

SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT

Bedoic Plus 40mg/180mg Tablet

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Rosuvastatin Calcium

Equivalent to rosuvastatin.....40mg

Bempedoic acid180mg

For full list of excipients, see section 6.1

3.PHARMACEUTICAL FORM

Film-coated tablet.

Light Brown to Brown Round shape, biconvex, film coated tablets, plain on both sides.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

Bempedoic acid and Rosuvastatin is used in the treatment of High cholesterol. It inhibits an enzyme called adenosine triphosphate-citrate lyase (ACL) and blocks the production of cholesterol in the liver.

4.2 Posology and method of administration

Posology

Rosuvastatin

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

Rosuvastatin may be given at any time of day, with or without food.

Treatment of hypercholesterolaemia

The recommended start dose is 5 or 10 mg orally once daily in both statin-naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses, a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment

goal on

20 mg, and in whom routine follow-up will be performed . Specialist supervision is recommended when the 40 mg dose is initiated.

Prevention of cardiovascular events

In the cardiovascular events risk reduction study, the dose used was 20 mg daily.

Paediatric population

Paediatric use should only be carried out by specialists.

Children and adolescents 6 to 17 years of age (Tanner Stage <II-V)

Heterozygous familial hypercholesterolaemia

In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily.

- In children 6 to 9 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-10 mg orally once daily. Safety and efficacy of doses greater than 10 mg have not been studied in this population.
- In children 10 to 17 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-20 mg orally once daily. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations . Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

Homozygous familial hypercholesterolaemia

In children 6 to 17 years of age with homozygous familial hypercholesterolaemia, the recommended maximum dose is 20 mg once daily. A starting dose of 5 to 10 mg once daily depending on age, weight and prior statin use is advised. Titration to the maximum dose of 20 mg once daily should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

There is limited experience with doses other than 20 mg in this population. The 40 mg tablet is not suitable for use in paediatric patients.

Children younger than 6 years

The safety and efficacy of use in children younger than 6 years has not been

studied. Therefore, Rosuvastatin is not recommended for use in children younger than 6 years.

Bempedoic acid.

Posology

The recommended dose of Bempedoic acid is one film-coated tablet of 180 mg taken once daily.

Concomitant simvastatin therapy

When Bempedoic acid is coadministered with simvastatin, simvastatin dose should be limited to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and high risk for cardiovascular complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks).

Special

populations

Elderly patients

No dose adjustment is necessary in elderly patients.

Patients with renal impairment

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 Bempedoic acid is administered.

Patients with hepatic impairment

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.

Paediatric population

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

Method of administration

Tablet should be taken orally with or without food. Tablet should be swallowed whole.

4.3 Contraindications

Rosuvastatin

Rosuvastatin is contraindicated:

- In patients with hypersensitivity to the active substance or to any of the excipients.

- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- 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.

The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/ rhabdomyolysis. Such factors include:

- Moderate renal impairment (creatinine clearance < 60 ml/min)
- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- Alcohol abuse
- Situations where an increase in plasma levels may occur
- Asian patients

Bempedoic acid.

Hypersensitivity to the active substance or to any of the excipients.

- Pregnancy.
- Breast-feeding.
- Concomitant use with simvastatin > 40 mg daily

4.4 Special warnings and precautions for use

Rosuvastatin

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at the 40 mg

dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal Muscle Effects

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

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

Liver Effects

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

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post- marketing use is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

Bempedoic acid.

Potential risk of myopathy with concomitant use of statins

Bempedoic acid increases plasma concentrations of statins. 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. 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. 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.

Myositis with a CPK level $> 10\times$ ULN was rarely reported with bempedoic acid and background simvastatin 40 mg therapy. Doses of simvastatin > 40 mg should not be used with Bempedoic acid .

Increased serum uric acid

Bempedoic acid may raise the serum uric acid level due to inhibition of renal tubular OAT2 and may cause or exacerbate hyperuricaemia and precipitate gout in patients with a medical history of gout or predisposed to gout. Treatment with Bempedoic acid should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.

Elevated liver enzymes

In clinical trials, elevations of $> 3\times$ ULN in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported with bempedoic acid. These elevations have been asymptomatic and not associated with elevations $\geq 2\times$ ULN in bilirubin or with cholestasis and have returned to baseline with continued treatment or after discontinuation of therapy. Liver function tests should be performed at initiation of therapy. Treatment with Bempedoic acid should be discontinued if an increase in transaminases of $> 3\times$ ULN persists.

Renal impairment

There is limited experience with bempedoic acid in patients with severe renal impairment (defined as $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), and patients with ESRD on dialysis have not been studied . Additional monitoring for adverse reactions may be warranted in these patients when Bempedoic acid is administered.

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Periodic liver function tests should be considered for patients with severe hepatic impairment.

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.

4.5 Interaction with other medicinal products and other forms of interaction Rosuvastatin

Effect of co-administered medicinal products on rosuvastatin

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

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

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

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

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

Ezetimibe: Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects . A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out .

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

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

Ticagrelor: Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis.

Bempedoic acid

Effects of other medicinal products on bempedoic acid

Transporter-mediated drug interactions

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.

Probenecid

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 area under the curve (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.

Effects of bempedoic acid on other medicinal products

Statins

The pharmacokinetic interactions between bempedoic acid 180 mg and simvastatin 40 mg, atorvastatin 80 mg, pravastatin 80 mg, and rosuvastatin 40 mg were evaluated in clinical trials.

Administration of a single dose of simvastatin 40 mg with steady-state bempedoic acid 180 mg resulted in a 2-fold increase in simvastatin acid exposure. Elevations of 1.4-fold to 1.5-fold in AUC of atorvastatin, pravastatin, and rosuvastatin (administered as single doses) and/or their major metabolites were observed when coadministered with bempedoic acid 180 mg. Higher elevations have been observed when these statins were coadministered with a supratherapeutic 240 mg dose of bempedoic acid.

Transporter-mediated drug interactions

Bempedoic acid and its glucuronide weakly inhibit OATP1B1 and OATP1B3 at clinically relevant concentrations. Coadministration of bempedoic acid with medicinal products that are substrates of OATP1B1 or OATP1B3 (i.e., bosentan, fimasartan, asunaprevir, glecaprevir, grazoprevir, voxilaprevir, and statins such as atorvastatin, pravastatin, fluvastatin, pitavastatin, rosuvastatin, and simvastatin) may result in increased plasma concentrations of these medicinal products.

Bempedoic acid inhibits OAT2 *in vitro*, which may be the mechanism responsible for minor elevations in serum creatinine and uric acid. Inhibition of OAT2 by bempedoic acid may also potentially increase plasma concentrations of medicinal products that are substrates of OAT2. Bempedoic acid may also weakly inhibit OAT3 at clinically relevant concentrations.

Ezetimibe

Total ezetimibe (ezetimibe and its glucuronide form) and ezetimibe glucuronide AUC and C_{max} increased approximately 1.6- and 1.8-fold, respectively, when a single dose of ezetimibe was taken with steady-state bempedoic acid. This increase is likely due to inhibition of OATP1B1 by bempedoic acid, which results in decreased hepatic uptake and subsequently decreased elimination of ezetimibe-glucuronide. Increases in AUC and C_{max} for ezetimibe were less than 20%. These elevations are not clinically meaningful and do not impact dosing recommendations.

4.6 Fertility, pregnancy and lactation

Rosuvastatin

Rosuvastatin is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures.

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

Bempedoic acid

Pregnancy

Bempedoic acid is contraindicated during pregnancy.

There are no or limited amount of data from the use of bempedoic acid in pregnant women. Studies in animals with bempedoic acid have shown reproductive toxicity.

Because bempedoic acid decreases cholesterol synthesis and possibly the synthesis of other cholesterol derivatives needed for normal foetal development, Bempedoic acid may cause foetal harm when administered to pregnant women. Bempedoic acid should be discontinued prior to conception or as soon as pregnancy is recognized.

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment. Breast-feeding

It is unknown whether bempedoic acid/metabolites are excreted in human milk. Because of the potential for serious adverse reactions, women taking Bempedoic acid should not breast-feed their infants. Bempedoic acid is contraindicated during breast-

feeding

4.7 Effects on ability to drive and use machines

Rosuvastatin

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

Bempedoic acid

Bempedoic acid has no or negligible influence on the ability to drive and use machines.

4.8 Und

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

Bempedoic acid

Summary of the safety profile

The safety profile of bempedoic acid has been studied in 4 controlled phase 3 clinical studies (N=3,621) including patients with hypercholesterolemia on maximum tolerated statin dose (2 studies; n=3008) and patients on no or low dose statins (2 studies; n=613). The most commonly reported adverse reactions with bempedoic acid during pivotal trials 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

to the National Regulatory Authority via Pharmacovigilance
Electronic Reporting System (PvERS)
<https://pv.pharmacyboardkenya.org/>

4.9 Overdose

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.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA

reductase inhibitors. ATC code: C10A A07

Pharmacotherapeutic group: Lipid modifying agents, other

lipid modifying agents. ATC code: C10AX15

Mechanism of action

Rosuvastatin

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

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 requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA. ACSVL1 is expressed primarily in the liver and not in skeletal muscle. 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. Additionally, inhibition of ACL by ETC-1002-CoA results in concomitant suppression of hepatic fatty acid biosynthesis.

5.2 Pharmacokinetic properties

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Absorption

Rosuvastatin

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

Bempedoic acid

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. Bempedoic acid pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Bempedoic acid can be considered a prodrug that is activated intracellularly by ACSVL1 to ETC-1002-CoA. The steady-state C_{max} and AUC following multiple dose administration in patients with hypercholesterolaemia were 24.8 (6.9) microgram/mL and 348 (120) microgram·h/mL, respectively. Bempedoic acid steady-state pharmacokinetics were generally linear over a range of 120 mg to 220 mg. There were no time-dependent changes in bempedoic acid pharmacokinetics following repeat administration at the recommended dose, and bempedoic acid steady-state was achieved after 7 days. The mean accumulation ratio of bempedoic acid was approximately 2.3-fold.

Concomitant food administration had no effect on the oral bioavailability of bempedoic acid when administered as Bempedoic acid 180 mg tablets. Food slows the absorption rate of bempedoic acid; the absorption rate constant with food is 0.32/h.

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

Bempedoic acid

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 red blood cells.

Biotransformation

Rosuvastatin

Rosuvastatin undergoes limited metabolism (approximately 10%). In vitro metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Bempedoic acid

In vitro metabolic interaction studies suggest that bempedoic acid, as well as its active metabolite and glucuronide forms are not metabolised by and do not inhibit or induce cytochrome P450 enzymes.

The primary route of elimination for bempedoic acid is through metabolism to 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 AUC_{0-48h} and its glucuronide being the next most prevalent (30%). ESP15228 and its glucuronide represented 10% and 11% of the plasma AUC_{0-48h}, respectively.

The steady-state C_{max} and AUC of the equipotent active metabolite (ESP15228) of bempedoic acid in patients with hypercholesterolaemia were 3.0 (1.4) microgram/mL and 54.1 (26.4) microgram·h/mL, respectively. ESP15228 likely made a minor contribution to the overall clinical activity of bempedoic acid based on systemic exposure and pharmacokinetic properties.

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Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Bempedoic acid

The steady-state clearance (CL/F) of bempedoic acid determined from a population PK analysis in patients with hypercholesterolaemia was 12.1 mL/min after once-daily dosing; renal clearance of unchanged bempedoic acid represented less than 2% of total clearance. The mean (SD) half-life for bempedoic acid in humans was 19 (10) hours at steady-state.

Following single oral administration of 240 mg of bempedoic acid (1.3 times the approved recommended dose), 62.1% of the total dose (bempedoic acid and its metabolites) was recovered in urine, primarily as the acyl glucuronide conjugate of bempedoic acid, and 25.4% was recovered in faeces. Less than 5% of the administered dose was excreted as unchanged bempedoic acid in faeces and urine combined.

5.3 Preclinical safety data

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.

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 or toxic to embryos or fetuses in pregnant rabbits at doses up to 80 mg/kg/day or 12 times the systemic exposure in humans at 180 mg. Pregnant rats given bempedoic acid at 10, 30, and 60 mg/kg/day during organogenesis had decreased numbers of viable fetuses and reduced foetal body weight at ≥ 30 mg/kg/day or 4 times the systemic exposure in humans at 180 mg. An increased incidence of foetal skeletal findings (bent scapula and ribs) were observed at all doses, at exposures below the systemic exposure in humans at 180mg. In a pre- and post-natal development study, pregnant rats administered bempedoic acid at 5, 10, 20 and 30 mg/kg/day throughout pregnancy and lactation had adverse maternal effects at ≥ 20 mg/kg/day and reductions in numbers of live pups and pup survival, pup growth and learning and memory at ≥ 10 mg/kg/day, with maternal exposures at 10 mg/kg/day, less than the exposure in humans at 180 mg.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose

Monohydrate

Microcrystalline

Cellulose PH 101

Povidone K30

Purified
Water
Magnesium
Stearate
Colloidal Anhydrous
Silica (Aerosil)
Croscarmellose
sodium
Hydroxy Propyl
Cellulose
Microcrystalline
Cellulose PH 102
Sodium Lauryl
Sulfate
Readycoat Naq Red
Oxide Of Iron Iso
Propyl Alcohol
Methylene Dichloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Nature and contents of container 3 X 10 Alu Alu Tablets.

6.5 Special precautions for disposal and other handling

No special requirements.

7.0 MARKETING AUTHORISATION HOLDER AND MANUFACTURING ADDRESS DAWA LIMITED

Baba Dogo Road,

Ruaraka, P.O.Box

16633-00620

Nairobi, Kenya

Manufacture Name:

Cubit Lifesciences LLP

Plot No. 39-40, Ozone Industrial Park,

At. & post: Kerala- Bhayla Near.

Kerala G.I.D.C, Taluka: Bavla, Dist.:

Ahmedabad-382220 Gujarat India.

8. MARKETING AUTHORISATION NUMBER(S)

H2025/CTD11701/25116

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

2025 September 17

10. DATE OF REVISION OF THE TEXT

2025 September 17

