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

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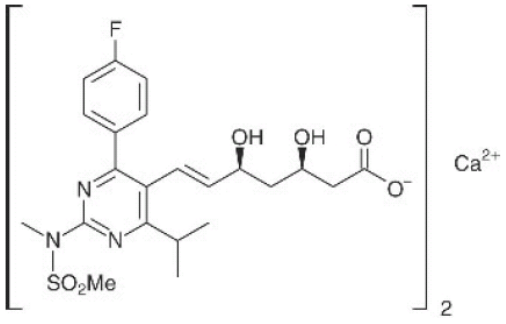
ROZUCOR F 20
Rosuvastatin 20 mg and Fenofibrate 160 mg Tablets I.P.

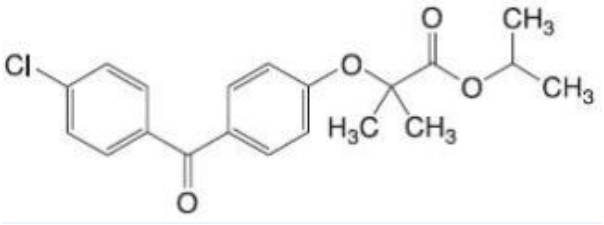
COMPOSITION
Rozucor F 20
Each film coated tablet contains:
Rosuvastatin calcium I.P.
Equivalent to Rosuvastatin 20 mg
Fenofibrate I.P……160 mg
Colors: Sunset yellow FCF & Titanium dioxide I.P.

DESCRIPTION
Rosuvastatin
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(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

Fenofibrate
Fenofibrate is a lipid regulating agent. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy] 2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79° to 82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

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 of cholesterol. *In vivo* studies in animals and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Fenofibrate

The active moiety of Fenofibrate is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of perxisome proliferators activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting decrease in TG produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be artherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo AI and apo AII.

Pharmacokinetics

Rosuvastatin

Absorption: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC

increased in approximate proportion to Rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%. Administration of Rosuvastatin with food did not affect the AUC of rosuvastatin. The AUC of rosuvastatin does not differ following evening or morning drug administration.

Distribution: Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

Excretion: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t1/2) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups However, pharmacokinetic studies, including one reported in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and Cmax) in Asian subjects when compared with a Caucasian control group.

Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.

Geriatric: There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).

Renal Impairment: Mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m2) not receiving hemodialysis compared with healthy subjects (CLcr > 80 mL/min/1.73 m2).

Hemodialysis: Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Impairment: In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A

disease, Cmax and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, Cmax and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Fenofibrate

Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the body to fenofibric acid which is the active constituent measurable in the circulation.

Absorption: The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Fenofibrate is insoluble in water and its bioavailability is optimized when taken with meals. However, after fenofibrate is dissolved, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur an average of 3 hours after administration. The extent of absorption of Fenofibrate (AUC) is comparable between fed and fasted conditions. Food increases the rate of absorption of Fenofibrate approximately 55%.

Distribution: In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism: Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma. Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine. *In vivo* metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Elimination: After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces. Fenofibric acid is eliminated with a half-life of approximately 16 hours, allowing once daily dosing.

Geriatrics: In elderly volunteers 77 to 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics: Pharmacokinetics of Fenofibrate has not been studied in pediatric patients.

Gender: No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race: The influence of race on the pharmacokinetics of fenofibrate has not been studied; however, fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability.

Renal Impairment: The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl ≤ 30 mL/min] < 30 mL/min or estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) showed 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30-80 mL/min or eGFR 30-59 mL/min/1.73m^2) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Fenofibrate should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment

Pharmacogenomics

Rosuvastatin

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (*SLCO1B1* 521T>C). The frequency of this genotype (i.e., *SLCO1B1* 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established. Doses should be titrated according to patient response and tolerability.

INDICATION

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

CONTRAINDICATION

Rosuvastatin

Rosuvastatin is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with Rosuvastatin [*see Adverse Reactions*]
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels [*see Warnings and Precaution]*
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, Rosuvastatin may cause fetal harm when administered to pregnant women. Additionally, there is no

apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy.

- Nursing mothers. Because another drug in this class passes into breast milk, and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require Rosuvastatin treatment should be advised not to nurse their infants [*see Use in Specific Populations]*

Cyclosporine increased rosuvastatin exposure (AUC) 7 fold. Therefore, exceed than Rosuvastatin 5 mg once daily is contraindicated with Cyclosporine.

Fenofibrate

Fenofibrate is contraindicated in:

- Patients with severe renal impairment, including those receiving dialysis.
- Patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities.
- Patients with preexisting gallbladder disease.
- Patients who have a known hypersensitivity to fenofibrate or fenofibric acid.
- Nursing mothers.

WARNINGS AND PRECAUTIONS

Rosuvastatin

Skeletal Muscle Effects Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. These risks can occur at any dose level, but are increased at the highest dose (40 mg).

Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment). The risk of myopathy during treatment with Rosuvastatin may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir. Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, coadministered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine [*see Drug Interactions]*

Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. Rosuvastatin therapy should also be temporarily withheld 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, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal

muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

All patients should be advised to promptly report to their physician unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Rosuvastatin.

Liver Enzyme Abnormalities
It is recommended that liver enzyme tests be performed before the initiation of Rosuvastatin, and if signs or symptoms of liver injury occur.

Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin**.** In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to Rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking Rosuvastatin versus 0.5% of patients treated with placebo.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Rosuvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart Rosuvastatin. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease [see Clinical Pharmacology]. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of Rosuvastatin.

Concomitant Coumarin Anticoagulants
Caution should be exercised when anticoagulants are given in conjunction with Rosuvastatin because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs [*see Drug Interactions*].

Proteinuria and Hematuria
In the Rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among Rosuvastatin treated patients. These findings were more frequent in patients taking Rosuvastatin 40 mg, when compared to lower doses of Rosuvastatin or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. Although the clinical

significance of this finding is unknown, a dose reduction should be considered for patients on Rosuvastatin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Endocrine Effects
Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin. Based on clinical trial data with Rosuvastatin, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus [see Adverse Reactions].

Although clinical studies have shown that Rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if Rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Fenofibrate
Mortality and Coronary Heart Disease Morbidity
The effect of Fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Skeletal Muscle
Fenofibrates increase the risk of myopathy and have been associated with rhabdomyolysis. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal insufficiency, or hypothyroidism.

Data from observational studies indicate that the risk for rhabdomyolysis is increased when fibrates, in particular gemfibrozil, are co-administered with an HMG-CoA reductase inhibitor (statin). The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase (CPK) levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and Fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy/myositis is suspected.

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates coadministered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicines.

Liver Function
Fenofibrate can increase serum transaminases [AST (SGOT) or ALT (SGPT)].

Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Baseline and regular periodic monitoring of liver tests, including serum ALT (SGPT) should be performed for the duration of Fenofibrate therapy and therapy should be discontinued if enzyme levels persist above three times the normal limit.

Serum Creatinine
Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown. Monitor renal function in patients with renal impairment taking Fenofibrate. Renal monitoring should also be considered for patients taking Fenofibrate at risk for renal insufficiency such as the elderly and patients with diabetes.

Cholelithiasis
Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

Coumarin Anticoagulants
Caution should be exercised when anticoagulants are given in conjunction with Fenofibrate because of the potentiation of coumarin-type anti-coagulant effects in prolonging the prothrombin time/International Normalized Ration (PT/INR). The dosage of the anticoagulant should be reduced to maintain the PT/INR at the desired level to prevent bleeding complications. Frequent PT/INR determinations are advisable until it has been definitely determined that the PT/INR has stabilized.

Pancreatitis
Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. 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.

Hematologic Changes
Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrate. Periodic monitoring of red and white cell counts is recommended during the first 12 months of Fenofibrate administration.

Hypersensitivity Reactions

Acute hypersensitivity reactions such as Stevens - Johnson syndrome and toxic epidermal necrolysis requiring patient hospitalization and treatment with steroids have been reported in individuals treated with fenofibrates. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Venothromboembolic Disease
In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ($p = 0.022$).

Paradoxical Decrease in HDL Cholesterol Levels
There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDLC is unknown. It is recommended that the HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDLC level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

DRUG INTERACTIONS
Rosuvastatin
Drug-Drug Interactions: Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of Rosuvastatin with medications that are inhibitors of these transporter proteins (e.g. cyclosporine, certain HIV protease inhibitors) may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy

Cyclosporine
Cyclosporine increased rosuvastatin exposure (AUC) 7 fold. Therefore, in patients taking cyclosporine, the dose of Rosuvastatin should not exceed 5 mg once daily.

Gemfibrozil
Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with Rosuvastatin and gemfibrozil should be avoided. If used together, the dose of Rosuvastatin should not exceed 10 mg once daily *[see Clinical Pharmacology]*.

Protease Inhibitors
Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold. For these combinations the dose of Rosuvastatin should not exceed 10 mg once daily. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir.

Coumarin Anticoagulants
Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with Rosuvastatin. In patients taking coumarin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs [*see Warnings and Precautions* and *Clinical Pharmacology]*

Niacin
The risk of skeletal muscle effects may be enhanced when Rosuvastatin is used in combination with lipid-modifying doses (≥1 g/day) of niacin; caution should be used when prescribing with Rosuvastatin [*see Warnings and Precautions]*

Fenofibrate
When Rosuvastatin was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concomitant use of fenofibrates, caution should be used when prescribing fenofibrates with Rosuvastatin [*see Warnings and Precautions* and *Clinical Pharmacology]*

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, coadministered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine [*see Warnings and Precautions]*

Fenofibrate
Drug-Drug Interactions*: 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 CYP2C8, CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Coumarin Anticoagulants
Potentiation of coumarin-type anticoagulant effects has been observed with prolongation of the PT/INR.

Caution should be exercised when coumarin anticoagulants are given in conjunction with Fenofibrate. The dosage of the anticoagulants should be reduced to maintain the PT/INR at the desired level to prevent bleeding complications. Frequent PT/INR determinations are advisable until it has been definitely determined that the PT/INR has stabilized.

Immunosuppressants
Immunosuppressants such as cyclosporine and tacrolimus can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including Fenofibrate, there is a risk that an interaction will lead to deterioration of renal function. The benefits and risks of using Fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed and renal function monitored.

Bile-Acid Binding Resins
Since bile acid binding resins may bind other drugs given concurrently, patients should take Fenofibrate at least 1 hour before or 4 to 6 hours after a bile acid binding resin to avoid impeding its absorption.

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates co-administered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine.

ADVERSE REACTIONS

Rosuvastatin

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) [*see Warnings and Precautions]*
- Liver enzyme abnormalities [*see Warnings and Precautions]*

In the Rosuvastatin controlled clinical trials database (placebo or active-controlled) of 5394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were:

- Myalgia
- Abdominal pain
- Nausea

The most commonly reported adverse reactions (incidence ≥ 2%) in the Rosuvastatin controlled clinical trial database of 5394 patients were:

- Headache
- Myalgia
- Abdominal pain
- Asthenia
- Nausea

Clinical Studies Experience

Adverse reactions reported in ≥ 2% of patients in placebo-controlled clinical studies and at a rate greater than placebo are shown in following Table. These studies had treatment duration of up to 12 weeks.

Adverse Reactions* Reported in ≥ 2% of Patients Treated with Rosuvastatin and > Placebo in Placebo-Controlled Trials (% of Patients)

Adverse Reactions	Rosuvastatin 5 mg N=291	Rosuvastatin 10 mg N=283	Rosuvastatin 20 mg N=64	Rosuvastatin 40 mg N=106	Total Rosuvastatin 5 mg – 40 mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

* Adverse reactions by COSTART preferred term.

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria [*see Warnings and Precautions*]; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

Pediatric patients 10 to 17 years of age

In a 12-week controlled study in boys and postmenarchal girls, the safety and tolerability profile of Rosuvastatin 5 to 20 mg daily was generally similar to that of placebo [*see Clinical Studies* and *Use in Specific Populations, Pediatric Use*].

However, elevations in serum creatine phosphokinase (CK) > 10 x ULN were observed more frequently in rosuvastatin compared with placebo-treated children. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10 mg and 2 treated with 20 mg) had increased CK > 10 x ULN, compared to 0 of 46 children on placebo.

Post marketing Experience

Arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, thrombocytopenia, depression, sleep disorders (including insomnia and nightmares) peripheral neuropathy and gynecomastia.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions]*.

There has been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Fenofibrate

Adverse reactions reported by 2% or more of patients treated with fenofibrate (and greater than placebo) during double-blind, placebo-controlled trials are listed in Table 1. Adverse reactions led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

Adverse Reactions Reported by 2% or More of Patients Treated with Fenofibrate and Greater than Placebo during the Double-Blind, Placebo-Controlled Trials

Body System Adverse Reaction	**Fenofibrate (N=439)**	**Placebo (N=365)**
Body As A Whole		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Digestive		
Abnormal Liver Function Tests	7.5%**	1.4%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
Metabolic and Nutritional Disorders		
Increased AST	3.4%**	0.5%
Increased ALT	3.0%	1.6%
Increased Creatine Phosphokinase	3.0%	1.4%
Respiratory		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

** Significantly different from placebo

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fenofibrate: myalgia, rhabdomyolysis, pancreatitis, muscle spasms, acute renal failure, hepatitis, cirrhosis, anemia, arthralgia, asthenia, and severely depressed HDL-cholesterol levels. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

USE IN SPECIFIC POPULATIONS

Rosuvastatin

Pregnancy Teratogenic effects: Pregnancy Category X.

Rosuvastatin is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy [*see Contraindications*].

There are no adequate and well-controlled studies of Rosuvastatin in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-fourfold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Rosuvastatin crosses the placenta in rats and rabbits. In rats, Rosuvastatin was not teratogenic at systemic exposures equivalent to a human therapeutic dose of 40 mg/day. At 10-12 times the human dose of 40 mg/day, there was decreased pup survival, decreased fetal body weight among female pups, and delayed ossification. In rabbits, pup viability decreased and maternal mortality increased at doses equivalent to the human dose of 40 mg/day [*see Non clinical Toxicology]*

Rosuvastatin may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking Rosuvastatin, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

Nursing Mothers

It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require Rosuvastatin treatment should be advised not to nurse their infants [*see Contraindications*

Pediatric Use

The safety and effectiveness of Rosuvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were reported in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with

mg, 10 mg, and 20 mg daily Rosuvastatin had an adverse experience profile generally similar to that of patients treated with placebo [*see Adverse Reactions*]. Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of Rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation [*see Clinical Studies*] in pediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on Rosuvastatin therapy [*see Use in Specific Populations*]. Rosuvastatin has not been studied in controlled clinical trials involving prepubertal patients or patients younger than 10 years of age. Doses of Rosuvastatin greater than 20 mg have not been studied in the pediatric population.

Geriatric Use
Of the 10,275 patients in clinical studies with Rosuvastatin, 3159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients are at higher risk of myopathy and Rosuvastatin should be prescribed with caution in the elderly.

Renal Impairment
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m2); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. Rosuvastatin dosing should be adjusted in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m^2) not requiring hemodialysis.

Hepatic Impairment
Rosuvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; Rosuvastatin should be used with caution in these patients.

Asian Patients
Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. Rosuvastatin dosage should be adjusted in Asian patients.

Fenofibrate
Pregnancy
Pregnancy Category C
Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to ating through weaning, maternal toxicity was observed at 0.3 times the maximum recommended human dose (MRHD), based on body surface area comparisons; mg/m2.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons: mg/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

Nursing Mothers
Fenofibrate should not be used in nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use
Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. Since elderly patients have a higher incidence of renal impairment, dose selection for the elderly should be made on the basis of renal function. Elderly patients with normal renal function should require no dose modifications. Consider monitoring renal function in elderly patients taking Fenofibrate.

Renal Impairment
The use of Fenofibrate should be avoided in patients with severe renal impairment. Dose reduction is required in patients with mild to moderate renal impairment. Monitoring renal function in patients with renal impairment is recommended.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Rosuvastatin
In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

Fenofibrate

Carcinogenesis: Two dietary carcinogenicity studies have been reported in rats with fenofibrate. In the first 24-month study, Wistar rats were dosed with fenofibrate at 10, 45 and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m^2). At a dose of 200 mg/kg/day (at 6 times MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed in males at 6 times the MRHD. In a second 24-month study in a different strain of rats (Sprague-Dawley), doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD.

Mutagenesis: Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis in primary rat hepatocytes.

Impairment of Fertility: In fertility studies rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (approximately 10 times the MRHD, based on mg/m^2 surface area comparisons).

Animal Toxicology and/or Pharmacology

Rosuvastatin

Embryo-fetal Development

Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times the human exposure at 40 mg/day based on AUC).

In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥ 12 times the human exposure at 40 mg/day based on body surface area.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to the human exposure at 40 mg/day based on body surface area, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at ≤ 25 mg/kg/day or in rabbits ≤ 3 mg/kg/day (systemic exposures equivalent to the human exposure at 40 mg/day based on AUC or body surface area, respectively).

Central Nervous System Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤ 30 mg/kg/day (systemic exposures ≤ 60 times the human exposure at 40

mg/day based on AUC) did not reveal retinal findings during treatment for up to one year.

DOSAGE AND ADMINISTRATION
Rozucor F 20 is given orally once daily with or without food.

OVERDOSAGE
Rosuvastatin
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. Hemodialysis does not significantly enhance clearance of rosuvastatin.

Fenofibrate
There is no specific treatment for overdose with Fenofibrate. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

EXPIRY DATE
Do not use later than the date of expiry

STORAGE
Store below 30°C. Protect from light and moisture.

PRESENTATION
10 Blister strips of 10 Tablets

MARKETED BY:
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