

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rosuvastatine/Fenofibraat Viatris 10 mg/160 mg filmomhulde tabletten
Rosuvastatine/Fenofibraat Viatris 20 mg/160 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium) and 160 mg of fenofibrate.
Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium) and 160 mg of fenofibrate.

Excipient(s) with known effect

Each tablet contains 164.54 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

10 mg/160 mg: Film-coated tablet.

Yellow, oval shaped film coated tablets (approximately 17.2 mm x 8.7 mm), debossed with "F1" on one side and plain on other side.

20 mg/160 mg: Film-coated tablet.

Yellow, oval shaped film coated tablets (approximately 19.2 mm x 9.5 mm), debossed with "F2" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Invented name> is indicated as adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for treatment of mixed dyslipidaemia as substitution therapy in adult patients at high cardiovascular risk 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

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

The recommended daily dose is one film-coated tablet of the given strength, with food.

<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.

Paediatric population

The safety and efficacy of rosuvastatin + fenofibrate in children below the age of 18 years has not yet been established. Currently available data are described in section 4.4, 4.5, 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. The fixed dose 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

The fixed dose combination is not suitable for initial therapy. The use of <Invented name> in patients with moderate (creatinine clearance <60 ml/min) to severe renal impairment (creatinine clearance <30 ml/min) is contraindicated for all doses (see sections 4.3, 4.4 and 5.2).

Hepatic impairment

<Invented name> has not been studied in patients with hepatic impairment and is therefore not recommended in this population. The fixed dose combination is not suitable for initial therapy. <Invented name> is contraindicated in patients with active liver disease (see section 4.3).

Ethnicity

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

Genetic polymorphisms

Specific types of genetic polymorphisms are known to 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.

The fixed dose combination is not suitable for initial therapy. Monocomponent products should be used to start the treatment or to modify the dose.

Dosage in patients with predisposing factors to myopathy

The recommended start dose is 5 mg/160 mg in patients with predisposing factors to myopathy (see section 4.4). The fixed dose combination is not suitable for initial therapy. Monocomponent products 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 rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin, ticagrelor 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 <Invented name> dosing adjustments should be carefully considered (see section 4.5).

Method of administration

For oral use.

<Invented name> should be taken each day once at the same time of the day during a meal with a drink of water..

4.3 Contraindications

<Invented name> is contraindicated:

- in patients with hypersensitivity to the active substances (rosuvastatin, fenofibrate) or to any of the excipients listed in section 6.1.

- in patients with known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- in patients with active liver disease including biliary cirrhosis and unexplained, persistent elevations of serum transaminases exceeding 3x the upper limit of normal (ULN) (see section 4.4).
- in patients with known gallbladder disease
- in patients with chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia
- during pregnancy, breast-feeding and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6).
- in patients with moderate to severe renal impairment (creatinine clearance <60 ml/min) (see section 5.2).
- in patients with personal history of myopathy and/or rhabdomyolysis with statins and/or fibrates or confirmed creatine phosphokinase elevation above 5 times the upper limit of normal (ULN) under previous statin treatment (see section 4.4)
- in patients receiving concomitant ciclosporin (see section 4.5)
- in patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

(see sections 4.4, 4.5 and 5.2)

4.4 Special warnings and precautions for use

Renal Effects

<Invented name> is contraindicated in patients with moderate to severe renal impairment (creatinine clearance <60 ml/min) <Invented name> should be used with caution in patients with mild renal insufficiency whose estimated glomerular filtration rate is 60 to 89 mL/min/1.73 m² (see section 4.2).

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.

Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment. During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 µmol/L with co-administered fenofibrate and simvastatin versus 4.4% with statin monotherapy. 0.3% of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 µmol/L.

Treatment should be interrupted when creatinine level is 50% above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter.

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 and in fenofibrate-treated patients.

If myopathy is suspected based on muscle symptoms or is confirmed by a creatine kinase (CK) level > 5 times the ULN, fenofibrate, 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 should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

The risk of muscle toxicity may be increased if fenofibrate is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in case of pre-existing muscular disease.

Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use.

Creatine Kinase Measurement

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

Before Treatment

<Invented name> 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
- hypoalbuminaemia
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)

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 ($>5\times\text{ULN}$) 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 ($>5\times\text{ULN}$) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are $\leq 5\times\text{ULN}$). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.

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

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 fibrin acid derivatives including gemfibrozil, ciclosporin, 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 <Invented name> and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of <Invented name> with niacin should be carefully weighed against the potential risks of such combinations.

<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).

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> 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 <Invented name>,

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

If the patient has developed a serious reaction such as SJS or DRESS with the use of rosuvastatin, treatment with rosuvastatin must not be restarted in this patient at any time.

Liver Effects

Increases in transaminase levels have been reported in some patients treated with rosuvastatin or fenofibrate. In the majority of cases these elevations were transient, minor and asymptomatic without the need for treatment discontinuation. As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Thereafter liver function tests are carried out periodically. <Invented name> should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, <Invented name> therapy should be discontinued.

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins and with fenofibrate, 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, <Invented name> 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/m², 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.

Veno thromboembolic events

In the FIELD study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p=0.022) and a statistically non-significant increase in deep vein thrombosis (placebo 1.0% 48/4900 patients) versus fenofibrate 1.4% (67/4895); p=0.074. The increased risk of venous thrombotic events may be related to the increased homocysteine level, a risk factor for thrombosis and other unidentified factors. The clinical significance of this is not clear. Therefore, caution should be exercised in patients with a history of pulmonary embolism.

Secondary causes of hyperlipidaemia

Secondary causes of hyperlipidaemia, such as pharmacological treatment (like amiodarone, ciclosporine, estrogen, progestins, glucocorticoids, isotretinoin, thiazide diuretics) or uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, alcoholism, should be adequately addressed or treated, before <Invented name> therapy is considered and patients should be placed on a standard cholesterol and triglycerides-lowering diet which should be continued during treatment.

Ciclosporin: See section 4.3 and 4.5.

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). Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of <Invented name> and fusidic acid should only be considered on a case-by-case basis and under close medical supervision.

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 <Invented 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. Concomitant use with certain protease inhibitors is not recommended unless the dose of <Invented name> is adjusted (see sections 4.2 and 4.5).

Ethnicity

Rosuvastatin pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2 and 5.2).

Paediatric Population

The safety and efficacy of fenofibrate+rosuvastatin in children below the age of 18 years has not yet been established, therefore its use is not recommended in this age group.

Lactose Intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

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

Rosuvastatin

Effect of co-administered medicinal products on rosuvastatin

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of <Invented 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 1).

Ciclosporin: During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1).

<Invented name> is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.

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

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

Based on data from specific interaction studies no clinically relevant pharmacokinetic interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur.

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 <Invented name> and ezetimibe cannot be ruled out (see section 4.4).

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

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

Ticagrelor:

Ticagrelor inhibits the transporter BCRP, causing a 2.6-fold increase in rosuvastatin AUC, which may result in increased risk of myopathy. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations. In some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis..

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

Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of Rosuvastatin should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of rosuvastatin 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 the medicinal product is observed to increase the AUC of rosuvastatin less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20mg.

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.

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 drug 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	10mg 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	5mg, 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 ↑
Roxadustat 200 mg q.d.d.	10 mg, single dose	2.9-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Momelotinib 200 mg OD, 6 days	10 mg, single dose	2.7-fold ↑
Ticagrelor 90 mg BID, 2 days	10 mg, single dose	2.6-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Teriflunomide, Leflunomide	Not Available	2.5-fold ↑
Vadadustat 600 mg d.d., 8 days	20 mg, single dose	2.5-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 ↑
Capmatinib 400mg BID	10 mg, single dose	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Fostamatinib 100 mg twice daily	20 mg, single dose	2.0-fold ↑
Tafamidis 61 mg bdd on Days 1 & 2, followed by dd on Days 3 to 9	10 mg, single dose	2.0-fold ↑
Feboxustat 120mg OD	10 mg, single dose	1.9-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑

Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
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 ↑**
Decrease in AUC of rosuvastatin		
Interacting drug 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 relevant effect on the AUC ratio of rosuvastatin at coadministration:

Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fenofibric acid choline salt 135 mg (delayed release) 10 days OD dosing; Fluconazole 200mg 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.

Effect of rosuvastatin on co-administered medicinal products

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.

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.

Other medicinal products:

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

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. The risk of

myopathy, including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Paediatric population

Interaction studies have only been performed in adults.

Fenofibrate

Effect of fenofibrate on co-administered medicinal products

Oral anticoagulants: Fenofibrate enhances oral anticoagulant effect and may increase the risk of bleeding. It is recommended that the dose of anticoagulants is reduced by one third at the start of <Invented name> therapy and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

Ciclosporin: Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and ciclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMG-CoA reductase inhibitors and other fibrates:

Based on data from specific interaction studies no clinically relevant pharmacokinetic interaction between rosuvastatin and fenofibrate is expected, however a pharmacodynamic interaction may occur. HMG-CoA reductase inhibitors, gemfibrozil and other fibrates increase the risk of myopathy when given concomitantly with fenofibrate, probably because they can produce myopathy when given alone.

Glitazones:

Some cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL-cholesterol if one of these components is added to the other and stopping of either therapy if HDL-cholesterol is too low.

Cytochrome P450 enzymes: In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Patients co-administered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

4.6 Fertility, pregnancy and lactation

<Invented name> is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

Rosuvastatin

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

Fenofibrate

There are no adequate data from the use of fenofibrate in pregnant women. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3 Preclinical safety data). The potential risk for humans is unknown. Animal studies have not demonstrated any teratogenic effects.

Breast-feeding

Limited data from published reports indicate that rosuvastatin is present in human breast milk. It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. Rosuvastatin and fenofibrate are excreted in the milk of rats. A risk to the suckling child cannot be excluded. Therefore <Invented name> is contraindicated during breast-feeding (see section 4.3).

Fertility

There are no clinical data on fertility from the use of <Invented name>. Rosuvastatin at higher doses showed testicular toxicity in monkeys and dogs. Reversible effects on fertility have been observed in animals with fenofibrate (see section 5.3).

4.7 Effects on ability to drive and use machines

<Invented name> has no or negligible influence on the ability to drive and use machines. Studies to determine the effect of rosuvastatin and/or fenofibrate 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

Tabulated list of adverse reactions

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin and fenofibrate. As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

The frequencies of adverse reactions are ranked according to the following convention: Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); Not known (cannot be estimated from the available data).

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

MedDRA System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia ² Haemoglobin decreased ³ White blood cell count decreased ³		
Immune system disorders			Hypersensitivity reactions ^{2, 3} including angioedema ²		
Endocrine disorders	Diabetes mellitus ^{1,2}				
Psychiatric disorders					Depression ²

Nervous system disorders	Headache ^{2, 7} Dizziness ²			Polyneuropathy ² Memory loss ²	Peripheral neuropathy ² Sleep disturbances (including insomnia and nightmares) ² Myasthenia gravis ²
Eye disorders					Ocular myasthenia ²
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis) ⁴			
Respiratory, thoracic and mediastinal disorders					Cough ² , Dyspnoea ² Interstitial lung disease ⁴
Gastrointestinal disorders	Constipation ² Nausea ^{2,3} Abdominal Pain ^{2,3} Diarrhoea ^{3, 7} Flatulence ³ Vomiting ³	Pancreatitis ^{5, 7}			
Hepatobiliary disorders	Increased hepatic transaminases ^{3, 7}	Cholelithiasis ³	Hepatitis ^{3, 7}	Jaundice ^{2, 7}	Complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic) ⁴
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g. pruritus, rash, urticaria) ^{2,3}	Alopecia Photosensitivity reactions ³		Severe cutaneous reaction (e.g. Erythema multiforme, toxic epidermal necrolysis Stevens- Johnson syndrome ^{2, 4}) Drug reaction with eosinophilia and systemic symptoms (DRESS) ²
Musculoskeletal and connective tissue disorders	Myalgia ^{2, 7}	Muscle disorders (e.g. myositis ⁷ , muscular spasms and weakness) ³	Rhabdomyolysis ^{2, 4, 7} , Lupus-like syndrome ² Muscle rupture ²	Arthralgia ²	Tendon disorders, sometimes complicated by rupture ² , Immune-mediated necrotising myopathy ² ,
Renal and urinary disorders				Haematuria ²	

Reproductive system and breast disorders		Sexual dysfunction ³		Gynaecomastia ²	
General disorders and administration site conditions	Asthenia ²				Oedema ² Fatigue ⁴
Investigations	Blood homocysteine level increased ⁶	Blood creatinine increased ³	Blood urea increased ³		

¹ Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m², raised triglycerides, history of hypertension).

² Adverse reaction profile for rosuvastatin based on data from clinical studies and extensive post-marketing experience.

³ Adverse reaction profile for fenofibrate based on data from clinical studies.

⁴ Adverse reaction profile for fenofibrate based on extensive post-marketing experience.

⁵ In the FIELD-study, a randomized placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; $p = 0.031$). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; $p = 0.022$) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0% [48/4,900 patients] versus fenofibrate 1.4% [67/4,895 patients]; $p = 0.074$).

⁶ In the FIELD-study, the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 μ mol/L and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance of this is not clear.

⁷ Diarrhea frequency for rosuvastatin=Not known, Pancreatitis frequency for rosuvastatin=rare, Increased hepatic transaminases frequency for rosuvastatin=rare, Hepatitis frequency for rosuvastatin=very rare, Myopathy including myositis frequency for rosuvastatin=rare, Rhabdomyolysis frequency for fenofibrate=Not known, Headache frequency for Fenofibrate = Uncommon, Jaundice frequency for Fenofibrate = Not known, Myalgia frequency for Fenofibrate = Uncommon

Based on data from clinical studies with the combination of rosuvastatin and fenofibrate, the most frequently reported adverse events are increased hepatic transaminases and gastrointestinal disorders (nausea and vomiting).

A pharmacodynamic interaction between rosuvastatin and fenofibrate, in terms of adverse effects, cannot be ruled out (see section 4.5).

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. 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 ($>5 \times \text{ULN}$), treatment should be discontinued (see section 4.4).

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

The following adverse events have been reported with some statins:

Sexual dysfunction

Exceptional cases of interstitial lung disease, especially with long-term therapy (see section 4.4)

Reporting of suspected adverse reactions:

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

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit, fenofibrate cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents; Combinations of various lipid modifying agents.
ATC code: C10BA09

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, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 3). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 3. 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.

Fenofibrate

Mechanism of action

Through activation of PPAR α , fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPAR α also induces an increase in the synthesis of apoproteins AI and AII.

Pharmacodynamic effects

The above stated effects of fenofibrate on lipoproteins lead to a reduction in very low- and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII. Fenofibrate increases the LDL clearance and reduces small dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

During clinical trials with fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%. In hypercholesterolaemic patients LDL cholesterol levels are reduced by 20 to 35%.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08, $p = 0.32$; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C (≤ 34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥ 204 mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, $p = 0.03$; absolute risk reduction: 4.95%). Another prespecified subgroup analysis identified a statistically significant treatment-by-gender interaction ($p = 0.01$) indicating a possible treatment benefit of combination therapy in men ($p=0.037$) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy ($p=0.069$). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.

Rosuvastatin-fenofibrate combination

Clinical efficacy and safety

A 34-week (6-weeks of diet and lifestyle changes and 24 weeks of drug treatment followed by a 4-week safety follow-up), randomised, open-label, multi-center study compared rosuvastatin 10 mg–fenofibrate 160 mg combination therapy with rosuvastatin 10 mg monotherapy in 180 high-risk patients with mixed hyperlipidemia. After 24 weeks of treatment, rosuvastatin–fenofibrate combination compared to rosuvastatin monotherapy resulted in a significantly greater reduction in TG (48.4 and 32.4%, respectively, $p=0.001$) and higher elevations of HDL-C (21.7 and 8.8%, respectively, $p<0.001$). Both treatments were similar with regard to % changes in TC, LDL-C, and non-HDL-C.

The effects of rosuvastatin and fenofibrate alone or in combination in T2DM patients with combined hyperlipidaemia were evaluated in a randomised, parallel group, multinational, multicentre study with 2 periods. Two hundred and sixteen patients with TC ≥ 200 mg/dL (5.17 mmol/l) and TG ≥ 200 mg/dL (2.26 mmol/l) and < 800 mg/dL (9.04 mmol/l) were randomised to one of two placebo groups, rosuvastatin 5mg or rosuvastatin 10 mg for 6 weeks (fixed-dose double-blind phase)

During the subsequent 18-week open-label dose-titration phase, one placebo group received titrated rosuvastatin 10, 20 and 40 mg (placebo/rosuvastatin, $n=51$); one placebo group received titrated fenofibrate 67 mg once, twice and three times daily (placebo/fenofibrate, $n=49$); and patients receiving 5 or 10mg rosuvastatin received titrated fenofibrate as above (rosuvastatin 5 mg/fenofibrate, $n=60$ and rosuvastatin 10 mg/fenofibrate groups, $n=53$). Doses were increased at 6-week intervals if LDL-C remained >50 mg/dl (>1.3 mmol/l).

TG were reduced by 40.9% in the rosuvastatin 5mg plus fenofibrate group and by 47.1% in the rosuvastatin 10 mg plus fenofibrate group, with the latter reduction being significant, compared with 30.3% TG reduction in the placebo/rosuvastatin group ($P = 0.001$).

The 46.7% LDL-C reduction in the placebo/rosuvastatin group was significantly greater than the 34.1% reduction in the rosuvastatin 5mg plus fenofibrate group ($p < 0.001$) but not compared to the 42.2% reduction

in the rosuvastatin 10 mg plus fenofibrate group ($p = 0.237$). No significant differences were observed between the placebo/rosuvastatin group and either of the rosuvastatin plus fenofibrate groups on TC, HDL-C or Apo B

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 with elevated triglycerides (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Rosuvastatin and fenofibrate combination therapy

Bioequivalence was shown between <Invented name> 20mg/160mg and the simultaneous administration of 20 mg Crestor® film-coated tablets and 160 mg Secalip supra® film-coated tablets, after a single dose administration to healthy volunteers under fed conditions.

Based on data from specific interaction studies no clinically relevant pharmacokinetic interaction of rosuvastatin with fenofibrate is expected.

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.

Metabolism: 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.

Excretion: 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 gender: 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).

Ethnicity: 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 impairment had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic 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 Rosuvastatin is recommended.

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 or 6 to 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.

Fenofibrate

Absorption: Maximum plasma concentrations (C_{max}) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. The absorption of fenofibrate is increased when administered with food.

Distribution: Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Metabolism: After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

Excretion:

The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.

Pharmacokinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibric acid is not eliminated by haemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

5.3 Preclinical safety data

No preclinical studies have been performed with the fixed dose combination rosuvastatin/fenofibrate.

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.

Fenofibrate

In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I -slow oxidative- myofibres) and cardiac degeneration, anemia and decreased body weight were seen. No skeletal toxicity was noted at doses up to 30 mg/kg (approximately 17-time the exposure at the human maximum recommended dose (MRHD). No sign of cardiomyotoxicity were noted at an exposure about 3 times the exposure at MRHD. Reversible ulcers and erosions in the gastro-intestinal tract occurred in dogs treated for 3 months. No gastro-intestinal lesions were noted in that study at an exposure approximately 5 times the exposure at the MRHD.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses.

Reversible hypospermia and testicular vacuolation and immaturity of the ovaries were observed in a repeat-dose toxicity study with fenofibric acid in young dogs. However, no effects on fertility were detected in non-clinical reproductive toxicity studies conducted with fenofibrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rosuvastatin layer

Starch, pregelatinised
Microcrystalline Cellulose (E460)
Meglumine
Calcium hydrogen phosphate dihydrate (E341)
Crospovidone (E1202)
Silica, colloidal anhydrous (E551)
Sodium stearyl fumarate

Fenofibrate layer

Mannitol (E421)
Lactose monohydrate
Starch, pregelatinized
Crospovidone (E1202)
Sodium stearyl fumarate
Yellow iron oxide (E172)
Povidone (K-30) (E1201)
Silica, colloidal anhydrous (E551)
Sodium laurilsulfate (E487)

Film coating

Hypromellose (E463)
Titanium dioxide (E 171)
Macrogol 4000 (E1521)
Yellow iron oxide (E 172)

6.1 Incompatibilities

Not applicable.

6.2 Shelf life

30 months (10 mg/160 mg strength)

36 months (20 mg/ 160 mg strength)

6.3 Special precautions for storage

This medicinal product does not require any special storage conditions

6.4 Nature and contents of container

OPA/AL/PVC-Al blisters in outer carton

Packs of 30 and 90 film-coated tablets.

Not all pack sizes may be marketed.

6.5 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Viartis Healthcare B.V.

Krijgsman 20

1186 DM Amstelveen

8. MARKETING AUTHORISATION NUMBER(S)

RVG 133381- Rosuvastatine/Fenofibraat Viartis 10 mg/160 mg filmomhulde tabletten

RVG 133382 - Rosuvastatine/Fenofibraat Viartis 20 mg/160 mg filmomhulde tabletten

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 13 mei 2026

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubrieken 1 en 7: 7 augustus 2026