Bempeget™

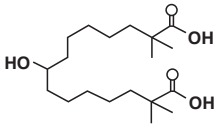
(Bempedoic Acid)

بیمپیگیٹ

Film-coated Tablets
180mg

DESCRIPTION

Bempeget contains Bempedoic Acid, it is an adenosine triphosphate citrate lyase (ACL) inhibitor. Its chemical name is 8-hydroxy-2,2,14,14 tetramethyl-pentadecanedioic Acid. Its molecular formula is $C_{19}H_{36}O_5$ and the structural formula is:



Bempedoic Acid

QUALITATIVE & QUANTITATIVE COMPOSITION

Bempeget (Bempedoic Acid) is available for oral administration as:

Bempeget Tablets 180mg
Each film-coated tablet contains:
Bempedoic Acid…180mg

CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacokinetics

Absorption

Bempedoic Acid is absorbed with a median time to maximum concentration of 3.5 hours when administered as Bempedoic Acid 180mg tablets. 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 hypercholesterolemia 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 120mg to 220mg. 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.

Effect of Food

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

Distribution

The Bempedoic Acid apparent volume of distribution (V/F) was 18L. 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.

Metabolism

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 hypercholesterolemia 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.

Elimination

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

Special Population

Patients with renal impairment

The mean Bempedoic Acid AUC in subjects with mild renal impairment were 1.5-fold higher compared to those with normal renal function. Relative to those with normal renal function, mean Bempedoic Acid AUCs were higher in patients with moderate or severe renal impairment by 2.3-fold and 2.4-fold, respectively.

Patients with hepatic impairment

Compared to patients with normal hepatic function, the Bempedoic Acid mean C_{max} and AUC were decreased by 11% and 22%, respectively, in patients with mild hepatic impairment and by 14% and 16%, respectively, in patients with moderate hepatic impairment. Compared to patients with normal hepatic function, the ESP15228 mean C_{max} and AUC were decreased by 13% and 23%, respectively, in patients with mild hepatic impairment and by 24% and 36%, respectively, in patients with moderate hepatic impairment. This is not expected to result in lower efficacy.

THERAPEUTIC INDICATIONS

Bempeget (Bempedoic Acid) is indicated:

- To reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with:
  - established cardiovascular disease (CVD), or
  - a high risk for a CVD event but without established CVD
- As an adjunct to diet, in combination with other low-density lipoprotein cholesterol (LDL-C) lowering therapies, or alone when concomitant LDL-C lowering therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).

DOSAGE AND ADMINISTRATION

The recommended dose of Bempeget (Bempedoic Acid) is one tablet of 180mg taken once daily.
Bempeget (Bempedoic Acid) should be taken orally with or without food.
After initiation of Bempeget (Bempedoic Acid), analyze lipid levels within 8 to 12 weeks.

Concomitant simvastatin therapy

When Bempeget (Bempedoic Acid) co-administered with simvastatin, simvastatin dose should be limited to 20mg daily (or 40mg daily for patients with severe hypercholesterolemia 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).

Pediatric population

The safety and efficacy of Bempeget (Bempedoic Acid) in children aged less than 18 years have not yet been established.

ADVERSE REACTIONS

Common: Anaemia, gout, hyperuricaemia, aspartate aminotransferase increased and pain in extremity.
Uncommon: Haemoglobin decreased, alanine aminotransferase increased, liver function test increased, blood creatinine increased, blood urea increased and glomerular filtration rate decreased.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

Bempedoic Acid is contraindicated in:

- Patients with hypersensitivity to the active substance or to any of the excipient of the product.
- Pregnancy.
- Breast-feeding.
- Concomitant use with simvastatin > 40mg daily.

PRECAUTIONS

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 > 10X 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 > 10X ULN was rarely reported with Bempedoic Acid and background simvastatin 40mg therapy.

Tendon Rupture

Bempedoic Acid is associated with an increased risk of tendon rupture or injury. 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.

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 hyperuricemia and precipitate gout in patients with a medical history of gout or predisposed to gout. Treatment with Bempedoic Acid should be discontinued if hyperuricemia accompanied with symptoms of gout appear.

Elevated liver enzymes

Liver function tests should be performed at initiation of therapy. Treatment with Bempedoic Acid tablets should be discontinued if an increase in transaminases of > 3X ULN persists.

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.

Renal impairment

Additional monitoring for adverse reactions may be warranted in patients with renal impairment when Bempedoic Acid is administered.

Hepatic impairment

Periodic liver function tests should be considered for patients with severe hepatic impairment.

Excipients

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

DRUG INTERACTIONS

Statins

The pharmacokinetic interactions between Bempedoic Acid 180mg and simvastatin 40mg, atorvastatin 80mg, pravastatin 80mg, and rosuvastatin 40mg were evaluated. Administration of a single dose of simvastatin 40mg with steady-state Bempedoic Acid 180mg 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. Higher elevations have been observed when these statins were coadministered with a supratherapeutic 240mg dose of Bempedoic Acid.

Transporter-mediated drug interactions

Bempedoic Acid and its glucuronide weakly inhibit OATP1B1 and OATP1B3. 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, 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.

OVERDOSAGE

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.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Bempeget (Bempedoic Acid) Tablets 180mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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