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

ROZUCOR B / BEMPESTA R

(Rosuvastatin and Bempedoic Acid Tablets**)**

1. Generic Name

Rosuvastatin and Bempedoic Acid Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains

Rosuvastatin Calcium I.P.

eq. to Rosuvastatin……40 mg

Bempedoic Acid……180 mg

Excipients……...q.s.

Colors: Titanium Dioxide I.P. and Ferric Oxide Red USP-NF

The excipients used are Microcrystalline Cellulose, Pregelatinised starch, Povidone K, Isopropyl alcohol, Sodium Starch Glycolate, Purified Talc, Calcium Stearate, Lactose Monohydrate, Ferric oxide red, Crospovidone, Magnesium Stearate, Instacoat Aqua brown, Purified water.

3. Dosage form and strength

Dosage form: film coated Tablets

Strength: Rosuvastatin 40 mg and Bempedoic Acid 180 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet daily. Each film-coated tablet contains a fixed dose of Bempedoic Acid and Rosuvastatin.

Method of administration

Bempedoic Acid and Rosuvastatin Tablets should be given orally once daily with or without food.

Special populations

Renal impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. .

The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses.

Hepatic impairment

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment.

Elderly (≥ 65 years)

A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.

Paediatric population

The safety and effectiveness of Bempedoic acid + Rosuvastatin have not been established in pediatric patients <18 years of age.

Pregnancy

Use of Bempedoic acid is contraindicated in pregnancy.

4.3 Contraindications

- In patients with hypersensitivity to bempedoic acid or rosuvastatin or to any of the excipients.
- In patients with simvastatin>40 mg
- 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).
- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- 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

Potential risk of myopathy with concomitant use of statins

Bempedoic acid increases plasma concentrations of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. In postmarketing experience with ezetimibe,

very rare cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe.

Patients receiving Bempedoic acid as adjunctive therapy to a statin should be monitored for adverse reactions that are associated with the use of high doses of statins. All patients receiving Bempedoic acid in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. If such symptoms occur while a patient is receiving treatment with Bempedoic acid and a statin, a lower maximum dose of the same statin or an alternative statin, or discontinuation of Bempedoic acid and initiation of an alternative lipid-lowering therapy should be considered under close monitoring of lipid levels and adverse reactions. If myopathy is confirmed by a creatine phosphokinase (CPK) level > 10× upper limit of normal (ULN), Bempedoic acid and any statin that the patient is taking concomitantly should be immediately discontinued.

Renal Effects

There is limited experience with bempedoic acid in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m2), and patients with ESRD on dialysis have not been studied with bempedoic acid. Additional monitoring for adverse reactions may be warranted in these patients when Bempedoic acid is administered.

Contraception

Women of childbearing potential must use effective contraception during treatment. Patients should be advised to stop taking Bempedoic acid before stopping contraceptive measures if they plan to become pregnant.

Hepatic impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate to severe hepatic impairment (Child-Pugh B and C), Bempedoic acid is not recommended in these patients.

Protease Inhibitors

Probenecid, an inhibitor of glucuronide conjugation, was studied to evaluate the potential effect of these inhibitors on the pharmacokinetics of bempedoic acid. Administration of bempedoic acid 180 mg with steady-state probenecid resulted in a 1.7-fold increase in bempedoic acid AUC and a 1.9-fold increase in bempedoic acid active metabolite (ESP15228) AUC. These elevations are not clinically meaningful and do not impact dosing recommendations.

Severe Cutaneous Adverse Reactions

In vitro drug interaction studies suggest bempedoic acid, as well as its active metabolite and glucuronide form, are not substrates of commonly characterised drug transporters with the exception of bempedoic acid glucuronide, which is an OAT3 substrate.

Lactose Intolerance

Bempedoic acid contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Interstitial Lung Disease

Fernandez and colleagues reported that interstitial lung disease (ILD), comprising a group of disorders with similar pathological findings including cellular infiltration, scarring and/or architectural disruption of the pulmonary parenchyma involving alveolar lining cells, small and

large airways, endothelial basement membranes and occasionally the pleura, was found in 0.01–0.4% of patients who had statin-induced adverse events. Recently, Xu et al reported a positive correlation between statin use and ILD in the cohort of smokers in the COPD Gene Study, with 38% of subjects with ILD taking statins compared with 27% of subjects without ILD.

Hyperuricemia

Bempedoic Acid inhibits renal tubular OAT2 and may increase blood uric acid levels. In clinical trials, 26% of Bempedoic Acid L-treated patients with normal baseline uric acid values (versus 9.5% placebo) experienced hyperuricemia one or more times, and 3.5% of patients experienced clinically significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). Increases in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment. After 12 weeks of treatment, the mean placebo-adjusted increase in uric acid compared to baseline was 0.8 mg/dL for patients treated with Bempedoic Acid.

Elevated blood uric acid may lead to the development of gout. Gout was reported in 1.5% of patients treated with Bempedoic Acid and 0.4% of patients treated with placebo. The risk for gout events was higher in patients with a prior history of gout (11.2% Bempedoic Acid versus 1.7% placebo), although gout also occurred more frequently than placebo in patients treated with Bempedoic Acid who had no prior gout history (1.0% Bempedoic Acid versus 0.3% placebo). Advise patients to contact their healthcare provider if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.

Tendon Rupture

Bempedoic Acid is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.5% of patients treated with Bempedoic Acid versus 0% of placebo-treated patients and involved the rotator cuff (the shoulder), biceps tendon, or Achilles tendon. Tendon rupture occurred within weeks to months of starting Bempedoic Acid. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders.

Discontinue Bempedoic Acid immediately if the patient experiences rupture of a tendon. Consider discontinuing Bempedoic Acid if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their healthcare provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis):

Risks increase with use of 40 mg dose, advanced age (≥65), hypothyroidism, renal impairment, and combination use with cyclosporine, darolutamide, regorafenib, certain anti-viral medicines or their combinations. Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness and discontinue rosuvastatin if signs or symptoms appear.

Creatinine Kinase Measurment

Rosuvastatin therapy should be discontinued if markedly elevated creatinine 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). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

While on treatment

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.

Liver enzyme abnormalities:

Persistent elevations in hepatic transaminases can occur. Perform liver enzyme tests before initiating therapy and as clinically indicated thereafter.
It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.
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.

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.

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.
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.

4.5 Drugs interactions

No interaction studies have been performed for Bempedoic Acid + Rosuvastatin tablets. The following statements reflect the information available on the individual active substances.

Bempedoic Acid

Pharmacokinetic interactions

Simvastatin	
Clinical Impact:	Concomitant use of Bempedoic Acid with simvastatin causes an increase in simvastatin concentration and may increase the risk of simvastatin-related myopathy.
Intervention:	Avoid concomitant use of Bempedoic Acid with simvastatin greater than 20 mg.
Pravastatin	
Clinical Impact:	Concomitant use of Bempedoic Acid with pravastatin causes an increase in pravastatin concentration and may increase the risk of pravastatin-related myopathy.
Intervention:	Avoid concomitant use of Bempedoic Acid with pravastatin greater than 40 mg.

Transporter mediated drug interaction
In vitro drug interaction studies suggest bempedoic acid, as well as its active metabolite and glucuronide form, are not substrates of commonly characterized drug transporters with the exception of bempedoic acid glucuronide, which is an OAT3 substrate. Bempedoic acid weakly inhibits OAT3 at high multiples of clinically relevant concentrations, and bempedoic acid and its glucuronide weakly inhibit OATP1B1, and OATP1B3 at clinically relevant concentrations. Bempedoic acid weakly inhibits OAT2 in vitro, which is likely the mechanism responsible for minor elevations in serum creatinine and uric acid.

Probenicid

Probenecid, an inhibitor of glucuronide conjugation, was studied to evaluate the potential effect of these inhibitors on the pharmacokinetics of bempedoic acid. Administration of bempedoic acid 180 mg with steady-state probenecid resulted in a 1.7-fold increase in bempedoic acid AUC and a 1.9-fold increase in bempedoic acid active metabolite (ESP15228) AUC. These elevations are not clinically meaningful and do not impact dosing recommendations.

Rosuvastatin

- Combination of sofosbuvir/velpatasvir/voxilaprevir or ledipasvir/sofosbuvir: Combination increases rosuvastatin exposure. Use with rosuvastatin is not recommended.
- Cyclosporine and darolutamide: Combination increases rosuvastatin exposure. Limit rosuvastatin dose to 5 mg once daily.
- Gemfibrozil: Combination should be avoided. If used together, limit rosuvastatin dose to 10 mg once daily.
- Atazanavir/ritonavir, lopinavir/ritonavir, simeprevir or combination of dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir: Combination increases rosuvastatin exposure. Limit rosuvastatin dose to 10 mg once daily.
- Regorafenib: Combination increases rosuvastatin exposure. Limit rosuvastatin dose to 10 mg once daily.
- Coumarin anticoagulants: Combination prolongs INR. Achieve stable INR prior to starting rosuvastatin. Monitor INR frequently until stable upon initiation or alteration of rosuvastatin therapy.
- Concomitant lipid-lowering therapies: Use with fibrates or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with rosuvastatin.
- No clinically significant pharmacokinetic interactions were seen when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.
- Concomitant use of antacid: When taking Rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration.
- Erythromycin combination decreases Rosuvastatin exposure.
- Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.
- Vitamin K antagonists Concomitant use of Vitamin K antagonists (VKA) and statins is frequent in cardiovascular patients. However, clinical guidelines on this drug combination are divergent. The reported increases in mean INR ranged from 0.15-0.65. The effect is likely to be of limited clinical relevance but should be evaluated individually.

- Oral Contraceptives/hormone replacement therapy (HRT) There was no detectable effect of rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation
- Digoxin decreases Rosuvastatin exposure.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no available data on drug use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
Due to lack of human data, Bempedoic Acid and Rosuvastatin Tablets should not be used during pregnancy.
Women of child bearing potential should use appropriate contraceptive measures.
Breast-feeding

There is no information regarding the presence of Bempedoic Acid and Rosuvastatin in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The use of Bempedoic acid in lactation is contraindiacted.
Fertility

The effect of this medicinal product or Bempedoic Acid and Rosuvastatin on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Bempedoic Acid and Rosuvastatin have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Bempedoic Acid and Rosuvastatin have been demonstrated to be bioequivalent with co administered Bempedoic Acid and Rosuvastatin. There have been no therapeutic clinical studies conducted with Bempedoic Acid and Rosuvastatin tablets.

Tabulated list of adverse reactions of Bempedoic Acid

Adverse reactions reported with bempedoic acid are displayed by system organ class and frequency in table

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Table Adverse reactions of Bempedoic Acid

System Organ Class (SOC)	Adverse reactions	Frequency Categories
	Anaemia	Common

Blood and lymphatic system disorders	Haemoglobin decreased	Uncommon
Metabolism and nutrition disorder	Gout	Common
	Hyperuricaemia[a]	Common
Hepatobiliary disorders	Aspartate aminotransferase increased	Common
	Alanine aminotransferase increased	Uncommon
	Liver function test increased	Uncommon
Musculoskeletal and connective tissue disorders	Pain in extremity	Common
Renal and urinary disorders	Blood creatinine increased	Uncommon
	Blood urea increased	Uncommon
	Glomerular filtration rate decreased	Uncommon

a. Hyperuricaemia includes hyperuricaemia and blood uric acid increased

The safety profile of bempedoic acid has been studied in clinical studies. The most commonly reported adverse reactions with bempedoic acid during pivotal studies were hyperuricaemia (3.8%), pain in extremity (3.1%), and anaemia (2.5%). More patients on bempedoic acid compared to placebo discontinued treatment due to muscle spasms (0.7% versus 0.3%), diarrhoea (0.5% versus <0.1%). pain in extremity (0.4% versus 0), and nausea (0.3% versus 0.2%), although differences between bempedoic acid and placebo were not significant.

Tabulated list of adverse reactions of Rosuvastatin

Adverse reactions reported with rosuvastatin are displayed by system organ class and frequency in table 2.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Table Adverse reactions of Rosuvastatin

System Organ Class (SOC)	Adverse reactions	Frequency Categories

Blood and lymphatic system disorders	Thrombocytopenia	Rare
Immune system disorders	Hypersensitivity reactions including angioedema	Rare
Endocrine disorders	Diabetes mellitus	Common
Psychiatric disorders	Depression	Not known
Nervous system disorders	Headache Dizziness	Common
	Polyneuropathy Memory loss	Very rare
	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)	Not known
Respiratory, thoracic and mediastinal disorders	Cough Dyspnoea	Not known
Gastrointestinal disorders	Constipation Nausea Abdominal pain	Common
	Pancreatitis	Rare
	Diarrhoea	Not known
Hepatobiliary disorders	Increased hepatic transaminases	Rare
	Jaundice Hepatitis	Very Rare
Skin and subcutaneous tissue disorders	Pruritus Rash	Uncommon

	Urticaria	
	Stevens-Johnson syndrome	Not known
Musculoskeletal and connective tissue disorders	Myalgia	Common
	Myopathy (including myositis) Rhabdomyolysis Lupus-like syndrome Muscle rupture	Rare
	Arthralgia	Very Rare
	Immune-mediated necrotising myopathy Tendon disorders, sometimes complicated by rupture	Not known
Renal and urinary disorders	Haematuria	Very Rare
Reproductive system and breast disorders	Gynaecomastia	Very Rare
General disorders and administration site conditions	Asthenia	Common
	Oedema	Not Known

4.9 Overdose

Bempedoic Acid

Doses up to 240 mg/day (1.3 times the approved recommended dose) have been administered in clinical trials with no evidence of dose limiting toxicity.

No adverse events were observed in animal studies at exposures up to 14-fold higher than those in patients treated with bempedoic acid at 180 mg once daily.

There is no specific treatment for a Bempedoic Acid overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

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

Pharmacological properties

5. Pharmacological properties

Pharmacotherapeutic group: Drugs used in hypercholesterolaemia and lipid-lowering therapies.

5.1 Mechanism of Action

Bempedoic acid

Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid and its active metabolite, ESP15228, require coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA and ESP15228-CoA, respectively. ACSVL1 is expressed primarily in the liver. Inhibition of ACL by ETC-1002-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of low-density lipoprotein receptors.

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.

5.2 Pharmacodynamic properties

Bempedoic acid

Administration of bempedoic acid in combination with maximally tolerated statins, with or without other lipid modifying agents, decreases LDL-C, non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apo B), and total cholesterol (TC) in patients with hyperlipidemia.

Because patients with diabetes are at elevated risk for atherosclerotic cardiovascular disease, the clinical trials of bempedoic acid included patients with diabetes mellitus. Among the subset of patients with diabetes, lower levels of HbA1c were observed as compared to placebo (on average 0.2%). In patients without diabetes, no difference in HbA1c was observed between bempedoic acid and placebo and there were no differences in the rates of hypoglycaemia.

Cardiac Electrophysiology at a dose of 240 mg (1.3 times the approved recommended dose), bempedoic acid does not prolong the QT interval to any clinically relevant extent.

Rosuvastatin

Rosuvastatin dose dependently reduces elevated LDL-cholesterol and reduces total cholesterol and triglycerides and increases HDL-cholesterol. A therapeutic response to Rosuvastatin is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that. Individualization of drug dosage should be based on the therapeutic response.

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

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
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 safety and efficacy: There were no adverse events or serious adverse events or deaths reported in the study. Upon completion of the clinical phase of the study, assessment of the vital signs measurements, post-study laboratory test results and the overall state of health of all the participated subjects were concluded to be clinically fit. Both products were found to be safe and well tolerated in participated subjects

5.3 Pharmacokinetic properties

Bempedoic acid

Absorption

Pharmacokinetic data indicate that bempedoic acid is absorbed with a median time to maximum concentration of 3.5 hours when administered as bempedoic acid 180 mg tablets.

Effect of Food

Concomitant food administration had no effect on the oral bioavailability of bempedoic acid.

Distribution

The bempedoic acid apparent volume of distribution (V/F) was 18 L. Plasma protein binding of bempedoic acid, its glucuronide and its active metabolite, ESP15228, were 99.3%, 98.8% and 99.2%, respectively. Bempedoic acid does not partition into blood cells.

Metabolism

The primary route of elimination for bempedoic acid is through metabolism of the acyl glucuronide. Bempedoic acid is also reversibly converted to an active metabolite (ESP15228) based on aldo- keto reductase activity observed in vitro from human liver. Mean plasma AUC metabolite/parent drug ratio for ESP15228 following repeat-dose administration was 18% and remained constant over time. Both compounds are converted to inactive glucuronide conjugates in vitro by UGT2B7. Bempedoic acid, ESP15228 and their respective conjugated forms were detected in plasma with bempedoic acid accounting for the majority (46%) of the AUC0-48h and its glucuronide being the next most prevalent (30%). ESP15228 and its glucuronide represented 10% and 11% of the plasma AUC0-48h, respectively.

Excretion

Following single oral administration of 240 mg of bempedoic acid (1.3 times the approved recommended dose), approximately 70% of the total dose (bempedoic acid and its metabolites) was recovered in urine, primarily as the acyl glucuronide conjugate of bempedoic acid, and approximately 30% was recovered in feces. Less than 5% of the administered dose was excreted as unchanged bempedoic acid in feces and urine combined.

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.

Elimination

Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Linearity: Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Renal, Hepatic impairment & paediatric

No dose adjustment is necessary in patients with mild or moderate renal impairment. There are limited data available in patients with severe renal impairment (defined as estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2), and patients with end-stage renal disease (ESRD) on dialysis have not been studied. Additional monitoring for adverse reactions may be warranted in these patients when Nilemdo is administered.No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). No data are available in patients with severe hepatic impairment (Child-Pugh C). Periodic liver function tests should be considered for patients with severe hepatic impairment.

The safety and efficacy of Nilemdo in children aged less than 18 years have not yet been established. No data are available.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Bempedoic acid

The standard battery of genotoxicity studies has not identified any mutagenic or clastogenic potential of bempedoic acid. In full lifetime carcinogenicity studies in rodents, bempedoic acid increased the incidence of hepatocellular and thyroid gland follicular tumours in male rats and hepatocellular tumours in male mice. Because these are common tumours observed in rodent lifetime bioassays and the mechanism for tumourigenesis is secondary to a rodent-specific PPAR alpha activation, these tumours are not considered to translate to human risk.

Increased liver weight and hepatocellular hypertrophy were observed in rats only and were partially reversed after the 1-month recovery at ≥ 30 mg/kg/day or 4 times the exposure in humans at 180 mg. Reversible, non-adverse changes in laboratory parameters indicative of these hepatic effects, decreases in red blood cell and coagulation parameters, and increases in urea nitrogen and creatinine were observed in both species at tolerated doses. The NOAEL for adverse response in the chronic studies was 10 mg/kg/day and 60 mg/kg/day associated with exposures below and 15 times the human exposure at 180 mg in rats and monkeys, respectively.

Bempedoic acid was not teratogenic when given orally at doses of 60 and 80 mg/kg/day, resulting in 11 and 12 times the systemic exposure in humans at the maximum recommended human dose (MRHD) of 180 mg to pregnant rats and rabbits, respectively. In an embryofetal development study in rats, bempedoic acid was given orally to pregnant rats at 10, 30, and 60 mg/kg/day during the period of organogenesis from gestation day 6 to 17. There were increases in the incidence of non-adverse fetal skeletal variations (bent long bones and bent scapula and incomplete ossification) at doses ≥ 10 mg/kg/day (less than the clinical exposure) in the absence of maternal toxicity. At maternally toxic doses, bempedoic acid caused decreases in the numbers of viable fetuses, increases in post-implantation loss, and increased total resorptions at 60 mg/kg/day (11 times MRHD) and reduced fetal body weight at ≥ 30 mg/kg/day (4 times the MRHD). No adverse development effects were observed when bempedoic acid was given to pregnant rabbits during

the period of organogenesis (gestation day 6 to 18) at doses up to 80 mg/kg/day (12 times MRHD). In a pre- and post-natal development study in pregnant rats given oral doses of bempedoic acid at 5, 10, 20, 30 and 60 mg/kg/day throughout pregnancy and lactation (gestation day 6 to lactation day 20), there were adverse effects on delivery in the presence of maternal toxicity, including: increases in stillborn pups, reductions in numbers of live pups, pup survival, pup growth and slight delays in learning and memory at ≥ 10 mg/kg/day (at exposures equivalent to the MRHD).

No data are available on the effect of Bempedoic acid on human fertility. Administration of bempedoic acid to male and female rats prior to mating and through gestation day 7 in females resulted in changes in estrous cyclicity, decreased numbers of corpora lutea and implants at ≥ 30 mg/kg/day with no effects on male or female fertility or sperm parameters at 60 mg/kg/day (4 and 9 times the systemic exposure in humans at 180 mg, respectively)

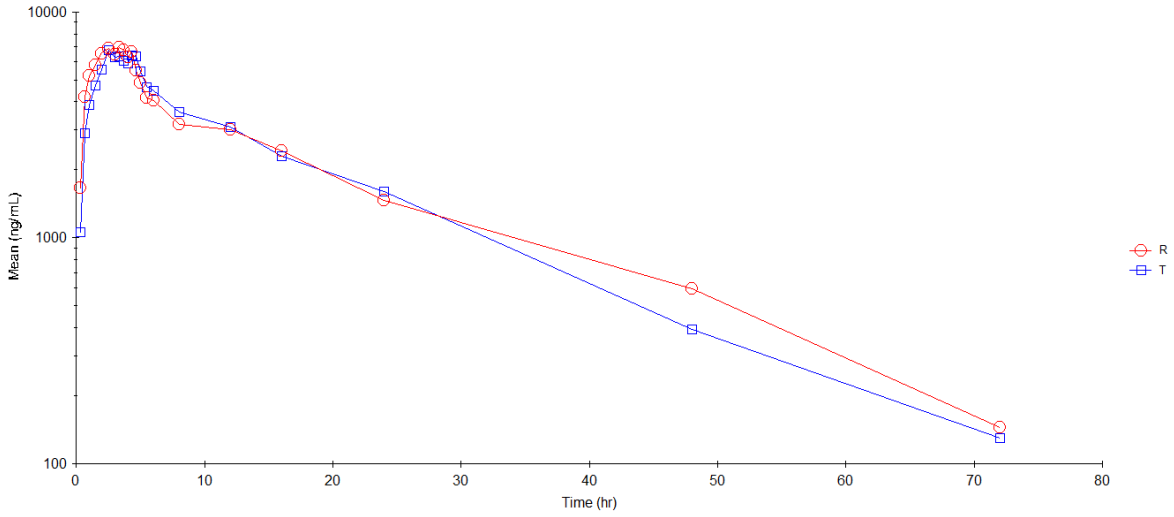
Rosuvastatin

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.

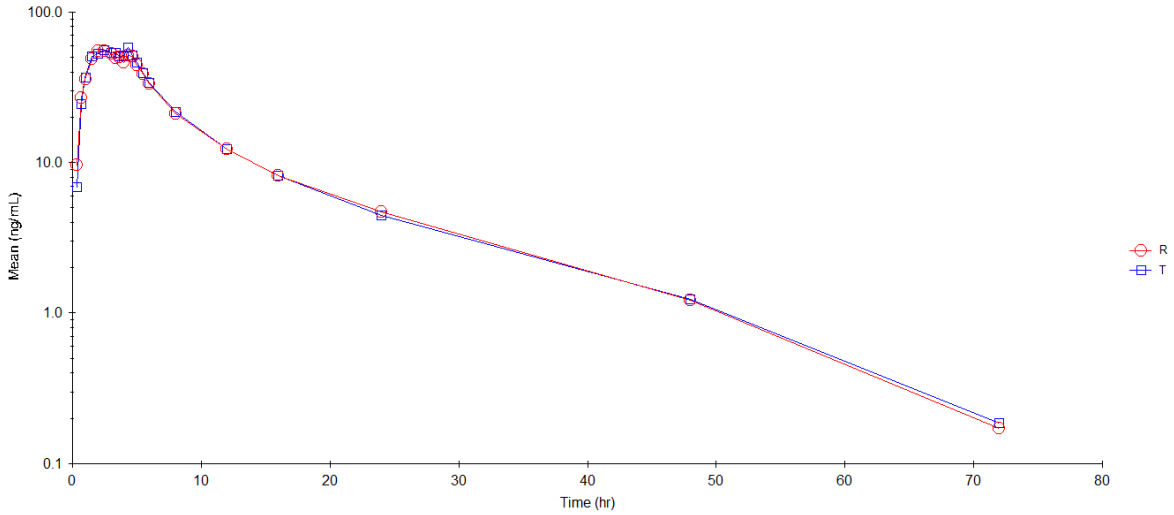
Clinical studies

An open label, randomized, balanced, two treatment, two sequence, two period, cross-over, single oral dose bioequivalence study in 24 healthy, adult, human subjects under fasting conditions were completed. Upon completion of the clinical phase of the study, assessment of the vital signs measurements, post-study laboratory test results and the overall state of health of all the participated subjects were concluded to be clinically fit. Both products were found to be safe and well tolerated in participated subjects. There were no adverse events or serious adverse events or deaths reported in the study.

Mean plot Bempedoic Acid

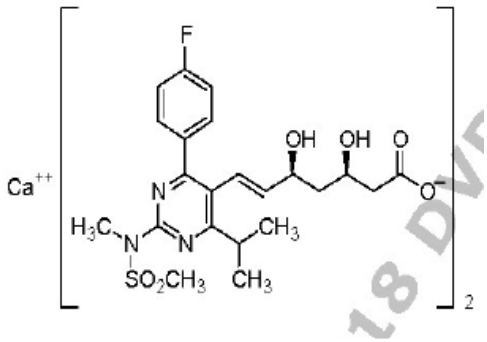


Mean plot Rosuvastatin

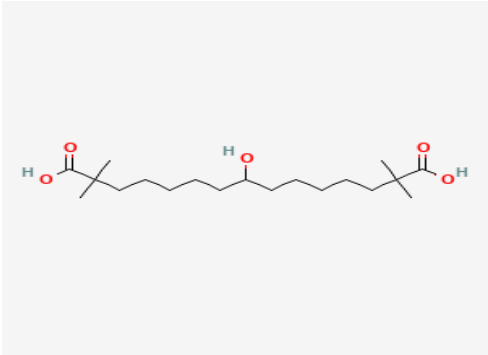


7. Description

Rosuvastatin Calcium is (E)-(3R, 5S)-7-{4-(4-fluorophenyl)-6-isopropyl-2-{methyl(methylsulphonylamino)] pyrimidin-5-yl}-3,5-dihydroxyhepten-6-oic avid calcium. The empirical formula is $(C_{22}H_{27}FN_3O_6S)_2$. Ca and its molecular weight is 1001.1 g/mol. The chemical structure of Rosuvastatin Calcium is:



Bempedoic Acid is 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid. The empirical formula is $C_{19}H_{36}O_5$ and its molecular weight is 344.5 g/mol. The chemical structure of Bempedoic Acid is:



ROZUCOR B / BEMPESTA R is Reddish brown colored, round, biconvex, film coated tablets, plain on both sides. The excipients used are Microcrystalline Cellulose, Pregelatinised starch, Povidone K, Isopropyl alcohol, Sodium Starch Glycolate, Purified Talc, Calcium Stearate, Lactose Monohydrate, Ferric oxide red, Crospovidone, Magnesium Stearate, Instacoat Aqua brown, Purified water.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

ROZUCOR B / BEMPESTA R is packed in Blister pack of 10 Tablets

8.4 Storage and handing instructions

Store below 30°C, Protect from moisture

Keep out of reach of children

9. Patient Counselling Information

ROZUCOR B / BEMPESTA R

Rosuvastatin and Bempedoic Acid 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 questions, or if there is anything you do not understand, 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 ROZUCOR B / BEMPESTA R is and what it is used for

Bempedoic acid and rosuvastatin tablet contains Bempedoic acid 180 mg and rosuvastatin 40 mg which is used for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL

How ROZUCOR B / BEMPESTA R works

Bempedoic acid acts by inhibiting adenosine triphosphate-citrate lyase (ACL) and consequently cholesterol biosynthesis, leading to increased expression of LDL receptors and increasing low-density lipoproteins (LDL-C) plasma clearance. Rosuvastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body to decrease the amount of cholesterol that may build up on the walls of the arteries and block blood flow to the heart, brain, and other parts of the body.

9.2 What you need to know before you use ROZUCOR B / BEMPESTA R

Do not take ROZUCOR B / BEMPESTA R:

If you are allergic to Bempedoic Acid and Rosuvastatin or any of the other ingredients of this medicine.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking ROZUCOR B / BEMPESTA R

-If symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.

-Discontinue medication immediately if you experiences rupture of a tendon. Consider discontinuing medication if you experiences joint pain, swelling, or inflammation. Please take rest at the first sign of tendinitis or tendon rupture and to contact healthcare provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy if you have history of tendon disorders or tendon rupture.

-Risks increase with use of 40 mg dose, advanced age (≥65), hypothyroidism, renal impairment, and combination use with cyclosporine, darolutamide, regorafenib, certain anti-viral medicines or their combinations. Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. Advise you to promptly report to your physician unexplained and/or persistent muscle pain, tenderness, or weakness and discontinue rosuvastatin if signs or symptoms appear.

-Persistent elevations in hepatic transaminases can occur. Perform liver enzyme tests before initiating therapy and as clinically indicated thereafter.

-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 (international normalized ratio). If you are taking coumarin anticoagulants and rosuvastatin concomitantly, INR(international normalized ratio). should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs.

-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 on rosuvastatin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

-Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including rosuvastatin.

Children and adolescents

The use of this combination product in children and adolescents up to 18 years of age is not recommended.

Other medicines and ROZUCOR B / BEMPESTA R

- Simvastatin

- Pravastatin

- Sofosbuvir/velpatasvir/voxilaprevir or ledipasvir/sofosbuvir

- Cyclosporine and darolutamide

- Gemfibrozil

- Atazanavir/ritonavir, lopinavir/ritonavir, simeprevir

- Dasabuvir/ombitasvir/paritaprevir/ritonavir

- Elbasvir/grazoprevir

- Sofosbuvir/velpatasvir

- Glecaprevir/pibrentasvir

- Regorafenib-Concomitant use of antacid: When taking Rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration.

-Erythromycin combination decreases Rosuvastatin exposure.

-Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

-Vitamin K antagonists

-Oral Contraceptives/hormone replacement therapy (HRT) There was no detectable effect of rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation

-Digoxin decreases Rosuvastatin exposure.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, don't take this medication.

Driving and using machines

If you feel dizzy while taking this medicine, do not drive or use machines.

How will I receive ROZUCOR B / BEMPESTA R?

Swallow the tablets whole with some water.

If you take more ROZUCOR B / BEMPESTA R Tablets than you should

If you have taken too many tablets, contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

If you forget to take ROZUCOR B / BEMPESTA R

If you miss a dose of Bempedoic Acid and Rosuvastatin Tablets, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the dose.

What are the possible side effects of ROZUCOR B / BEMPESTA R?

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

Stop taking this medicine and consult your doctor immediately if any of the following occur respiratory tract infection, muscle spasms, joint pain, stiffness in joints, back pain, abdominal pain, discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes, headache, myalgia, abdominal pain, asthenia and nausea.

–you may need medical treatment.

9.3 How to take ROZUCOR B / BEMPESTA R

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

How much to take and when

Your health care provider will decide how much to give you.

How to take ROZUCOR B / BEMPESTA R

Swallow the tablets whole with some water.

How long to take ROZUCOR B / BEMPESTA R

- Take ROZUCOR B / BEMPESTA R every day for as long as your doctor tells you. You may have to take this treatment over a long period of time.
- Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
- If you take more ROZUCOR B / BEMPESTA R than you should
- If you have taken too many tablets, contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

If you forget to take ROZUCOR B / BEMPESTA R

If you miss a dose of Bempedoic Acid and Rosuvastatin Tablets, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the dose.

If you stop taking ROZUCOR B / BEMPESTA R

Do not stop taking **ROZUCOR B / BEMPESTA R** unless your doctor tells you to. If you have questions about how long to take this medicine, talk to your doctor.

9.4 Possible Side Effects

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

Stop taking this medicine and consult your doctor immediately if any of the following occur respiratory tract infection, muscle spasms, joint pain, stiffness in joints, back pain, abdominal pain, discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes, headache, myalgia, abdominal pain, asthenia and nausea. You may need medical treatment in such events.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store ROZUCOR B / BEMPESTA R

Store below 30°C, Protect from moisture

9.6 What ROZUCOR B / BEMPESTA R contain:

The active substances are Rosuvastatin and Bempedoic Acid

Each tablet contains Rosuvastatin 40 mg and Bempedoic Acid 180 mg

The excipients used are Microcrystalline Cellulose, Pregelatinised starch, Povidone K, Isopropyl alcohol, Sodium Starch Glycolate, Purified Talc, Calcium Stearate, Lactose Monohydrate, Ferric oxide red, Crospovidone, Magnesium Stearate, Instacoat Aqua brown, Purified water

10 Details of manufacturer

Exemed Pharmaceuticals
Plot No. 133/1 & 133/2, G.I.D.C.,
Selvas Road, Vapi – 396195,
Dist.: Valsad, Gujarat

11 Details of permission or licence number with date

Mfg Licence No.: G/25/2011 issued on 21.09.2022

12 Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ROZUCOR B / BEMPESTA R/Sep-22/01/PI