered with a statin) or ezetimibe reported from post-marketing use either administered alone or with a statin. Adverse reactions were observed in patients treated with ezetimibe (n = 2 396) and at a greater incidence than placebo (n = 1 159) or in patients treated with ezetimibe co-administered with a statin (n = 11 308) and at a greater incidence than statin administered alone (n = 9 361). Post-marketing Adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin.

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 mg 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 × ULN), the 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) are higher at the 40 mg rosuvastatin dose.

Laboratory values
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 × ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe

co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4).
In clinical trials, CPK > 10 × ULN was reported for 4 of 1 674 (0.2%) patients administered ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) (see section 4.4).

Paediatric population
The safety and efficacy of <Product name> in children below the age of 18 years have not yet been established (see section 5.1).
Rosuvastatin: Creatine kinase elevations > 10 × ULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.
Ezetimibe:
Paediatric (6 to 17 years of age) patients
In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3 × ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10 × ULN). No cases of myopathy were reported.

In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥ 3 × ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10 × ULN). No cases of myopathy were reported.
These trials were not suited for comparison of rare adverse drug reactions.

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 published literature data on rosuvastatin overdose.
There is no specific treatment in the event of overdose with rosuvastatin.
In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5 000 mg/kg of ezetimibe in rats and mice and 3 000 mg/kg in dogs.
A few cases of overdosage with ezetimibe have been reported: most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

In the event of an overdose, symptomatic and supportive measures should be employed. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents; HMG CoA reductase inhibitors in combination with other lipid modifying agents, ATC code: C10BA06

Rosuvastatin
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.

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 (see Table below). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Dose response in patients with primary hypercholesterolaemia (type IIa and IIb)
(adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5 mg	17	-45	-33	13	-35	-44	-38	4
10 mg	17	-52	-36	14	-10	-48	-42	4
20 mg	17	-55	-40	8	-23	-51	-46	5
40 mg	18	-63	-46	10	-28	-60	-54	0

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.

Ezetimibe
Mechanism of action
Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

Pharmacodynamic effects
A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the

absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat-soluble vitamins A and D.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.
Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Rosuvastatin-ezetimibe co-administration

Clinical efficacy and safety
A 6-week, randomized, double-blind, parallel-group, clinical trial evaluated the safety and efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg (n = 440). Pooled data demonstrated that ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7% (between-group difference of 15.2%, $p < 0.001$). Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg (12.3% difference, $p < 0.001$), and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg (17.5% difference, $p < 0.001$).

A 6-week, randomized study was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease (n = 469). Significantly more patients receiving rosuvastatin/ezetimibe than rosuvastatin alone achieved their ATP III LDL cholesterol goal (< 100 mg/dl, 94.0% vs 79.1%, $p < 0.001$). Rosuvastatin 40 mg was effective at improving the atherogenic lipid profile in this high-risk population.

A randomized, open-label, 12-week study investigated the level of LDL reduction in each treatment arm (rosuvastatin 10 mg plus ezetimibe 10 mg, rosuvastatin 20 mg/ezetimibe 10 mg, simvastatin 40/ezetimibe 10 mg, simvastatin 80/ezetimibe 10 mg). The reduction from baseline with the low dose rosuvastatin combination**s** was 59.7%, significantly superior to the low dose simvastatin combinations, 55.2% ($p < 0.05$). Treatment with the high-dose rosuvastatin combo reduced LDL cholesterol 63.5% compared with a reduction of 57.4% with the high-dose simvastatin combination ($p < 0.001$).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with <Product name> in all subsets of the paediatric population in the treatment of elevated cholesterol (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Rosuvastatin and ezetimibe combination therapy
Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

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. The exposure in children and adolescents with heterozygous familial hypercholesterolaemia appears to be similar to or lower than that in adult patients with dyslipidaemia (see "Paediatric population" below).

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 impairment: 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 (CLcr < 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 impairment: 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 <Product name> is recommended.

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10-17 or 6-17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

Ezetimibe
Absorption: After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.
Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe. Ezetimibe can be administered with or without food.

Distribution: Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Biotransformation*:* Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination: Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special populations
Age and sex: Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly. Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Renal impairment: After a single 10 mg dose of ezetimibe in patients with severe renal disease (n = 8; mean CLcr ≤ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n = 9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.
An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Hepatic impairment: After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic impairment, <Product name> are not recommended in these patients (see section 4.4).

Paediatric population: The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

5.3 Preclinical safety data

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2 000 times the AUC level for the active metabolites).
In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.
The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed.

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.

Ezetimibe: Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.
Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1 000 mg/kg/day. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Silicified microcrystalline cellulose (Microcrystalline Cellulose (E 460) and Colloidal Anhydrous Silica (E 551))
Colloidal Anhydrous Silica (E 551)
Magnesium stearate (E 572)
Povidone (E 1201)
Croscarmellose Sodium (E 468)

Microcrystalline Cellulose (E 460)
Mannitol (E 421)
Sodium laurilsulfate (E 514)
Low-substituted hydroxypropyl cellulose (E 463)

Capsule shell

~~<Product name> 5 mg/10 mg hard capsules:~~
~~Cap: Titanium dioxide (E 171), Yellow iron oxide (E 172), Gelatine~~
~~Body: Titanium dioxide (E 171), Gelatine~~

<Product name> 10 mg/10 mg hard capsules:
Cap and body: Yellow iron oxide (E172), Titanium dioxide (E171), Gelatine

<Product name> 20 mg/10 mg hard capsules:
Cap: Red iron oxide (E172), Titanium dioxide (E171), Yellow iron oxide (E172), Gelatine
Body: Yellow iron oxide (E172), Titanium dioxide (E171), Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

~~5 mg/10 mg: Packs of 28, 30, 60, 90 hard capsules in cold blister (OPA/Al/PVC//Al)~~
10mg/10 mg and 20mg/10 mg: Packs of 7, 10, 28, 30, 56, 60, 84, 90 hard capsules in cold blister (OPA/Al/PVC//Al).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

<to be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<to be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT