SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 10 mg/10 mg film-coated tablets
<Invented name> 20 mg/10 mg film-coated tablets
<Invented name> 40 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Invented name> 10 mg/10 mg: Each film-coated tablet contains 10 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.
<Invented name> 20 mg/10 mg: Each film-coated tablet contains 20 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.
<Invented name> 40 mg/10 mg: Each film-coated tablet contains 40 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.

Excipient with known effect:

<Invented name> 10 mg/10 mg: Each film-coated tablet contains 111.2 mg of lactose (as lactose monohydrate).
<Invented name> 20 mg/10 mg: Each film-coated tablet contains 168.6 mg of lactose (as lactose monohydrate).
<Invented name> 40 mg/10 mg: Each film-coated tablet contains 286.0 mg of lactose (as lactose monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
<Invented name> 10 mg/10 mg: white to off-white oblong film-coated tablets.
<Invented name> 20 mg/10 mg: yellow to light yellow oblong film-coated tablets.
<Invented name> 40 mg/10 mg: pink oblong film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia/Homozygous Familial Hypercholesterolaemia (HoFH)
<Invented name> is indicated for substitution therapy in adult patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate products, as adjunct to diet for treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia.

Prevention of Cardiovascular Events
<Invented name> is indicated as substitution therapy in adult patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently, at the same dose level as in the fixed dose combination, but as separate products to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS).

4.2 Posology and method of administration

Posology

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with <Invented name>.

<Invented name> 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.

Patient should use the strength corresponding to their previous treatment.
The recommended dose is one <Invented name> tablet daily.

Co-administration with bile acid sequestrants

Dosing of <Invented name> should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see Section 4.5).

Paediatric population

The safety and efficacy of <Invented name> in children below the age of 18 years have not yet been established. Currently available data are described in section 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.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6). Treatment with <Invented 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). <Invented name> is contraindicated in patients with active liver disease (see section 4.3).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment.
The recommended start dose is rosuvastatin 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min).
The 40 mg/10 mg dose is contraindicated in patients with moderate renal impairment. The use of <Invented name> in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

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. <Invented name> 40 mg/10 mg film-coated tablets are contraindicated in these patients (see sections 4.3 and 5.2).

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 <Invented name> is recommended.

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is rosuvastatin 5 mg in patients with pre-disposing 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.
<Invented name> 40 mg/10 mg film-coated tablets are contraindicated in some of these patients (see section 4.3).

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when <Invented name> 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 <Invented name> therapy. In situations where co-administration of these medicinal products with <Invented 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
Route of administration is oral. <Invented name> can be administered at any time of the day, with or without food. The tablet should be swallowed whole with a drink of water.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Pregnancy, breast-feeding and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6).
- Active liver disease or unexplained persistent elevations in serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN) (see section 4.4).
- In patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).
- In patients with myopathy (see section 4.4).
- In patients receiving concomitant ciclosporin (see section 4.5).

The 40 mg/10 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- Moderate renal impairment (creatinine clearance <60 ml/min).
- Hypothyroidism.
- Personal or family history of hereditary muscular disorders.
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate.
- Alcohol abuse.
- Situations where an increase in plasma levels of rosuvastatin may occur.
- Asian patients.
- Concomitant use of fibrates.

(see sections 4.4, 4.5 and 5.2)

4.4 Special warnings and precautions for use

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. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

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 phosphokinase (CPK) level>10 times the ULN, <Invented name> and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with <Invented name> 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 result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before treatment
Caution should be exercised 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 sections 4.2, 4.5 and 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 (>5xULN) 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 (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are </=5x 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 of the patient. 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, cyclosporin, 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. The 40 mg dose of rosuvastatin is contraindicated with concomitant use of a fibrate (see sections 4.5 and 4.8). <Invented 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).

Liver effects
In controlled co-administration trials in patients receiving ezetimibe with statin, consecutive transaminase elevations (≥3 × the upper limit of normal [ULN]) have been observed.

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. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.
In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, <Invented name> is not recommended (see section 5.2).

Liver disease and alcohol
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.

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). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

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.

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.

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

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).

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established (see above and sections 4.3 and 4.5).

If cholelithiasis is suspected in a patient receiving <Invented name> and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

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

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

Race
Pharmacokinetic studies show an increase in exposure of rosuvastatin in Asian subjects compared with Caucasians (see sections 4.2, 4.3 and 5.2).

Paediatric population
<Invented name> is not recommended for use in children and adolescents of less than 18 years of age, due to insufficient data on safety and efficacy.

<Invented name> contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination:

Ciclosporin: Concomitant administration of <Invented name> with ciclosporin is contraindicated because of the rosuvastatin (see section 4.3). 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). Concomitant administration did not affect plasma concentrations of ciclosporin.
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:

Fibrates and other lipid-lowering products: 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 in all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

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 1g/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. The 40 mg/10 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4).

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). 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).

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).

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

Other interactions

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.

Antacids: 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.
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.

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).

Anticoagulants, Vitamin K antagonists: Concomitant administration of ezetimibe (10 mg once daily) had no significant 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 <Invented name> is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).
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.

Erythromycin: Concomitant use of rosuvastatin and erythromycin 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.

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 women 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).

Other medicinal products: Based on data from specific interaction studies with rosuvastatin no clinically relevant interaction with 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.

Rosuvastatin/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).

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 should be adjusted. 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 ritonavir/atazanavir (3.1-fold increase).

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 ↑
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 50mg 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 rosuvastatin dosages, the table shows the most significant ratio
OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

4.6 Fertility, pregnancy and lactation

<Invented name> is contraindicated during pregnancy and breast-feeding (see section 4.3). Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy
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).

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 <Invented name>, treatment should be discontinued immediately.

Breast-feeding
Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans (see section 4.3).

Fertility
No clinical trial data are available on the effects of ezetimibe or rosuvastatin on human fertility. Ezetimibe had no effects on the fertility of male or female rats, rosuvastatin at higher doses showed testicular toxicity in monkeys and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects

Summary of safety profile
Adverse drug reactions previously reported with one of the individual components (ezetimibe or rosuvastatin) may be potential undesirable effects with <Invented name>.

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2,396 patients, 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.

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

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

MedDRA system organ class	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	rare	thrombocytopenia[2]
	not known	thrombocytopenia[5]
Immune system disorders	rare	hypersensitivity reactions including angioedema[2]
	not known	hypersensitivity (including rash, urticaria, anaphylaxis and angioedema) [5]
Endocrine disorders	common	diabetes mellitus[1, 2]
Metabolism and nutrition disorders	uncommon	decreased appetite[3]
Psychiatric disorders	not known	depression[2, 5]
Nervous system disorders	common	headache[2, 4], dizziness[2]
	uncommon	paraesthesia[4]

	very rare	polyneuropathy[2], memory loss[2]
	not known	peripheral neuropathy[2], sleep disturbances (including insomnia and nightmares)[2], dizziness[5]; paraesthesia[5]
Vascular disorders	uncommon	hot flush[3], hypertension[3]
Respiratory, thoracic and mediastinal disorders	uncommon	cough[3]
	not known	cough[2], dyspnoea[2,5]
Gastrointestinal disorders	common	constipation[2], nausea[2], abdominal pain[2,3], diarrhoea[3], flatulence[3]
	uncommon	dyspepsia[3]; gastrooesophageal reflux disease[3]; nausea[3], dry mouth[4]; gastritis[4]
	rare	pancreatitis[2]
	not known	diarrhoea[2], pancreatitis[5]; constipation[5]
Hepatobiliary disorders	rare	increased hepatic transaminases[2]
	very rare	jaundice[2], hepatitis[2]
	not known	hepatitis[5], cholelithiasis[5], cholecystitis[5]
Skin and subcutaneous tissue disorders	uncommon	pruritus[2, 4], rash[2, 4], urticaria[2,4]
	not known	Stevens Johnson syndrome[2], erythema multiforme[5], drug reaction with eosinophilia and systemic symptoms (DRESS)[2]
Musculoskeletal and connective tissue disorders	common	myalgia[2, 4]
	uncommon	arthralgia[3]; muscle spasms[3]; neck pain[3], back pain[4]; muscular weakness[4]; pain in extremity[4]
	rare	myopathy (including myositis)[2], rhabdomyolysis[2], lupus-like syndrome, muscle rupture
	very rare	arthralgia[2]
	not known	immune-mediated necrotising myopathy[2], tendon disorders, sometimes complicated by rupture[2], myalgia[5]; myopathy/rhabdomyolysis[5] (see section 4.4)

Renal and urinary disorders	very rare	haematuria[2]
Reproductive system and breast disorders	very rare	gynaecomastia[2]
Investigations	common	ALT and/or AST increased[4]
	uncommon	ALT and/or AST increased[3]; blood CPK increased[3]; gamma-glutamyltransferase increased[3]; liver function test abnormal[3]
General disorders and administration site conditions	common	asthenia[2], fatigue[3]
	uncommon	chest pain[3], pain[3], asthenia[4]; oedema peripheral[4]
	not known	oedema[2], asthenia[5]

[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 / or extensive post-marketing experience.
[3] Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with ezetimibe (N=2,396) and at a greater incidence than placebo (N=1,159).
[4] Ezetimibe co administered with a statin. Adverse reactions were observed in patients with ezetimibe co-administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9,361).
[5] Additional adverse reactions of ezetimibe, reported in post-marketing experience (with or without 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 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 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 (>5xULN), 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 reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

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)

Laboratory values
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X 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 X 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 <Invented name> in children below the age of 18 years have not yet been established (see section 5.1).

Rosuvastatin: Creatine kinase elevations >10xULN 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: 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 (≥ 3X 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 (≥ 10X 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 (≥3X 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 (≥ 10X 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

In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

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.

Rosuvastatin
Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors in combination with other lipid modifying agents, rosuvastatin and ezetimibe
ATC code: C10BA06

Mechanism of action:
Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. <Invented name> contains rosuvastatin and ezetimibe, two lipid-lowering compounds with complementary mechanisms of action. <Invented name> reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol synthesis and absorption.

Ezetimibe

Mechanism of action
Ezetimibe inhibits 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.

Clinical efficacy and safety
In controlled clinical studies, ezetimibe, either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

Primary hypercholesterolaemia
In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72% and 19%, respectively. The corresponding LDL-C reductions were significantly different (25% and 4% for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10% or 0% from baseline, respectively.

In two, double-blind, randomised placebo-controlled, 12-week studies in 1,719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. In addition, ezetimibe had no effect on the plasma concentrations of fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid-lowering agents, did not impair adrenocortical steroid hormone production.

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 2). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 2: 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	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	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.

Clinical efficacy and safety

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.

From pooled phase III data, rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/l).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given rosuvastatin from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 20-40 mg. In the overall population, the mean LDL-C reduction was 22%.

Rosuvastatin/ezetimibe combination

Combination rosuvastatin with ezetimibe 10 mg enabled greater decreases in LDL cholesterol and allowed more patients to achieve LDL cholesterol goals. This has been demonstrated in a clinical study with 469 patients, who were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks.
The combination of rosuvastatin/ezetimibe reduced LDL cholesterol significantly more than rosuvastatin (3.4mmol/l vs. 2.8 mmol/l, $p < 0.001$). Other components of the lipid/lipoprotein profile were also significantly ($p < 0.001$) improved with rosuvastatin/ezetimibe. Both treatments generally were well tolerated.
Another 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.
The study population included 440 subjects at moderately high/high risk of coronary heart disease with low-density lipoprotein (LDL) cholesterol levels higher than the National Cholesterol Education Program Adult Treatment Panel III recommendations (<100 mg/dl for moderately high/high-risk subjects without atherosclerotic vascular disease or <70 mg/dl for high-risk subjects with atherosclerotic vascular disease). 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%. Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg, and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg. Compared to rosuvastatin up-titration, ezetimibe add-on achieved significantly greater attainment of LDL cholesterol levels of <70 or <100 mg/dl, and <70 mg/dl in all subjects; produced significantly greater reductions in total cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B; and resulted in similar effects on other lipid parameters. In conclusion, compared to up-titration doubling of the rosuvastatin dose, ezetimibe 10 mg added to stable rosuvastatin 5 mg or 10 mg produced greater improvements in many lipid parameters.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with <Invented 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

There is no substantial pharmacokinetic interaction between the two components of this fixed-dose preparation.
Mean AUC and C_{max} values for total rosuvastatin and ezetimibe were not different between the monotherapy and coadministration groups of rosuvastatin 10 mg and ezetimibe 10 mg.

Absorption

Ezetimibe

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 when administered as ezetimibe 10-mg tablets. Ezetimibe can be administered with or without food.

Rosuvastatin

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

Distribution

Ezetimibe

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

Rosuvastatin

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

Ezetimibe

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.

Rosuvastatin

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

Ezetimibe

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.

Rosuvastatin

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:

Hepatic impairment

Ezetimibe
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, ezetimibe is not recommended in these patients (see section 4.4).

Rosuvastatin

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.

Renal impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73m^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.

Rosuvastatin

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.

Age and gender

Ezetimibe

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.

Rosuvastatin

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults.

Paediatric population

Ezetimibe

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.

Rosuvastatin

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.

Race

Rosuvastatin

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.

Genetic polymorphisms

Rosuvastatin

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.

5.3 Preclinical safety data

In co-administration studies with statins and ezetimibe, 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).

The co-administration of statins and ezetimibe 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.

In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential.

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.

Long-term carcinogenicity tests on ezetimibe were negative.

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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<Invented name> 10 mg/10 mg:
Core
Lactose monohydrate
Microcrystalline cellulose
Sodium laurilsulfate
Povidone 25
Colloidal silicon dioxide
Croscarmellose sodium
Magnesium Stearate

Coating layer:
Hypromellose 2910/5 (E464)
Macrogol 6000
Titanium dioxide (E171)
Talc (E553)

<Invented name> 20 mg/10 mg:
Core
Lactose monohydrate
Microcrystalline cellulose
Sodium laurilsulfate
Povidone 25
Colloidal silicon dioxide
Croscarmellose sodium
Magnesium Stearate

Coating layer:
Hypromellose 2910/5 (E464)
Macrogol 6000
Titanium dioxide (E171)
Talc (E553)
Iron oxide yellow (E172)

<Invented name> 40 mg/10 mg:
Core
Lactose monohydrate
Microcrystalline cellulose
Sodium laurilsulfate
Povidone 25
Colloidal silicon dioxide
Croscarmellose sodium
Magnesium Stearate

Coating layer:
Hypromellose 2910/5 (E464)

Macrogol 6000
Titanium dioxide (E171)
Talc (E553)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

OPA/Aluminium/PVC/Aluminium blister
Pack sizes: 28, 30, 84, 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Paper folding box

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 10 mg/10 mg film-coated tablets
<Invented name> 20 mg/10 mg film-coated tablets
<Invented name> 40 mg/10 mg film-coated tablets
rosuvastatin/ezetimibe

2. STATEMENT OF ACTIVE SUBSTANCE(S)

<Invented name> 10 mg/10 mg: Each film-coated tablet contains 10 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.
<Invented name> 20 mg/10 mg: Each film-coated tablet contains 20 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.
<Invented name> 40 mg/10 mg: Each film-coated tablet contains 40 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.

3. LIST OF EXCIPIENTS

Contains lactose.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28 tablets
30 tablets
84 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Invented name> 10 mg/10 mg
<Invented name> 20 mg/10 mg
<Invented name> 40 mg/10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 10 mg/10 mg film-coated tablets
<Invented name> 20 mg/10 mg film-coated tablets
<Invented name> 40 mg/10 mg film-coated tablets
rosuvastatin/ezetimibe

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
(MAH logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Package leaflet: Information for the patient

<Invented name> 10 mg/10 mg film-coated tablets
<Invented name> 20 mg/10 mg film-coated tablets
<Invented name> 40 mg/10 mg film-coated tablets
rosuvastatin/ezetimibe

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What <Invented name> is and what it is used for

<Invented name> contains two different active substances in one tablet. One of the active substances is rosuvastatin, belonging to the group of so called statins, the other active substance is ezetimibe. <Invented name> is a medicine used to lower levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, <Invented name> raises levels of "good" cholesterol (HDL cholesterol).

<Invented name> works to reduce your cholesterol in two ways. It reduces the cholesterol absorbed in your digestive tract, as well as the cholesterol your body makes by itself.

Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol.

It is used for patients who cannot control their cholesterol levels by diet alone. You should always stay on a cholesterol-lowering diet while taking this medicine.

<Invented name> is used in addition to your cholesterol lowering diet if you have: a raised cholesterol level in your blood due to

- primary hypercholesterolaemia [heterozygous familial and non-familial]
- a hereditary illness (homozygous familial hypercholesterolaemia) for which you have used a statin and ezetimibe as separate tablets.
    - You may also receive other treatments.

If you have heart disease, <Invented name> reduces the risk of heart attack, stroke, surgery to increase heart blood flow, or hospitalisation for chest pain.

<Invented name> does not help you lose weight.

For most people, high cholesterol does not affect the way they feel because it does not produce any symptoms. However, if it is left untreated, fatty deposits can build up in the walls of your blood vessels causing them to narrow.

Sometimes, these narrowed blood vessels can get blocked which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. If you correct your cholesterol levels, you can reduce your risk of having a heart attack, a stroke or related health problems.

You need to keep taking <Invented name>**,** even if it has got your cholesterol to the right level, because it prevents your cholesterol levels from creeping up again and causing build up of fatty deposits**.**
However, you should stop if your doctor tells you to do so, or you have become pregnant.

2. What you need to know before you take <Invented name>

Do not take <Invented name>:

- If you are allergic to rosuvastatin, ezetimibe or any of the other ingredients of this medicine (listed in section 6).
- If you currently have liver problems.
- If you are pregnant or breast-feeding. If you become pregnant while taking <Invented name> stop taking it immediately and tell your doctor. Women should avoid becoming pregnant while taking <Invented name> by using suitable contraceptive measures.
- If you have severe kidney problems.
- If you have repeated or unexplained muscle aches or pains (myopathy).
- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking <Invented name> or other rosuvastatin containing medicinal products.
- If you take a drug called ciclosporin (used, for example, after organ transplants).

If any of the above applies to you (or you are in doubt), please go back and see your doctor.

In addition, do not take <Invented name> 40 mg/10 mg (the highest dose):

- If you have moderate kidney problems (if in doubt, please ask your doctor).
- If your thyroid gland is not working properly (hypothyroidism).
- If you have had any repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines.
- If you regularly drink large amounts of alcohol.
- If you are of Asian origin (Japanese, Chinese, Filipino, Vietnamese, Korean and Indian).
- If you take other medicines called fibrates to lower your cholesterol (see section "Other medicines and <Invented name>").

If any of the above applies to you (or you are in doubt), please go back and see your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before taking <Invented name>:

- If you have problems with your kidneys.
- If you drink large amounts of alcohol or have ever had liver disease. <Invented name> may not be right for you.
- If you have had repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines. Tell your doctor immediately if you have unexplained muscle aches or pains especially if you feel unwell or have a fever. Also tell your doctor or pharmacist if you have a muscle weakness that is constant.
- If your thyroid gland is not working properly.

- If you have severe respiratory failure.
- If you take medicines used to fight the HIV infection e.g. ritonavir with lopinavir and/or atazanavir, please see "Other medicines and <Invented name>"
- If you are over 70 (as your doctor needs to choose the right start dose of <Invented name> to suit you).
- If you take other medicines called fibrates to lower your cholesterol (Please see "Other medicines and <Invented name>").
- If you are due to have an operation. You may need to stop taking <Invented name> for a short time.
- If you are of Asian origin - that is Japanese, Chinese, Filipino, Vietnamese, Korean and Indian. Your doctor needs to choose the right start dose of <Invented name> to suit you.
- If you are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and <Invented name> can lead to serious muscle problems (rhabdomyolysis).

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

In a small number of people, statins can affect the liver. This is identified by a simple test which looks for increased levels of liver enzymes in the blood. For this reason, your doctor will regularly carry out this blood test (liver function test) during treatment with <Invented name>. It is important to go to the doctor for the prescribed laboratory checks.

Serious skin reactions including Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with <Invented name> treatment. Stop using <Invented name> and seek medical attention immediately if you notice any of the symptoms described in section 4.

Children and adolescents
<Invented name> is not suitable for use in children and adolescents below 18 years of age.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor if you are taking medicine(s) with any of the following active ingredients:

- ciclosporin (often used in organ transplant patients). **Do not take <Invented name> while taking ciclosporin.**
- Medicines with an active ingredient to prevent blood clots, such as warfarin or clopidogrel, phenprocoumon, acenocoumarol or fluindione (anticoagulants).
- colestyramine (also used to lower cholesterol), because it affects the way <Invented name> works.
- fibrates such as gemfibrozil, fenofibrate (also used to lower cholesterol). **Do not take the <Invented name> 40 mg/10 mg tablets with concomitant use of a fibrate.**
- indigestion remedies containing aluminium and magnesium (used to neutralise acid in your stomach).
- erythromycin (an antibiotic).
- an oral contraceptive (the pill).
- hormone replacement therapy
- regorafenib (used to treat cancer)
- any of the following drugs used to treat viral infections, including HIV or hepatitis C infection, alone or in combination (see Warnings and precautions): ritonavir, lopinavir,

atazanavir, ombitasvir, paritaprevir, dasabuvir, velpatasvir, grazoprevir, elbasvir, glecaprevir, pibrentasvir
- fusidic acid - if you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart <Invented name>. Taking <Invented name> with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4.

You should also tell any doctor who is prescribing a new medicine for you that you are taking <Invented name>.

<Invented name> with alcohol
Do not take <Invented name> 40 mg/10 mg tablets (the highest dose), if you regularly drink large amounts of alcohol.

Pregnancy and breast-feeding
Do not take <Invented name> if you are pregnant, are trying to get pregnant or think you may be pregnant. If you get pregnant while taking <Invented name>, stop taking it immediately and tell your doctor.
Do not take <Invented name> if you are breast-feeding, because it is not known if the medicine is passed into breast milk.

Driving and using machines
<Invented name> is not expected to interfere with your ability to drive or to use machinery. However, it should be taken into account that some people may get dizzy after taking <Invented name>.

<Invented name> contains lactose (a type of sugar) and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take <Invented name>

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- Before starting <Invented name>, you should be on a diet to lower your cholesterol.
- You should keep on this cholesterol lowering diet whilst taking <Invented name>.

Your doctor will determine the appropriate tablet strength for you, depending on your current treatment and your personal risk status.

The recommended dose is one <Invented name> tablet once a day.

<Invented name> is not suitable to start a treatment. Treatment initiation or dose adjustment if necessary, should only be done by giving the active substances separately as monocomponents and after setting the appropriate doses the switch to <Invented name> of the appropriate strength is possible.

The maximum daily dose of rosuvastatin is 40 mg. It is only for patients with high cholesterol levels and a high risk of heart attacks or stroke whose cholesterol levels are not lowered enough with 20 mg.

Try to take your tablet at the same time every day to help you to remember it. You can take it with or without food. Swallow each tablet whole with a drink of water.

If your doctor has prescribed <Invented name> along with another medicine for lowering cholesterol containing the active ingredient colestyramine or any other medicine containing bile acid sequestrant, you should take <Invented name> at least 2 hours before or 4 hours after taking the bile acid sequestrant.

Regular cholesterol checks
It is important to go back to your doctor for regular cholesterol checks to make sure your cholesterol has reached and is staying at the correct level. Your doctor may decide to increase your dose so that you are taking the amount of the medicine that is right for you.

If you take more <Invented name> than you should
Please contact your doctor or pharmacist.

If you forget to take <Invented name>
Do not take a double dose to make up for a forgotten tablet.

If you stop taking <Invented name>
Talk to your doctor or pharmacist because your cholesterol may rise again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking <Invented name> and seek medical help immediately if you experience any of the following symptoms:

- any unexplained muscle pain, tenderness, or weakness which go on for longer than expected. This is because, muscle problems, including muscle breakdown resulting in kidney damage, can be serious and may become a potentially life-threatening condition (rhabdomyolysis). This is rare (may affect up to 1 in 1,000 people).

- severe allergic reaction (angioedema) - signs include swelling of the face, lips, tongue and/or throat, difficulty in swallowing and breathing and a severe itching of the skin (with raised lumps). This is rare (may affect up to 1 in 1,000 people).

- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).

- widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

- lupus-like disease syndrome (including rash, joint disorders and effects on blood cells.

- muscle rupture.

Other known side effects:

Common (may affect up to 1 in 10 people):
Diarrhoea; flatulence; feeling tired; elevations in some laboratory blood tests of liver function (transaminases); headache; stomach pain; constipation; feeling sick; muscle pain; feeling weak;

dizziness; an increase in the amount of protein in the urine - this usually returns to normal on its own without having to stop taking <Invented name> (only rosuvastatin 40 mg); diabetes - this is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

Uncommon (may affect up to 1 in 100 people):
Elevations in some laboratory blood tests of muscle (CK) function; cough; indigestion; heartburn; joint pain; muscle spasms; neck pain; decreased appetite; pain; chest pain; hot flush; high blood pressure; tingling sensation; dry mouth; inflammation of the stomach; itching; rash; hives or other skin reactions; back pain; muscle weakness; pain in arms and legs; swelling, especially in the hands and feet; an increase in the amount of protein in the urine - this usually returns to normal on its own without having to stop taking <Invented name> (only rosuvastatin 10 mg and 20 mg).

Rare (may affect up to 1 in 1,000 people):
Reduction in blood cell counts, which may cause bruising/bleeding (thrombocytopenia); a severe stomach pain (inflamed pancreas).

Very rare (may affect up to 1 in 10,000 people):
Jaundice (yellowing of the skin and eyes); hepatitis (an inflamed liver); traces of blood in your urine; damage to the nerves of your legs and arms (such as numbness); memory loss; gynecomastia (breast enlargement in men).

Not known (frequency cannot be estimated from the available data):
shortness of breath; swelling; sleep disturbances including sleeplessness and nightmares; sexual difficulties; depression; breathing problems including persistent cough and/or shortness of breath or fever; tendon injury; muscle weakness that is constant; raised red rash, sometimes with target shaped lesions (erythema multiforme); muscle tenderness; gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <Invented name>

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What <Invented name> contains
- The active substances are rosuvastatin and ezetimibe. Each tablet contains 10 mg/ 20 mg/ 40 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg of ezetimibe.
- The other ingredients are:

- Core: lactose monohydrate, microcrystalline cellulose, sodium laurilsulfate, povidone 25, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate.
- Coating layer: hypromellose 2910/5 (E464), macrogol 6000, titanium dioxide (E171), talc (E553).

<Invented name> 20 mg/10 mg also contains iron oxide yellow (E172).
<Invented name> 40 mg/10 mg also contains iron oxide red (E172).

What <Invented name> looks like and contents of the pack
<Invented name> 10 mg/10 mg are white to off-white oblong film-coated tablets (tablets).
<Invented name> 20 mg/10 mg are yellow to light yellow oblong film-coated tablets (tablets).
<Invented name> 40 mg/10 mg are pink oblong film-coated tablets (tablets).

Pack sizes: 28, 30, 84, 90 film-coated tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

Country	Invented Name
CZ	Zenon
SK	Zenon 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg
BG	Зенон 10 мг / 10 мг, 20 мг /10 мг, 40 мг /10 мг
PL	Suvezen

This leaflet was last revised in <MM/YYYY>

[To be completed nationally]