For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ROSTAR F

1. Generic Name

Rosuvastatin and Fenofibrate Tablets I.P.

2. Qualitative and quantitative composition

Each film coated tablet contains:

Rosuvastatin Calcium I.P.

Equivalent to Rosuvastatin. ……10 mg

Fenofibrate I.P. (Micronised). ……160 mg

Excipients……. q.s.

Colours: Tartrazine Lake and Titanium Dioxide I.P.

Other ingredients are :. Lactose, Croscarmellose Sodium, Calcium Carbonate, Sodium Lauryl Sulphate, PVP K30, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Colorezy 17F580012 and Tartrazine Lake.

3. Dosage Form and Strength

Dosage Form: Film Coated Tablet

Strength: Rosuvastatin. 10 mg and Fenofibrate 160 mg

4. Clinical particulars

4.1 Therapeutic Indication

For the treatment of combined hyperlipidemia in patients with normal hepatic and renal function

4.2 Posology and Method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines. ROSTAR F may be given at any time of day, with or without food.

Method of Administration: Tablet should be swallowed whole during a meal.

4.3 Contraindications

It is contraindicated:

- In patients with hypersensitivity to rosuvastatin, fenofibrate or to any of the excipients.
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN). Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality.
- Known gallbladder disease

- Severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m^2). In patients with severe renal impairment (creatinine clearance <30 ml/min).
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- In patients with myopathy.
- In patients receiving concomitant ciclosporin.
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures. The 40 mg dose is contraindicated in patients with predisposing factors for myopathy/rhabdomyolysis.
- 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 may occur
- Asian patients
- Concomitant use of fibrates.

4.4 Special Warnings and Precautions for Use

Rosuvastatin

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. 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.

Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamics interaction cannot be excluded and caution should be exercised with their combined use. 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.

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

Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

• Renal impairment

• Hypothyroidism

• Personal or family history of hereditary muscular disorders

• Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate

• Alcohol abuse

• Age >70 years

• Situations where an increase in plasma levels may occur

• 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 ≤5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including Rosuvastatin. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In reported clinical trials, there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and 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 is contraindicated with concomitant use of a fibrate.

Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. Patients should be advised to seek

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

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

Liver Effects

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

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. 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 hypercholesterolemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians.

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.

Lactose Intolerance

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

Interstitial Lung Disease

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

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins

and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in Rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/l.

Paediatric Population

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age taking Rosuvastatin is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected.

In a clinical trial of children and adolescents receiving Rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults.

Fenofibrate

Secondary causes of hyperlipidemia:

Secondary cause of hypercholesterolemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease or alcoholism should be adequately treated before Fenofibrate therapy is considered. Secondary cause of hypercholesterolemia related to pharmacological treatment can be seen with diuretics, βblocking agents, estrogens, progestogens, combined oral contraceptives, immunosuppressive agents and protease inhibitors. In these cases, it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by these therapeutic agents).

Liver function:

As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and thereafter periodically. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occurs (e.g. jaundice, pruritus) and diagnosis is confirmed by laboratory testing, Fenofibrate therapy should be discontinued.

Pancreas:

Pancreatitis has been reported in patients taking fenofibrate

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.

Muscle:

Muscle toxicity, including rare cases of rhabdomyolysis, with or without renal failure, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in case of hypoalbuminaemia and previous renal insufficiency. Patients with predisposing factors for myopathy and/or rhabdomyolysis, including age above 70 years, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of developing

rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the upper normal range). In such cases treatment with fenofibrate should be stopped.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in case of pre-existing muscular disease. Consequently, the coprescription of fenofibrate with HMG-CoA reductase inhibitor or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and with a close monitoring of potential muscle toxicity.

Renal function:

Fenofibrate 160 mg is contraindicated in severe renal impairment.

Fenofibrate 160 mg should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated glomerular filtration rate is 30 to 59 mL/min/1.73 m^2.

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.

4.5 Drugs Interactions

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 Rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

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). Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin. 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.

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

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamics interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

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 pharmacodynamics interaction, in terms of adverse effects, between Rosuvastatin and ezetimibe cannot be ruled out.

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

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

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

Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer Rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of Rosuvastatin should be adjusted. Start with a 5 mg once daily dose of Rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. 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 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 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Iitraconazole 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 "↔", and 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		

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 an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant Rosuvastatin and HRT, 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 pharmacodynamics 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.

Paediatric population: Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

Fenofibrate

Oral anticoagulants:

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

Cyclosporin:

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. 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: The risk of serious muscle toxicity is increased if a fibrate is used concomitantly with HMGCoA reductase inhibitors or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity.

Glitziness:

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 Coadministered 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 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Rosuvastatin

Fertility, pregnancy and lactation

Rosuvastatin is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures.

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. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

Fenofibrate

Pregnancy: There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity. The potential risk for humans is unknown. Therefore, Fenofibrate should only be used during pregnancy after a careful benefit/risk assessment.

Lactation: It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore, fenofibrate should not be used during breastfeeding.

Fertility: Reversible effects on fertility have been observed in animals. There are no clinical data on fertility from the use of Fenofibrate.

4.7 Effects on Ability to Drive and Use Machines

Studies to determine the effect of ROSTAR F on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamics properties, Rosuvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable Effects

Reported adverse events of ROSTAR F

The adverse reactions seen are generally mild and transient.

The most commonly reported ADRs during therapy are digestive, gastric or intestinal disorders.

Tabulated list of adverse reactions

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

The frequencies of adverse reactions are ranked according to the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

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

System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia Haemoglobin decreased White blood cell count decreased		

Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus[1]				
Psychiatric disorders					Depression
Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*			
Respiratory, thoracic and mediastinal disorders					Cough Dyspnoea Interstitial lung disease
Gastro-intestinal disorders	Constipation- Nausea Abdominal pain Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)	Pancreatitis*			Diarrhoea

Hepatobiliary disorders	Transaminases increased (see section 4.4)	Cholelithiasis (see section 4.4)	Increased hepatic transaminases Hepatitis	Jaundice Hepatitis	jaundice, complications of cholelithiasis a (e.g. cholecystitis, cholangitis, biliary colic)
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g. rash, pruritus, urticaria)	Alopecia Photosensitivity reactions		Stevens-Johnson syndrome Severe cutaneous reactions[a] (e.g. erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis)
Musculo-skeletal and connective tissue disorders	Myalgia	Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness)	Myopathy (including myositis) Rhabdomyolysis Lupus-like syndrome Muscle rupture	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathyRhabdomyolysis[a] Rhabdomyolysis[a]
Renal and urinary disorders				Haematuria	
Reproductive system and breast disorders		Sexual dysfunction		Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema Fatigue[a]
[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).					

Rosuvastatin

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 ROSTAR F. 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 in reported 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 (>5xULN), treatment should be discontinued.

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.

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.

Paediatric population: Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week of reported 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.

Fenofibrate

* In the reported 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).

** In the reported FIELD-study, the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 µmol/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.

4.9 Overdose

Only anecdotal cases of fenofibrate over dosage have been received. In the majority of cases no overdose symptoms were reported.

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

5. Pharmacological properties

5.1 Mechanism of Action

Rosuvastatin

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.

Fenofibrate

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα). Through activation of PPARα, fenofibrate increases the lipolysis and elimination of atherogenic triglyceride rich particles from plasma by activating lipoprotein lipase and reducing production of Apo protein CIII. Activation of PPARα also induces an increase in the synthesis of Apo proteins AI and AII.

The above stated effects of fenofibrate on lipoproteins lead to a reduction in very low and low density fractions (VLDL and LDL) containing Apo protein B and an increase in the high density lipoprotein fraction (HDL) containing Apo protein AI and AII.

5.2 Pharmacodynamics Properties

Pharmacotherapeutic group: HMG CoA reductase inhibitors in combination with other lipid modifying agents

ATC code: C10BA09

Rosuvastatin

Pharmacodynamics 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 Apo-I (see Table 4). 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 4 Dose response in patients with primary hypercholesterolemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	Non HDL-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 hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolemia.

From pooled phase III data, Rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolemia (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 hypercholesterolemia 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%. Thirty-three percent (33%) of patients reached EAS guidelines for LDL-C levels (<3 mmol/L).

In a force-titration, open label trial, 42 patients (including 8 paediatric patients) with homozygous familial hypercholesterolemia were evaluated for their response to Rosuvastatin 20 – 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Rosuvastatin has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin.

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/L (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Rosuvastatin 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolemia at high cardiovascular risk.

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of

major atherosclerotic cardiovascular disease events was assessed in 17,802 men (≥50 years) and women (≥60 years).

Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.

LDL-cholesterol concentration was reduced by 45% (p<0.001) in the rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score >20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high-risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥5% (extrapolated to include subjects above 65 yrs.) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high-risk group (p=0.076).

In the JUPITER trial, there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).

Paediatric population

In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n=176, 97 males and 79 female) followed by a 40-week (n=173, 96 males and 77 female), open-label, rosuvastatin dose-titration phase, patients 10 to 17 years of age (Tanner stage II-V, females at least 1-year post-menarche) with heterozygous familial hypercholesterolemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 to 13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/L.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. This trial (n=176) was not suited for comparison of rare adverse drug events.

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolemia aged 6 to 17 years (88 males and 110 females, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was -43% (Baseline: 236 mg/dL, Month 24: 133 mg/dL). For each

age group, the LS mean percent reductions from baseline values in LDL-C were -43% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), -45% (Baseline: 234 mg/dL, Month 24: 124 mg/dL) and -35% (Baseline: 241 mg/dL, Month 24: 153 mg/dL) in the 6 to <10, 10 to <14, and 14 to <18 age groups, respectively.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, and ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment.

Rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multi-centre, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolaemia. The study included an active 4-week dietary lead-in phase during which patients were treated with rosuvastatin 10 mg, a cross-over phase that consisted of a 6-week treatment period with rosuvastatin 20 mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy continued the treatment throughout the entire study.

A statistically significant (p=0.005) reduction in LDL-C (22.3%, 85.4 mg/dL or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003) and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. The reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20 mg following 6 weeks of treatment with placebo was maintained over 12 weeks of continuous therapy. One patient had a further reduction in LDL-C (8.0%), Total-C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40 mg after up-titration.

During an extended open-label treatment in 9 of these patients with 20 mg rosuvastatin for up to 90 weeks, the LDL-C reduction was maintained in the range of -12.1% to -21.3%.

In the 7 evaluable children and adolescent patients (aged from 8 to 17 years) from the force-titration open label study with homozygous familial hypercholesterolaemia (see above), the percent reduction in LDL-C (21.0%), Total-C (19.2%) and non-HDL-C (21.0%) from baseline following 6 weeks of treatment with rosuvastatin 20 mg was consistent with that observed in the aforementioned study in children and adolescents with homozygous familial hypercholesterolaemia.

The European Medicines Agency has waived the obligation to submit the results of studies with rosuvastatin in all subsets of the paediatric population in the treatment of homozygous familial hypercholesterolaemia, primary combined (mixed) dyslipidaemia and in the prevention of cardiovascular events.

Fenofibrate

Serum Lipid Reducing Agents / Cholesterol and Triglycerides Reducers / Fibrates.

In addition, through modulation of the synthesis and the catabolism of VLDL fractions 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 hypercholesterolaemia patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, all of which are markers of atherogenic risk.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all-cause mortality in the primary or secondary prevention of cardiovascular disease.

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 nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.791.08, p = 0.32; absolute risk reduction: 0.74%). In the prespecified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDLC (≤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 0.490.97, p = 0.03; absolute risk reduction: 4.95%). Another pre-specified 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 dyslipidaemia women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp (a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

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.

Fenofibrate has been shown to possess an antiaggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.

5.3 Pharmacokinetic Properties

Rosuvastatin

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

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

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 sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial hypercholesterolemia appears to be similar to or lower than that in adult patients with dyslipidaemia (see "Paediatric population" below).

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and Cmax. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

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

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

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1

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

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 and excretion:

After oral administration, fenofibrate is rapidly hydrolysed by esterase 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.

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.

Kinetic 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 17time the exposure at the human maximum recommended dose (MRHD). No sign of cardio myotoxicity were noted at an exposure about 3 times the exposure at MRHD. Reversible ulcers and erosions in the gastrointestinal tract occurred in dogs treated for 3 months. No gastrointestinal 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.

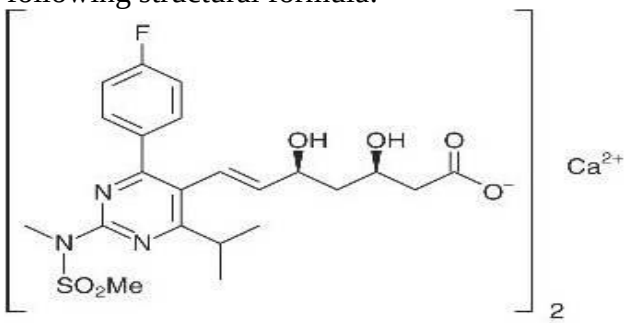
Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses.

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 nonclinical reproductive toxicity studies conducted with fenofibrate.

7. DESCRIPTION

Rosuvastatin Calcium

Rosuvastatin calcium is a synthetic lipid-lowering agent for oral administration. The chemical name for rosuvastatin calcium is bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methyl sulfonyl) amino] pyrimidin-5-yl] (3R, 5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The molecular formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2$.Ca and the molecular weight is 1001.1 g/mol. Rosuvastatin calcium is off-white to creamish white powder that is freely soluble in acetonitrile and soluble in acetone.

Fenofibrate

The chemical name for Fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester. The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83. Its structural formula is:

Fenofibrate is white or almost white crystalline powder. It is very soluble in dichloromethane, slightly soluble in ethanol (95%); practically insoluble in water.

Rosuvastatin and Fenofibrate Tablets are Yellow colour, round shape, biconvex, film coated tablets having both sides plain. The excipients used are Lactose, Croscarmellose Sodium, Calcium Carbonate, Sodium Lauryl Sulphate, PVP K30, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Colorezy 17F580012 and Tartrazine Lake.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

ROSTAR F is packed in strips of 10 tablets.

8.4 Storage and Handing Instructions

Store below 25°C in a dry place Protect from light.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: information for the patient

Rosuvastatin and Fenofibrate film-coated tablets

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.

What is in this leaflet?

9.1.What ROSTAR F is and what it is used for

9.2.What you need to know before you take ROSTAR F

9.3.How to take ROSTAR F

9.4.Possible side effects

9.5.How to store ROSTAR F

9.6.Contents of the pack and other information

9.1 What ROSTAR F is and what it is used for

ROSTAR F is combination of Rosuvastatin and Fenofibrate. Rosuvastatin belongs to a group of medicines called statins. Fenofibrate belongs to a group of medicines, commonly known as fibrates.

You have been prescribed ROSTAR F because**:**

- You have a high cholesterol level. This means you are at risk from a heart attack or stroke. ROSTAR F is used for the treatment of combined hyperlipidemia in patients with normal hepatic and renal function.
- You have been advised to take ROSTAR F, because changing your diet and doing more exercise were not enough to correct your cholesterol levels. You should continue with your cholesterol-lowering diet and exercise while you are taking ROSTAR F.

Or

- You have other factors that increase your risk of having a heart attack, stroke or related health problems.

Heart attack, stroke and other problems can be caused by a disease called atherosclerosis. Atherosclerosis is due to build-up of fatty deposits in your arteries.

9.2 **What you need to know before you take ROSTAR F**

Do not take ROSTAR F:

- If you have ever had an allergic reaction to ROSTAR F, or to any of its ingredients.
- If you are pregnant or breast-feeding. If you become pregnant while taking ROSTAR F stop taking it immediately and tell your doctor. Women should avoid becoming pregnant while taking ROSTAR F by using suitable contraception.
- If you have repeated or unexplained muscle aches or pains.
- 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 ROSTAR F:
- If you have moderate kidney problems (if in doubt, please ask your doctor).
- If your thyroid gland is not working properly.
- 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.
- you are allergic to peanut or arachis oil or soya lecithin or related products

- while taking other medicines (such as an anti-inflammatory medicine called 'ketoprofen'), you have had an allergic reaction or skin damage from sunlight or UV light
- you have severe liver, kidney or gallbladder problems
- you have pancreatitis (an inflamed pancreas which causes abdominal pain) which is not caused by high levels of fat in the blood
- 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 ROSTAR F.

- If you have problems with your kidneys.
- If you have problems with your liver. You may have an inflamed liver (hepatitis) - signs include yellowing of the skin and the whites of the eyes (jaundice), an increase in liver enzymes (shown in blood tests), stomach pain and itching
- 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.

  The risk of muscle breakdown is higher in some patients. In particular, tell your doctor if:

- you have kidney problems
- you have thyroid problems
- you or a close family member has muscle problem which runs in the family
- you drink large amounts of alcohol
- you are taking medicines called statins to lower cholesterol (such as simvastatin, atorvastatin, pravastatin, ROSTAR F or fluvastatin)
- You have ever had muscle problems during treatment with statins or fibrates (such as, bezafibrate or gemfibrozil).
- If you regularly drink large amounts of alcohol.
- If your thyroid gland is not working properly.
- If you take medicines used to treat the HIV infection e.g. ritonavir with lopinavir and/or atazanavir.

If any of the above apply to you (or you are not sure), talk to your doctor before taking ROSTAR F

“Other medicines and ROSTAR F”.

- 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 ROSTAR F can lead to serious muscle problems (rhabdomyolysis), please see “Other medicines and ROSTAR F”.
- If you are over 70 (as your doctor needs to choose the right start dose of ROSTAR F to suit you)
- If you have severe respiratory failure.

- 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 ROSTAR F to suit you.
- If any of the above applies to you (or if you are not sure):
- Do not take ROSTAR F and check with your doctor or pharmacist before you actually start taking any dose of ROSTAR F.

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 usually carry out this blood test (liver function test) before and during treatment with ROSTAR F.

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.

Children and adolescents

- If the patient is under 6 years old: ROSTAR F should not be given to children younger than 6 years.
- If the patient is below 18 years of age: The ROSTAR F tablet is not suitable for use in children and adolescents below 18 years of age.

Other medicines and ROSTAR F

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines

Tell your doctor if you are taking any of the following:

- Ciclosporin (used for example, after organ transplants),
- Warfarin or Clopidogrel (or any other drug used for thinning the blood),
- Fibrates (such as gemfibrozil) or any other medicine used to lower cholesterol (such as ezetimibe),
- Indigestion remedies (used to neutralise acid in your stomach),
- Erythromycin (an antibiotic), fusidic acid (an antibiotic – please see below and Warnings and precautions),
- An oral contraceptive (the pill),
- Regorafenib (used to treat cancer),
- Hormone replacement therapy
- Any of the following drugs used to treat viral infections, including HIV or hepatitis C infection, alone or in combination (please see Warnings and precautions): ritonavir, lopinavir, atazanavir, ombitasvir, paritaprevir, dasabuvir, velpatasvir, grazoprevir, elbasvir, glecaprevir, pibrentasvir.
- A particular class of medicines to treat diabetes (such as rosiglitazone or pioglitazone)

The effects of these medicines could be changed by ROSTAR F or they could change the effect of ROSTAR F.

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 ROSTAR F. Taking

ROSTAR F with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis).

Pregnancy, breast-feeding and fertility

- Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. This is because it is not known how ROSTAR F may affect your unborn baby. You should only use ROSTAR F if your doctor tells you to.
- Do not use ROSTAR F if you are breast-feeding or planning to breast-feed your baby. This is because it is not known whether ROSTAR F passes into human milk

Driving and using machines

Most people can drive a car and operate machinery while using ROSTAR F – it will not affect their ability. However, some people feel dizzy during treatment with ROSTAR F. If you feel dizzy, consult your doctor before attempting to drive or use machines.

9.3 How to take ROSTAR F

Always take this medicine as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Usual doses in adults

The choice of your start dose will depend upon:

- Your cholesterol levels.
- The level of risk you have of experiencing a heart attack or stroke.
- Whether you have a factor that may make you more sensitive to possible side effects.

Please check with your doctor or pharmacist which start dose of ROSTAR F will best suit you.

- Your doctor may decide to give you the lowest dose if:
- You are of Asian origin (Japanese, Chinese, Filipino, Vietnamese, Korean and Indian).
- You are over 70 years of age.
- You have moderate kidney problems.
- You are at risk of muscle aches and pains (myopathy).

Taking this medicine

Take the tablet with food — it will not work as well if your stomach is empty.

- Swallow the tablet with a glass of water.
- Do not crush or chew the tablet.

Remember that as well as taking **ROSTAR F**, it is also important that you:

- Have a low fat diet
- Take regular exercise.

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 ROSTAR F that is right for you.

If you take more ROSTAR F than you should

Contact your doctor or nearest hospital for advice.

If you go into hospital or receive treatment for another condition, tell the medical staff that you're taking **ROSTAR F.**

If you forget to take ROSTAR F

Don't worry, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking ROSTAR F

Talk to your doctor if you want to stop taking ROSTAR F. Your cholesterol levels might increase again if you stop taking **ROSTAR F**.

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

9.4 Possible side effects

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

It is important that you are aware of what these side effects may be. They are usually mild and disappear after a short time.

Stop taking ROSTAR F and seek medical help immediately if you have any of the following allergic reactions:

- Difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat.
- Swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing.
- Severe itching of the skin (with raised lumps).

Also, stop taking ROSTAR F and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than you might expect. Muscle symptoms are more common in children and adolescents than in adults. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life threatening muscle damage known as *rhabdomyolysis*.

Common possible side effects (these may affect between 1 in 10 and 1 in 100 patients):

- Headache, stomach pain, constipation, feeling sick, muscle pain, feeling weak, dizziness. Diarrhoea, wind (flatulence)
- feeling sick (nausea)
- being sick (vomiting)
- raised levels of liver enzymes in the blood - shown in tests
- increase in homocysteine (too much of this amino acid in the blood has been associated to a higher risk of coronary heart disease, stroke and peripheral vascular disease, although a causal link has not been established)
- An increase in the amount of protein in the urine -

- 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 possible side effects (these may affect between 1 in 100 and 1 in 1,000 patients):

- Rash, itching or other skin reactions.
- An increase in the amount of protein in the urine - cramps or painful, tender or weak muscles - these may be signs of muscle inflammation or breakdown, which can cause kidney damage or even death
- stomach pain - this may be a sign that your pancreas is inflamed (pancreatitis) chest pain and feeling breathless - these may be signs of a blood clot in the lung (pulmonary embolism)
- Pain, redness or swelling in the legs - these may be signs of a blood clot in the leg (deep vein thrombosis). headache
- gallstones
- reduced sex drive
- increase in creatinine (produced by the kidneys) - shown in tests

Rare possible side effects (these may affect between 1 in 1,000 and 1 in 10,000 patients):

- Severe allergic reaction – signs include swelling of the face, lips, tongue and/or throat, difficulty in swallowing and breathing, a severe itching of the skin (with raised lumps).
- hair loss
- increase in urea (produced by the kidneys) - shown in tests
- skin is more sensitive to sunlight, sun lamps and sunbeds
- drop in haemoglobin (that carries oxygen in blood) and white blood cells - shown in tests

If you think you are having an allergic reaction, then stop taking ROSTAR F and seek medical help immediately.

Muscle damage in adults – as a precaution, stop taking ROSTAR F and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than expected.

- A severe stomach pain (inflamed pancreas).
- Increase in liver enzymes in the blood.
- Bleeding or bruising more easily than normal due to low level of blood platelets. Yellowing of the skin and whites of the eyes (jaundice), or an increase in liver enzymes - these may be signs of an inflamed liver (hepatitis)

Very rare possible side effects (these may affect less than 1 in 10,000 patients):

- 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), joint pain, memory loss and breast enlargement in men (gynaecomastia).

Side effects of unknown frequency may include:

Diarrhoea (loose stools), Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals), cough, shortness of breath, oedema (swelling), sleep disturbances,

including insomnia and nightmares, sexual difficulties, depression, breathing problems, including persistent cough and/or shortness of breath or fever, tendon injury and muscle weakness that is constant.

- severe skin rash which reddens, peels and swells and looks like a severe burn
- long-term lung problems
- muscle breakdown
- complications of gallbladder stones
- feeling exhausted (fatigue)

9.5 How to store ROSTAR F

Store below 25°C in a dry place.

Protect from light.

Keep out of reach of children.

9.6 Contents of the pack and other information

The active substance in ROSTAR F is Rosuvastatin and .fenofibrate.

Other ingredients are:. Lactose, Croscarmellose Sodium, Calcium Carbonate, Sodium Lauryl Sulphate, PVP K30, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Colorezy 17F580012 and Tartrazine Lake.

10. Details of manufacturer

Manufactured by:
Ravenbhel Healthcare Pvt Ltd.

16-17, EPIP, SIDCO, Kartholi, Bari Brahmana, Jammu – 181133.

11. Details of permission or licence number with date

Mfg Lic No. JK/01/56 issued on 24.05.2018

12. DATE OF REVISION

Dec, 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ROSTAR F 10,160mg/Dec-20/02/PI