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

BEMPESTA

1. Generic Name:

Bempedoic Acid Tablets 180 mg

2. Qualitative and quantitative composition:

Each film coated tablets contains:

Bempedoic Acid ……. 180 mg

Excipients…….. Q.S.

Colour : Titanium Dioxide I.P.

The excipients are Pregelatinised Starch, Microcrystalline Cellulose, Sodium Starch Glycollate, Isopropyl Alcohol, povidone, calcium stearate, purified talc, instacoat universal white.

3. Dosage form and strength:

Dosage form: Film coated tablets **Strength:** 180 mg

4. Clinical particulars:

4.1 Therapeutic indication:

It is Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL –C.

Limitation of use: The effect of the drug on cardiovascular morbidity and mortality has not been stablished.

4.2 Posology and method of administration:

Posology

The dose of BEMPESTA tablet must be taken as prescribe by physician

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

Concomitant simvastatin therapy

When Bempedoic Acid Tablets 180 mg 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 Tablets 180 mg 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 Tablets 180 mg in children aged less than 18 years have not yet been established. No data are available.

Method of administration

Each film-coated tablet should be taken orally with or without food. Tablet should be swallowed whole.

4.3 Contraindications:

- 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:

Potential risk of myopathy with concomitant use of statins

Bempedoic acid increases plasma concentrations of statins. Patients receiving Bempedoic Acid Tablets 180 mg 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 Tablets 180 mg 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 Tablets 180 mg and a statin, a lower maximum dose of the same statin or an alternative statin, or discontinuation of Bempedoic Acid Tablets 180 mg 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 Tablets 180 mg and any statin that the patient is taking concomitantly should be immediately discontinued.

Myositis with a CPK level > 10× 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 Tablets 180 mg.

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 (see section 4.8). Treatment with Bempedoic Acid Tablets 180 mg should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.

Elevated liver enzymes

In clinical trials, elevations of > 3× 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 ≥ 2× 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 Tablets 180 mg 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 m2), and patients with ESRD on dialysis have not been studied. Additional monitoring for adverse reactions may be warranted in these patients when Bempedoic Acid Tablets 180 mg 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 Tablets 180 mg before stopping contraceptive measures if they plan to become pregnant.

4.5 Drug-Interaction:

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 Cmax 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 Cmax for ezetimibe were less than 20%. These elevations are not clinically meaningful and do not impact dosing recommendations.

Other interactions studied

Bempedoic acid had no effect on the pharmacokinetics or pharmacodynamics of metformin or the pharmacokinetics of oral contraceptive norethindrone/ethinyl estradiol.

4.6 Use in special populations:

Pregnancy

Bempedoic Acid Tablets 180 mg is contraindicated during pregnancy.

There are no or limited amount of reported data from the use of bempedoic acid in pregnant women. Studies in animals with bempedoic acid have shown reproductive toxicity (see section 5.3). Because bempedoic acid decreases cholesterol synthesis and possibly the synthesis of other cholesterol derivatives needed for normal foetal development, Bempedoic Acid Tablets 180 mg may cause foetal harm when administered to pregnant women. Bempedoic Acid Tablets 180 mg 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 Tablets 180 mg should not breast-feed their infants. Bempedoic Acid Tablets 180 mg is contraindicated during breastfeeding.

Fertility

No reported data on the effect of Bempedoic Acid Tablets 180 mg on human fertility are available. Based on animal studies, no effect on reproduction or fertility is expected with Bempedoic Acid Tablets 180 mg.

4.7 Effects on ability to drive and use machines:

Bempedoic Acid Tablets 180 mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects:

Summary of the safety profile:

The safety profile of bempedoic acid has been studied in reported 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.

Tabulated list of adverse reactions:

Adverse reactions reported with bempedoic acid are displayed by system organ class and frequency in table 1. 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).

System organ class (SOC)	Adverse reactions	Frequency categories
Blood and lymphatic system disorders	Anaemia	Common
	Haemoglobin decreased	UnCommon
Metabolism and nutrition disorders	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

Description of selected adverse reactions

Hepatic enzyme elevations increases in serum transaminases (AST and/or ALT) have been reported with bempedoic acid. In controlled clinical studies, the incidence of elevations (≥ 3× ULN) in hepatic transaminase levels was 0.7% for patients treated with bempedoic acid and 0.3% for placebo. These elevations in transaminases were not associated with other evidence of liver dysfunction .

Increased serum uric acid

Increases in serum uric acid were observed in reported clinical trials with bempedoic acid possibly related to inhibition of renal tubular OAT2. In the pooled placebo-controlled trials, a mean increase of 0.8 mg/dL (47.6 micromole/L) in uric acid compared to baseline was observed with bempedoic acid at week 12. The elevations in serum uric acid usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation of treatment. Gout was reported in 1.4% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. In both treatment groups, patients who reported gout were more likely to have a medical history of gout and/or baseline levels of uric acid above the ULN.

Effects on serum creatinine and blood urea nitrogen

Bempedoic acid has been shown to increase serum creatinine and BUN. In the pooled placebo-controlled trials, a mean increase of 0.05 mg/dL (4.4 micromole/L) in serum creatinine and a mean increase of 1.7 mg/dL (0.61 mmol/L) in BUN compared to baseline was observed with bempedoic acid at week 12. The elevations in serum creatinine and BUN usually occurred within the first 4 weeks of treatment, remained stable, and returned to baseline following discontinuation of treatment.

The observed elevations in serum creatinine may be associated with bempedoic acid inhibition of OAT2-dependent renal tubular secretion of creatinine, representing a drug-endogenous substrate interaction and does not appear to indicate worsening renal function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients on Bempedoic Acid Tablets 180 mg therapy, particularly in patients with medical conditions or receiving medicinal

products that require monitoring of estimated creatinine clearance.

Decreased haemoglobin

Decreases in haemoglobin were observed in clinical trials with bempedoic acid. In the pooled placebo-controlled trials, a decrease in haemoglobin from baseline of ≥ 20 g/L and < lower limit of normal (LLN) was observed in 4.6% of patients in the bempedoic acid group compared with 1.9% of patients on placebo. Greater than 50 g/L and < LLN decreases in haemoglobin were reported at similar rates in bempedoic acid and placebo groups (0.2% versus 0.2%, respectively). The decreases in haemoglobin usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation of treatment. Among patients who had normal haemoglobin values at baseline, 1.4% in the bempedoic acid group and 0.4% in the placebo group experienced haemoglobin values below LLN while on treatment. Anaemia was reported in 2.5% of patients treated with bempedoic acid and 1.6% of patients treated with placebo.

Elderly population

Of the 3,621 patients treated with bempedoic acid in the reported placebo-controlled studies, 2,098 (58%) were > 65 years old. No overall difference in safety was observed between elderly and the younger population.

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.

4.9 Overdose:

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

No adverse events were observed in reported 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 Tablets 180 mg overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5. Pharmacological properties:

5.1 Mechanism of Action:

Pharmacotherapeutic group: Lipid modifying agents, other lipid modifying agents,

ATC code: C10AX15

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-glutarylcoenzyme 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 Pharmacodynamic properties:

Administration of bempedoic acid alone and in combination with other lipid modifying medicinal products decreases LDLC, non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apo B), and total cholesterol (TC) in patients with hypercholesterolaemia or mixed dyslipidaemia.

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.

5.3 Pharmacokinetic properties:

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 Tablets 180 mg. 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 Cmax 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 Tablets 180 mg 180 mg 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 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

In reported 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 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. The steady-state Cmax 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.

Elimination

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.

Pharmacokinetic Results:

The following pharmacokinetic parameters were calculated on data obtained from completed subjects for test and reference products.

Summary of Pharmacokinetic Profile of Reference product (R)

Pharmacokinetic Parameter	**N**	**Arithmetic Mean ± Standard Deviation**	**Coefficient of Variation**	**Median**	**Minimum**	**Maximum**
C_{max} (ng/mL)	23	25342.7221±6485.5906	25.5915	24858.0820	14865.3550	39267.0260
AUC_{0-t} (ng.hr/mL)	23	358014.7844±134044.1805	37.4410	339005.9645	114109.3608	702203.3758
$AUC_{0-\infty}$ (ng.hr/mL)	23	405750.1402±177454.1390	43.7348	359880.6746	127884.0912	897208.0523
t_{max} (hr)	23	2.8913±1.0548	36.4825	2.5000	1.5000	4.5000
K_{el} (1/hr)	23	0.0344±0.0121	35.0980	0.0342	0.0152	0.0735
$t_{1/2}$(hr)	23	22.5639±8.2322	36.4837	20.2600	9.4200	45.5200
$AUC_{\_\%Extrap\_obs}$	23	9.9143±8.0776	81.4735	6.0400	2.9100	28.6500
Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
Cmax (ng/mL)	23	24386.6703±6353.4451	26.0529	23353.3290	12428.5730	35420.1550
AUC0-t (ng.hr/mL)	23	398071.6015±158211.9451	39.7446	395066.1143	121517.8235	782338.9030
AUC0-∞ (ng.hr/mL)	23	451208.0890±191479.8883	42.4372	417790.9027	134156.4846	921473.5561
tmax (hr)	23	3.2609±1.0539	32.3191	3.0000	2.0000	5.0000
Kel (1/hr)	23	0.0308±0.0080	25.9170	0.0315	0.0194	0.0464
t1/2(hr)	23	24.0170±6.1318	25.5312	21.9900	14.9300	35.7400
AUC_%Extrap_obs	23	10.6287±6.6343	62.4184	9.4200	2.3700	25.2800

Statistical Results of Log Transformed Test product (T) versus Reference product (R)

Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Interval
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	23528.740	24571.295	14.31	95.76	99.69	89.08 TO 102.94
AUC_{0-t} (ng.hr/mL)	365470.50	331888.25	12.88	110.12	99.91	103.17 TO 117.53
$AUC_{0-\infty}$ (ng.hr/mL)	409850.81	369605.52	15.15	110.89	99.43	102.72 TO 119.71

Special populations

Renal impairment

Pharmacokinetics of bempedoic acid was evaluated in a population PK analysis performed on reported pooled data from all clinical trials (n=2,261) to assess renal function on the steady-state AUC of bempedoic acid and in a single-dose pharmacokinetic study in subjects with varying degrees of renal function. Compared to patients with normal renal function, the mean bempedoic acid exposures were higher in patients with mild or moderate renal impairment by 1.4-fold (90% PI: 1.3, 1.4) and 1.9-fold (90% PI: 1.7, 2.0), respectively (see section 4.4). There is limited information in patients with severe renal impairment; in a single dose study, the bempedoic acid AUC was increased by 2.4-fold in patients (n=5) with severe renal impairment (eGFR < 30 mL/min/1.73 m2) compared to those with normal renal function. Clinical studies of bempedoic acid did not include patients with ESRD on dialysis (see section 4.4).

Hepatic impairment

The pharmacokinetics of bempedoic acid and its metabolite (ESP15228) was studied in patients with normal hepatic function or mild or moderate hepatic impairment (Child-Pugh A or B) following a single dose (n=8/group). Compared to patients with normal hepatic function, the bempedoic acid mean Cmax 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.This is not expected to result in lower efficacy. Therefore, no dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Bempedoic acid was not studied in patients with severe hepatic impairment (Child-Pugh C).

Other special populations

The pharmacokinetics of bempedoic acid were not affected by age, gender, or race. Body weight was a statistically significant covariate. The lowest quartile of body weight (< 73 kg) was associated with an approximate 30% greater exposure. The increase in exposure was not clinically significant and no dose adjustments are recommended based on weight.

6. Nonclinical properties:

6.1 Animal Toxicology or Pharmacology

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

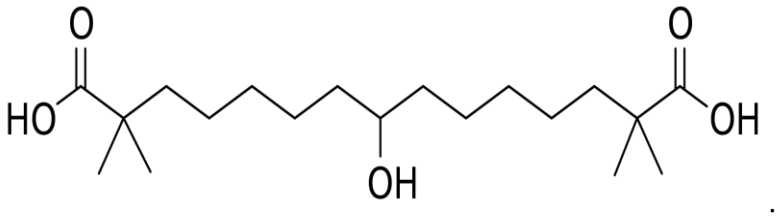
at 180 mg. Reversible, non-adverse changes in laboratory parameters indicative of these hepatic effects, decreases in red blood cell and coagulation parameters, and increases in urea nitrogen and creatinine were observed in both species at tolerated doses. The NOAEL for adverse response in the chronic 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 foetuses 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 foetuses 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 180 mg. In a pre- and postnatal 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.

No reported data are available on the effect of Bempedoic Acid Tablets 180 mg 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).

7. Description:

Bempedoic acid is in a class of medications called adenosine triphosphate-citrate lyase (ACL) inhibitors. It works by blocking the production of cholesterol in the liver. Bempedoic Acid is chemically (8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid. Its empirical formula is $C_{19}H_{36}O_5$ and its structural formula is:



Bempedoic Acid is a White to off white solid with a molecular weight of 344.5. it is highly soluble in ethanol, isopropanol and pH 8 phosphate buffer, and insoluble in water and aqueous solutions below pH 5

Bempedoic Acid Tablets

White to off white, oval, biconvex, film coated tablets , plain on both side.
The excipients are Pregelatinised Starch, Microcrystalline Cellulose, Sodium Starch Glycollate, Isopropyl Alcohol, povidone, calcium stearate, purified talc, instacoat universal white.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than date of expiry.

8.3 Packaging information:

Available in Blister strip pack of 10 tablets.

8.4 Storage and handing instructions:

Store at a temperature not exceeding 30°C.

9. Patient Counselling Information

Package leaflet: Information for the user

BEMPESTA

Bempedoic Acid Tablets 180 mg

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 further questions, 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. See section 4.

What is in this leaflet?

9.1. What BEMPESTA Tablets is and what it is used for

"Bempedoic Acid Tablets 180 mg is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who required additional lowering of LDL-C"

9.2. What you need to know before you take BEMPESTA

If you are allergic to Bempedoic Acid or any of the other ingredients of this medicine. If you think you may be allergic to Bempedoic Acid or any of the other ingredients of Bempedoic Acid, do not take this medicine and talk to your doctor.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Bempedoic Acid.

Risk of Hyperuricemia

Advise patients of the risk of elevated serum uric acid levels, including development of gout. Inform patients that serum uric acid levels may be monitored during treatment with Bempedoic acid. Patients with signs or symptoms of hyperuricemia should contact their healthcare provider

if symptoms occur.

Risk of Tendon Rupture

Inform patients of the risk of tendon rupture. Advise patients to rest at the first sign of tendinitis or tendon rupture and to immediately contact their healthcare provider if tendinitis or tendon rupture symptoms occur.

Risk of Myopathy with Concomitant Use of Simvastatin or Pravastatin

Advise patients to notify their healthcare provider(s) if they are taking, or plan to take simvastatin or pravastatin. The risk of myopathy occurring with the use of simvastatin or pravastatin may be increased when taken with Bempedoic acid.

Pregnancy Advise pregnant women of the potential risk to a fetus based on Bempedoic Acid mechanism of action. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Paediatric population

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

Other medicines and Bempedoic Acid Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may wish to alter your dose of Bempedoic Acid.

if you are taking other medicines such as:

- Statins (Atorvastatin, Pravastatin, Fluvastatin, Pitavastatin, Rosuvastatin, and Simvastatin)

- Ezetimibe

- Bosentan, Fimasartan, Asunaprevir, Glecaprevir, Grazoprevir and Voxilaprevir.

Pregnancy, breast feeding and fertility

Bempedoic acid tablets should be discontinued prior to conception or as soon as pregnancy is recognized.

Driving and using machines

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

Driving and operating machines

BEMPESTA Tablets do not affect the ability to drive or operate machinery.

9.3. How to take BEMPESTA Tablets

Swallow the tablets whole with some water.

If you take more BEMPESTA 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 miss a dose of BEMPESTA Tablets

If you miss a dose of Bempedoic Acid 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.

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 side effects occur upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes

–you may need medical treatment.

– you should promptly consult your doctor.

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.

9.5. How to store BEMPESTA TABLETS

Store at a temperature not exceeding 30°C.

9.6. Contents of the pack and other information.

What BEMPESTA Tablets contains

The active substances in BEMPESTA tablets is Bempedoic Acid.

The other excipients are pregelatinised Starch, Microcrystalline Cellulose, Sodium Starch Glycollate, Isopropyl Alcohol, povidone, calcium stearate, purified talc, instacoat universal white.

Contents of the pack: Available in Blister strip pack of 10 tablets

10. Details of manufacturer

EXEMED PHARMACEUTICALS

PLOT NO: 133/1 & 133/2,

SELVAS ROAD, VAPI, DIST:

VALSAD-396195

11. Details of permission or licence number with date

Mfg Lic No.: G/25/2011 issued on 11/05/2022

12. Date of revision

Not applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/BEMPESTA 180 mg/May-22/01/PI