Bempeget-EZ™

(Bempedoic Acid + Ezetimibe)

بیمپیگیٹ-ای ذی

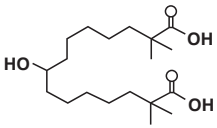
Film-coated Tablets 180mg + 10mg

DESCRIPTION

Bempeget-EZ, contain Bempedoic Acid, an adenosine triphosphate-citrate lyase (ACL) inhibitor, and Ezetimibe, a dietary cholesterol absorption inhibitor.

Bempedoic Acid

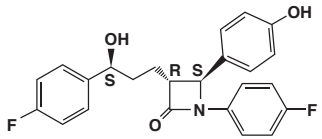
The chemical name for Bempedoic Acid is 8-hydroxy-2, 2, 14, 14-tetramethyl-pentadecanedioic Acid. Its molecular formula is $C_{19}H_{36}O_5$ and the structural formula is:



Bempedoic Acid

Ezetimibe

The chemical name for Ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S) hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2 azetidinone. Its molecular formula is $C_{24}H_{21}F_2NO_3$ and the structural formula is:



Ezetimibe

QUALITATIVE AND QUANTITATIVE COMPOSITION

Bempeget-EZ (Bempedoic Acid + Ezetimibe) is available for oral administration as:

Bempeget-EZ Tablets 180mg + 10mg
Each film-coated tablet contains:
Bempedoic Acid…180mg
Ezetimibe…10mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Bempedoic Acid

Bempedoic Acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers 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, requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA ESP15228-CoA, respectively. ACSVL1 is expressed primarily in the liver and not in skeletal muscle. Inhibition of ACL by ETC-1002-CoA and 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.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.

Pharmacokinetics

Absorption

Bempedoic Acid

Following single oral administration of Bempedoic Acid + Ezetimibe Tablet (180mg of Bempedoic Acid and 10mg of Ezetimibe), mean (± SD) C_{max} and AUC of Bempedoic Acid were 12.6 (± 2.80)µg/mL and 202 (± 43.4) µg.hr/mL, respectively; the median time to maximum concentration (T_{max}) was 3.0 hours. Following multiple-dose administration of Bempedoic Acid monotherapy, the steady state maximum plasma concentration (C_{max}) and AUC at 180mg/day were 20.6 ± 6.1µg/mL and 289.0 ± 96.4µg·h/mL, respectively. Bempedoic Acid steady-state pharmacokinetics were generally linear over a range of >60mg to 220mg (approximately 33% to 122% of the recommended dosage of 180mg daily). There were no time-dependent changes in Bempedoic Acid pharmacokinetics following repeat administration at the recommended dosage, and Bempedoic Acid steady-state was achieved after 7 days. The mean accumulation ratio was approximately 2.3-fold.

The steady-state C_{max} and AUC of the active metabolite (ESP15228) of Bempedoic Acid were 2.8 ± 0.9µg/mL and 51.2 ± 17.2µg·h/mL, respectively. ESP15228 likely made a minor contribution to the overall clinical activity of Bempedoic Acid based on systemic exposure, relative potency and pharmacokinetic properties.

Ezetimibe

After a single dose of Bempedoic Acid + Ezetimibe Tablet to fasted adults, mean ± SD Ezetimibe C_{max} of 3.56 ± 1.90 ng/mL were attained with a median T_{max} of 5 hr. Ezetimibe-glucuronide mean C_{max} values of 107 ± 46 ng/mL were achieved with a median T_{max} of 1 hr. For Ezetimibe monotherapy, there was no substantial deviation from dose proportionality between 5mg and 20mg (0.5- to 2-fold the recommended dosage). The absolute bioavailability of Ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection.

Effect of Food

After the administration of Bempedoic Acid + Ezetimibe Tablet with a high-fat, high calorie breakfast in healthy subjects, the AUC for Bempedoic Acid and ezetimibe were comparable to the fasted state. This effect of food is not considered to be clinically meaningful.

Distribution

Bempedoic Acid

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 blood cells.

Ezetimibe

Ezetimibe and Ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism

Bempedoic Acid

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 Bempedoic Acid and ESP15228 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 $AUC_{0\text{-}48h}$ and its glucuronide being the next most prevalent (30%). ESP15228 and its glucuronide represented 10% and 11% of the plasma $AUC_{0\text{-}48h}$, respectively.

Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to Ezetimibe-glucuronide. Ezetimibe and Ezetimibe glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10% to 20% and 80% to 90% of the total drug in plasma, respectively. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Elimination

Bempedoic Acid

The steady-state clearance (CL/F) of Bempedoic Acid was 11.2 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 21 ± 11 hours at steady-state.

Following single oral administration of 240mg 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.

Ezetimibe

Both Ezetimibe and Ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both.

Ezetimibe was the major component in feces, and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Patients with Hepatic Impairment

Bempedoic Acid + Ezetimibe Tablet is not recommended in patients with moderate or severe hepatic impairment due to the unknown effects of the increased exposure to ezetimibe.

THERAPEUTIC INDICATIONS

Bempeget EZ (Bempedoic Acid + Ezetimibe) is indicated:

Hypercholesterolemia and mixed dyslipidemia

Bempeget EZ (Bempedoic Acid + Ezetimibe) Tablet is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

- In combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to Ezetimibe.
- Alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with Ezetimibe alone.
- In patients already being treated with the combination of Bempedoic Acid and Ezetimibe as separate tablets with or without statin.

Cardiovascular disease

Bempeget-EZ (Bempedoic Acid + Ezetimibe) Tablet is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- In patients on a maximum tolerated dose of a statin and not adequately controlled with additional Ezetimibe treatment or,
- In patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with Ezetimibe treatment or,
- In patients already being treated with the combination of Bempedoic Acid and Ezetimibe as separate tablets.

DOSAGE AND ADMINISTRATION

- The recommended dosage of Bempeget-EZ (Bempedoic Acid + Ezetimibe) is one tablet orally once daily. Swallow the tablet whole.
- Bempeget-EZ (Bempedoic Acid + Ezetimibe) Tablet can be taken with or without food.

- If a dose is missed, take the missed dose as soon as possible. Do not double the next dose.
- After initiation of Bempeget-EZ (Bempedoic Acid + Ezetimibe) Tablet, analyze lipid levels within 8 to 12 weeks.

Coadministration with Bile Acid Sequestrants
Administer Bempeget-EZ (Bempedoic Acid + Ezetimibe) tablet either at least 2 hours before or at least 4 hours after administration of a bile acid sequestrant.

Concomitant simvastatin therapy
When Bempeget-EZ (Bempedoic Acid + Ezetimibe) Tablet is coadministered with simvastatin, simvastatin dose should be limited to 20mg daily (or 40mg 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 m^2), and patients with end-stage renal disease (ESRD) on dialysis have not been studied with Bempedoic Acid. Additional monitoring for adverse reactions may be warranted in these patients when Bempeget-EZ (Bempedoic Acid + Ezetimibe) Tablet is administered.

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). Treatment with Bempeget-EZ (Bempedoic Acid + Ezetimibe) Tablet is not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment due to the unknown effects of the increased exposure to Ezetimibe.

Pediatric population
The safety and efficacy of Bempeget EZ (Bempedoic Acid + Ezetimibe) 180mg + 10mg Tablet in children aged less than 18 years have not been established.

ADVERSE REACTIONS
Common
Anaemia, decreased haemoglobin, hyperuricaemia, decreased appetite, gout, dizziness, headache, hypertension, cough, constipation, diarrhea, abdominal pain, nausea, dry mouth, flatulence, gastritis, liver function test increased, aspartate aminotransferase increased, back pain, muscle spasms, myalgia, pain in extremity, arthralgia, blood CPK increased, blood creatinine increased, glomerular filtration rate decreased, fatigue, asthenia.

Uncommon
Weight decreased, hot flush, dyspepsia gastroesophageal reflux disease, aspartate aminotransferase increased, alanine aminotransferase increased gammaglutamyltransferase increased, neck pain, muscular weakness, blood urea increased, chest pain, pain, edema peripheral, pruritus.

Not known
Thrombocytopenia, paraesthesia, dyspnea, pancreatitis, hypersensitivity, including rash, urticaria, anaphylaxis and angio-edema, depression, erythema multiforme, myopathy/rhabdomyolysis, hepatitis, cholelithiasis, cholecystitis.

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

CONTRAINDICATIONS
Bempedoic Acid + Ezetimibe is contraindicated in:
- Patients with hypersensitivity to the active substances or to any of the excipient of the product.
- Pregnancy.
- Breast-feeding
- Concomitant use with simvastatin > 40mg daily.
- Bempedoic Acid + Ezetimibe Tablet when coadministered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

PRECAUTIONS
Hyperuricemia
Elevations in serum uric acid have occurred. Assess uric acid levels periodically as clinically indicated. Monitor 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. Discontinue Bempedoic Acid + Ezetimibe immediately if the patient experiences rupture of a tendon. Consider discontinuing Bempedoic Acid + Ezetimibe if the patient experiences joint pain, swelling, or inflammation.

Potential risk of myopathy with concomitant use of statins
All patients receiving Bempedoic Acid + Ezetimibe in addition to a statin should be advised of the potential increased risk of myopathy. If myopathy is confirmed by a creatine phosphokinase (CPK) level > 10× upper limit of normal (ULN), Bempedoic Acid + Ezetimibe and any statin that the patient is taking concomitantly should be immediately discontinued.

Elevated liver enzymes
Elevations of > 3× ULN in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported with Bempedoic Acid. Liver function tests should be performed at initiation of therapy. Treatment with Bempedoic Acid + Ezetimibe Tablet should be discontinued if an increase in transaminases of > 3× ULN persists.

Renal impairment
There is limited experience with Bempedoic Acid in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2), 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 + Ezetimibe Tablet is administered.

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 + Ezetimibe Tablet is not recommended in these patients.

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

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

Effects on ability to drive and use machines
Bempedoic acid + Ezetimibe Tablet has minor influence on the ability to drive and use machines. When driving vehicles or using machines, it should be taken into account that dizziness has been reported with Bempedoic Acid and Ezetimibe.

DRUG INTERACTION
Simvastatin
Concomitant use of Bempedoic Acid + Ezetimibe with simvastatin causes an increase in simvastatin concentration and may increase the risk of simvastatin-related myopathy. Avoid concomitant use of Bempedoic Acid + Ezetimibe with simvastatin greater than 20mg.

Pravastatin
Concomitant use of Bempedoic Acid + Ezetimibe with pravastatin causes an increase in pravastatin concentration and may increase the risk of pravastatin-related myopathy. Avoid concomitant use of Bempedoic Acid + Ezetimibe with pravastatin greater than 40mg.

Cyclosporine
Concomitant use of Bempedoic Acid + Ezetimibe and cyclosporine increases Ezetimibe and cyclosporine concentrations. The degree of increase in Ezetimibe exposure may be greater in patients with severe renal insufficiency. Monitor cyclosporine concentrations in patients receiving Bempedoic Acid + Ezetimibe and cyclosporine. In patients treated with cyclosporine, weigh the potential effects of the increased exposure to Ezetimibe from concomitant use against the benefits of alterations in lipid levels provided by Bempedoic Acid + Ezetimibe.

Fibrates
Both Fenofibrate and Ezetimibe may increase cholesterol excretion into the bile, leading to cholelithiasis. Coadministration of Bempedoic Acid + Ezetimibe with fibrates other than Fenofibrate is not recommended. If cholelithiasis is suspected in a patient receiving Bempedoic Acid + Ezetimibe and Fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered.

Cholestyramine
Concomitant use of Bempedoic Acid + Ezetimibe and cholestyramine decreases Ezetimibe concentration. This may result in a reduction of efficacy. Administer Bempedoic Acid + Ezetimibe either at least 2 hours before or at least 4 hours after bile acid sequestrants.

Anticoagulants
If Bempedoic Acid + Ezetimibe is added to warfarin, other Coumarin anticoagulants, or Fluindione, INR should be appropriately monitored.

Transporter-mediated drug interactions
Bempedoic acid and its glucuronide weakly inhibit OATP1B1 and OATP1B3 at clinically relevant concentrations. Bempedoic Acid inhibits OAT2 in vitro, which may be the mechanism responsible for minor elevations in serum creatinine and uric acid. Bempedoic Acid may also weakly inhibit OAT3 at clinically relevant concentrations.

OVERDOSAGE
In the event of 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-EZ (Bempedoic Acid + Ezetimibe) Tablets 180mg+10mg 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:

Getz pharma (PVT) LIMITED
www.getzpharma.com

29-30/27,
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