เอกสารกำกับยาฉบับภาษาอังกฤษ

NEXLETOL®
(Bempedoic acid)

1. NAME OF THE MEDICINAL PRODUCT

Nexletol 180 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 180 mg of bempedoic acid.

Excipient(s) with known effect
Each 180 mg film-coated tablet contains 28.5 mg of lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, oval, film-coated tablet of approximately 13.97 mm × 6.60 mm × 4.80 mm debossed with "180" on one side and "ESP" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia and mixed dyslipidaemia
Nexletol is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin (see sections 4.2, 4.3, and 4.4) or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Cardiovascular disease
Nexletol 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 with or without ezetimibe or,
- alone or in combination with ezetimibe in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

4.2 Posology and method of administration

Posology

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

Concomitant simvastatin therapy
When Nexletol 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) (see sections 4.4 and 4.5).

Special populations
Elderly patients
No dose adjustment is necessary in elderly patients (see section 5.2).

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. Additional monitoring for adverse reactions may be warranted in these patients when Nexletol is administered (see section 4.4).

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 (see section 4.4).

Paediatric population
The safety and efficacy of Nexletol 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 listed in section 6.1.
- Pregnancy (see section 4.6).
- Breast-feeding (see section 4.6).
- Concomitant use with simvastatin > 40 mg daily (see sections 4.2, 4.4, and 4.5).

4.4 Special warnings and precautions for use

Potential risk of myopathy with concomitant use of statins

Bempedoic acid increases plasma concentrations of statins (see section 4.5). Patients receiving Nexletol 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 Nexletol 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 Nexletol and a statin, a lower maximum dose of the same statin or an alternative statin, or discontinuation of Nexletol 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), Nexletol 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 Nexletol (see sections 4.2 and 4.3).

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 Nexletol 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 Nexletol should be discontinued if an increase in transaminases of > 3× ULN persists (see section 4.8).

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 (see section 5.2). Additional monitoring for adverse reactions may be warranted in these patients when Nexletol is administered.

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). 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 Nexletol before stopping contraceptive measures if they plan to become pregnant.

Excipients

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

This medicine contains less than 1 mmol sodium (23 mg) per 180 mg film-coated tablet (daily dose), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of 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 (see section 4.4).

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 [see section 4.4]) 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 (see section 4.8). 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.

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 Fertility, pregnancy and lactation

Pregnancy

Nexletol is contraindicated during pregnancy (see section 4.3).

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 (see section 5.3).

Because bempedoic acid decreases cholesterol synthesis and possibly the synthesis of other cholesterol derivatives needed for normal foetal development, Nexletol may cause foetal harm when administered to pregnant women. Nexletol should be discontinued prior to conception or as soon as pregnancy is recognized (see section 4.3).

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment (see section 4.4).

Breast-feeding

It is unknown whether bempedoic acid/metabolites are excreted in human milk. Because of the potential for serious adverse reactions, women taking Nexletol should not breast-feed their infants. Nexletol is contraindicated during breast-feeding (see section 4.3).

Fertility

No data on the effect of Nexletol on human fertility are available. Based on animal studies, no effect on reproduction or fertility is expected with Nexletol (see section 5.3).

4.7 Effects on ability to drive and use machines

Nexletol 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 4 placebo-controlled phase 3 primary hyperlipidaemia 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%), and gout (1.4%) . 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. The safety profile in the cardiovascular outcomes study (CLEAR Outcomes; N=13 965) was consistent with the overall safety profile described in the phase 3 primary hyperlipidaemia studies.

Tabulated list of adverse reactions

Adverse reactions reported with bempedoic acid, based on incidence rates from phase 3 primary hyperlipidemia studies and exposure adjusted incidence rates from CLEAR Outcome study, 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).

Table 1: Adverse reactions

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
	Weight decreased[b]	Uncommon
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	Glomerular filtration rate decrease	Common
	Blood creatinine increased	Uncommon
	Blood urea increased	Uncommon

a. Hyperuricaemia includes hyperuricaemia and blood uric acid increased
b. (CLEAR Outcomes study) Weight decrease was observed only in patients with a baseline body mass index (BMI) of $\geqslant$30 kg/m^2, with a mean body weight reduction of -2.28 kg at month 36. Mean reduction in body weight was $\leqslant$0.5 kg inpatients with a baseline BMI of 25 to <30 kg/m^2. Bempedoic acid was not associated with a mean change in body weight in patients with a baseline BMI of < 25 kg/m^2

Description of selected adverse reactions

Hepatic enzyme elevations
Increases in serum transaminases (AST and/or ALT) have been reported with bempedoic acid. In the phase 3 primary hyperlipidaemia studies, the incidence of elevations ($\geq$ 3× ULN) in hepatic transaminase levels was 0.7% for patients treated with bempedoic acid and 0.3% for placebo. In the CLEAR Outcomes study, the incidence of elevations > 3× ULN in hepatic transaminase levels also occurred more frequently in bempedoic acid-treated patients (1.6%) than in placebo-treated patients (1.0%). These elevations in transaminases were not associated with other evidence of liver dysfunction (see section 4.4).

Increased serum uric acid
Increases in serum uric acid were observed in clinical trials with bempedoic acid possibly related to inhibition of renal tubular OAT2 (see section 4.5). In the phase 3 primary hyperlipidemia studies, a mean increase of 47.6 micromole/L (0.8 mg/dL) 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. In the phase 3 primary hyperlipidemia studies, gout was reported in 1.4% of patients treated with bempedoic acid and 0.4% of patients treated with placebo (see section 4.4). In the CLEAR Outcomes study, a mean increase of 47.6 micromole/L (0.8 mg/dL) in uric acid compared to baseline was observed in bempedoic acid treated patients at month 3, and gout was also reported more frequently in bempedoic acid-treated patients (3.1%) than placebo-treated patients (2.1%). 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 blood urea nitrogen (BUN). In thephase 3 primary hyperlipidemia studies, a mean increase of 4.4 micromole/L (0.05 mg/dL) in serum creatinine and a mean increase of 0.61 mmol/L (1.7 mg/dL) 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. Similar mean increases in serum creatinine (5.8 micromole/L (0.066 mg/dL)) and BUN (0.82 mmol/L (2.3 mg/dL)) were observed with bempedoic acid in the CLEAR Outcomes study.

The observed elevations in serum creatinine may be associated with bempedoic acid inhibition of OAT2-dependent renal tubular secretion of creatinine (see section 4.5), 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 Nexletol 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 phase 3 primary hyperlipidaemia studies, 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. In the phase 3 primary hyperlipidemia studies, anaemia was reported in 2.5% of patients treated with bempedoic acid and 1.6% of patients treated with placebo. In the CLEAR Outcomes study, similar decreases in haemoglobin were observed, and anaemia was also reported more frequently in bempedoic acid-treated patients (4.7%) compared to placebo-treated patients (3.9%).

Elderly population

Of the 3,621 patients treated with bempedoic acid in the phase 3 primary heperlipidemia studies, 2,098 (58%) were > 65 years old. In the CLEAR Outcomes study, 4,141 patients (59%) treated with bempedoic acid were ≥65 years of age and 1 066 patients (15%) treated with bempedoic acid were ≥75 years of age. No overall difference in safety was observed between elderly and the younger population.

4.9 Overdose

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 Nexletol 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: Lipid modifying agents, other lipid modifying agents, ATC code: C10AX15

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 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.

Pharmacodynamic effects

Administration of bempedoic acid alone and in combination with other lipid modifying medicinal products decreases LDL-C, non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apo B), total cholesterol (TC), and C-reactive protein (CRP) 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.

Clinical efficacy and safety

Clinical efficacy and safety in primary hypercholesterolaemia and mixed dyslipidaemia
The efficacy of Nexletol was investigated in four multi-centre, randomised, double-blind, placebo-controlled phase 3 primary hyperlipidaemia studies involving 3,623 adult patients with hypercholesterolaemia or mixed dyslipidaemia, with 2,425 patients randomised to bempedoic acid. All patients received bempedoic acid 180 mg or placebo orally once daily. In two trials, patients were taking background lipid-modifying therapies consisting of a maximum tolerated dose of statin, with or without other lipid-modifying therapies. Two trials were conducted in patients with documented statin intolerance. The primary efficacy endpoint in all Phase 3 trials was the mean percent reduction from baseline in LDL-C at week 12 as compared with placebo.

Combination therapy with statins
CLEAR Wisdom (Study 1002-047) was a multi-centre, randomised, double-blind, placebo-controlled, 52-week phase 3 primary hyperlipidaemia study in patients with hypercholesterolaemia or mixed dyslipidaemia. Efficacy of Nexletol was evaluated at week 12. The trial included 779 patients randomised 2:1 to receive either bempedoic acid (n=522) or placebo (n=257) as add-on to a maximum tolerated lipid lowering therapy. Maximum tolerated lipid lowering therapy was defined as a maximum tolerated statin dose (including statin regimens other than daily dosing and no to very low doses) alone or in combination with other lipid-lowering therapies. Patients on simvastatin 40 mg/day or higher were excluded from the trial.

Overall, the mean age at baseline was 64 years (range: 28 to 91 years), 51% were ≥ 65 years old, 36% were women, 94% were White, 5% were Black, and 1% were Asian. The mean baseline LDL-C was 3.1 mmol/L (120.4 mg/dL). At the time of randomisation, 91% of patients were receiving statin therapy and 53% were receiving high-intensity statin therapy. Bempedoic acid significantly reduced LDL-C from baseline to week 12 compared with placebo ($p < 0.001$). Bempedoic acid also significantly reduced non-HDL-C, apo B, and TC.

CLEAR Harmony (Study 1002-040) was a multi-centre, randomised, double-blind, placebo-controlled 52-week phase 3 primary hyperlipidaemia study evaluating safety and efficacy of bempedoic acid in patients with hypercholesterolaemia or mixed dyslipidaemia. Efficacy of Nexletol was evaluated at week 12. The trial included 2,230 patients randomised 2:1 to receive either bempedoic acid (n=1,488) or placebo (n=742) as add-on to a maximum tolerated lipid lowering therapy. Maximum tolerated lipid

lowering therapy was defined as a maximum tolerated statin dose (including statin regimens other than daily dosing and very low doses) alone or in combination with other lipid lowering therapies. Patients on simvastatin 40 mg per day or higher and patients on PCSK9 inhibitors were excluded from the trial.

Overall, the mean age at baseline was 66 years (range: 24 to 88 years), 61% were ≥ 65 years old, 27% were women, 96% were White, 3% were Black, and 1% were Asian. The mean baseline LDL-C was 2.7 mmol/L (103.2 mg/dL). At the time of randomisation, all patients were receiving statin therapy and 50% were receiving high-intensity statin therapy. Bempedoic acid significantly reduced LDL-C from baseline to week 12 compared with placebo ($p < 0.001$). A significantly higher proportion of patients achieved an LDL-C of < 1.81 mmol/L (< 70 mg/dL) in the bempedoic acid group as compared with placebo at week 12 (32% versus 9%, $p < 0.001$), bempedoic acid also significantly reduced non-HDL-C, apo B, and TC (see table 2).

Table 2. Treatment effects of Nexletol compared with placebo in patients with primary hypercholesterolaemia or mixed dyslipidaemia - mean percent change from baseline to week 12

	CLEAR Wisdom (Study 1002-047) (N=779)		CLEAR Wisdom (Study 1002-040) (N=2,230)	
	Nexletol n=522	**Placebo n=257**	**Nexletol n=1,488**	**Placebo n=742**
LDL-C[a], n	498	253	1,488	742
LS Mean	-15.1	2.4	-16.5	1.6
non-HDL-C[a], n	498	253	1,488	742
LS Mean	-10.8	2.3	-11.9	1.5
apo B[a], n	479	245	1,485	736
LS Mean	-9.3	3.7	-8.6	3.3
TC[a], n	499	253	1,488	742
LS Mean	-9.9	1.3	-10.3	0.8

apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL C=low-density lipoprotein cholesterol; LS=least squares; TC=total cholesterol.
Background statin (1002-047): atorvastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin, and lovastatin.
Background statin (1002-040): atorvastatin, simvastatin, pravastatin.
a. Percent change from baseline was analysed using analysis of covariance (ANCOVA), with treatment and randomisation strata as factors and baseline lipid parameter as a covariate.

Statin intolerant patients
CLEAR Tranquility (Study 1002-048) was a multi-centre, randomised, double-blind, placebo-controlled 12-week phase 3 primary hyperlipidaemia study evaluating the efficacy of Nexletol versus placebo in lowering LDL-C when added to ezetimibe in patients with elevated LDL-C who had a history of statin intolerance and were unable to tolerate more than the lowest approved starting dose of a statin. The trial included 269 patients randomised 2:1 to receive either bempedoic acid (n=181) or placebo (n=88) as add-on to ezetimibe 10 mg daily for 12 weeks.

Overall, the mean age at baseline was 64 years (range: 30 to 86 years), 55% were ≥ 65 years old, 61% were women, 89% were White, 8% were Black, 2% were Asian, and 1% were other. The mean baseline LDL-C was 3.3 mmol/L (127.6 mg/dL). At the time of randomisation, 33% of patients on bempedoic acid versus 28% on placebo were receiving statin therapy at less than or equal to lowest approved doses. Bempedoic acid significantly reduced LDL-C from baseline to week 12 compared with placebo ($p < 0.001$). Bempedoic acid also significantly reduced non-HDL-C, apo B, and TC (see table 3).

CLEAR Serenity (Study 1002-046) was a multi-centre, randomised, double-blind, placebo-controlled 24-week phase 3 primary hyperlipidaemia study evaluating the efficacy of Nexletol versus placebo in patients with elevated LDL-C who were statin-intolerant or unable to tolerate two or more statins, one at the lowest dose. Patients able to tolerate a dose that was less than the approved starting dose of a statin were allowed to stay on that dose during the study. Efficacy of bempedoic acid was evaluated at week 12. The trial included 345 patients randomised 2:1 to receive either bempedoic acid (n=234) or placebo (n=111) for 24 weeks. At the time of randomisation, 8% of patients on bempedoic acid versus 10% on

placebo were receiving statin therapy at less than the lowest approved doses and 36% of patients on bempedoic acid versus 30% of patients on placebo were on other nonstatin lipid-modifying therapies.

Overall, the mean age at baseline was 65 years (range: 26 to 88 years), 58% were ≥ 65 years old, 56% were women, 89% were White, 8% were Black, 2% were Asian, and 1% were other. The mean baseline LDL-C was 4.1 mmol/L (157.6 mg/dL).

Bempedoic acid significantly reduced LDL-C from baseline to week 12 compared with placebo ($p < 0.001$). Bempedoic acid also significantly reduced non-HDL-C, apo B, and TC (see table 3).

Treatment in the absence of lipid-modifying therapies
In CLEAR Serenity (Study 1002-046), 133 patients in the bempedoic acid group and 67 patients in the placebo group were on no background lipid-modifying therapies. Bempedoic acid significantly reduced LDL-C from baseline to week 12 compared with placebo in this subgroup. The difference between bempedoic acid and placebo in mean percent change in LDL-C from baseline to week 12 was -22.1% (CI: -26.8%, -17.4%; $p < 0.001$).

Table 3. Treatment effects of Nexletol compared with placebo in statin intolerant patients - mean percent change from baseline to week 12

	CLEAR Tranquility (Study 1002-048) (N=269)		**CLEAR Serenity (Study 1002-046) (N=345)**	
	Nexletol n=181	**Placebo n=88**	**Nexletol n=234**	**Placebo n=111**
LDL-C[a], n	175	82	224	107
LS Mean	-23.5	5.0	-22.6	-1.2
non-HDL-C[a], n	175	82	224	107
LS Mean	-18.4	5.2	-18.1	-0.1
apo B[a], n	174	81	218	104
LS Mean	-14.6	4.7	-14.7	0.3
TC[a], n	176	82	224	107
LS Mean	-15.1	2.9	-15.4	-0.6

apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL C=low-density lipoprotein cholesterol; LS=least squares; TC=total cholesterol.
Background statin (1002-048): atorvastatin, simvastatin, rosuvastatin, pravastatin, lovastatin
Background statin (1002-046): atorvastatin, simvastatin, pitavastatin, rosuvastatin, pravastatin, lovastatin
b. Percent change from baseline was analysed using analysis of covariance (ANCOVA), with treatment and randomisation strata as factors and baseline lipid parameter as a covariate.

In all four trials, the maximum LDL-C lowering effects were observed as early as week 4 and efficacy was maintained throughout the trials. These results were consistent across all subgroups studied in any of the trials, including age, gender, race, ethnicity, region, history of diabetes, baseline LDL-C, body mass index (BMI), HeFH status, and background therapies.

Clinical efficacy and safety in prevention of cardiovascular events
CLEAR Outcomes (Study 1002-043) was a multi-centre randomised, double-blind, placebocontrolled, event-driven trial in 13 970 adult patients with established atherosclerotic cardiovascular disease (CVD) (70%), or at high risk for atherosclerotic CVD (30%). Patients with established CVD had documented history of coronary artery disease, symptomatic peripheral arterial disease, and/or cerebrovascular atherosclerotic disease. Patients without established CVD were considered at high risk for CVD based on meeting at least one of the following criteria: (1) diabetes mellitus (type 1 or type 2) in women over 65 years of age, or men over 60 years of age, or (2) a Reynolds Risk score >30% or a SCORE Risk score >7.5% over 10 years, or 3) a coronary artery calcium score >400 Agatston units at any time in the past. Patients were randomised 1:1 to receive either Nexletol 180 mg per day (n = 6 992) or placebo (n = 6 978) alone or as an add on to other background lipid lowering therapies that could include very low doses of statins. Overall, more than 95% of patients were followed until the end of the trial or death, and less than 1% were lost to follow up. The median follow-up duration was 3.4 years.

At baseline, the mean age was 65.5 years, 48% were women, 91% were White. Selected additional baseline characteristics included hypertension (85%), diabetes mellitus (46%), pre-diabetes mellitus (42%), current tobacco user (22%), eGFR < 60 mL/min per 1.73 m^2 (21%), and a mean body mass index 29.9 kg/m^2. The mean baseline LDL-C was 3.6 mmol/L (139 mg/dL). At baseline, 41% of patients were taking at least one lipid modifying therapy including ezetimibe (12%), and very low dose of statins (23%).

Nexletol significantly reduced the risk for the primary composite endpoint of major adverse cardiovascular events (MACE-4) consisting of cardiovascular death, non-fatal myocardial infarction,non-fatal stroke, or coronary revascularization by 13% compared to placebo (Hazard Ratio: 0.87; 95% CI: 0.79, 0.96; p = 0.0037); and the risk of the key secondary MACE-3 composite endpoint (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was significantly reduced by 15% compared to placebo (Hazard Ratio: 0.85; 95% CI: 0.76, 0.96; p = 0.0058). The primary composite endpoint result was generally consistent across prespecified subgroups (including baseline age, race, ethnicity, sex, LDL-C category, statin use, ezetimibe use, and diabetes). Impact of Nexletol on the individual components of the primary endpoint included a 27% reduction in the risk of nonfatal myocardial infarction and a 19% reduction in the risk of coronary revascularization compared to placebo. There was no statistically significant difference in the reduction of non-fatal stroke and risk of cardiovascular death compared to placebo. The results of the primary and key secondary efficacy endpoints are shown in Table 4. The Kaplan-Meier curve estimates of the cumulative incidence of the MACE-4 primary and the MACE-3 secondary endpoint are shown in Figures 1 and 2 below. The cumulative incidence of the MACE-4 primary endpoint is separated by month 6.
Further, the difference between Nexletol and placebo in mean percent change in LDL-C from baseline to month 6 was -20% (95% CI: -21%, -19%).

Table 4: Effect of Nexletol on Major Cardiovascular Events

	Nexletol N=6,992	**Placebo N=6,978**	**Nexletol vs. Placebo**
Endpoint	**n (%)**	**n (%)**	**Hazard Ratio[a] (95% CI) *p*-value[b]**
Primary Composite Endpoint			
Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization (MACE-4)	819 (11.7)	927 (13.3)	0.87 (0.79, 0.96) 0.0037
Components of Primary Endpoint			
Non-fatal myocardial infarction	236 (3.4)	317 (4.5)	0.73 (0.62, 0.87
Coronary revascularization	435 (6.2)	529 (7.6)	0.81 (0.72, 0.92)
Non-fatal stroke	119 (1.7)	144 (2.1)	0.82 (0.64, 1.05)
Cardiovascular death	269 (3.8)	257 (3.7)	1.04 (0.88, 1.24)
Key Secondary Endpoints			
Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (MACE-3)	575 (8.2)	663 (9.5)	0.85 (0.76, 0.96) 0.0058

Endpoint	Nexletol N=6,992 n (%)	Placebo N=6,978 n (%)	Nexletol vs. Placebo Hazard Ratio[a] (95% CI) *p*-value[b]
Fatal and non-fatal myocardial infarction	261 (3.7)	334 (4.8)	0.77 (0.66, 0.91) 0.0016
Coronary revascularization	435 (6.2)	529 (7.6)	0.81 (0.72, 0.92) 0.0013
Fatal and non-fatal stroke	135 (1.9)	158 (2.3)	0.85 (0.67, 1.07) NS

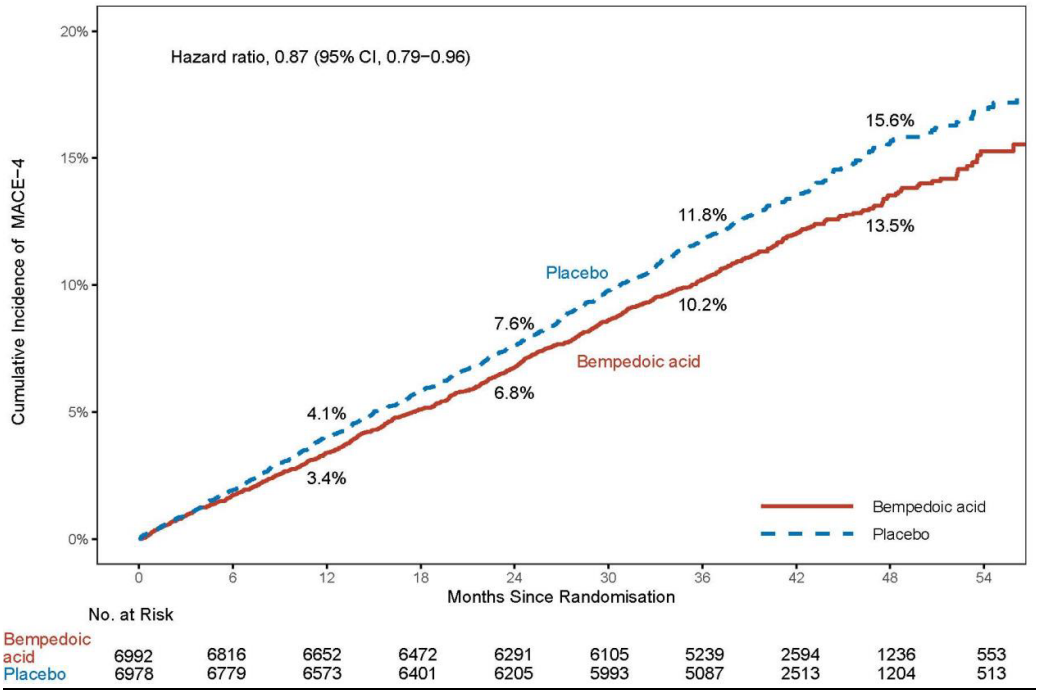
CI = confidence interval; MACE = major adverse cardiovascular event; NS=not significant

a. Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable.

b. p-value was based on log rank test.

Note: this table also presents the time to first occurrence for each of the components of MACE; patients may be included in more than 1 category

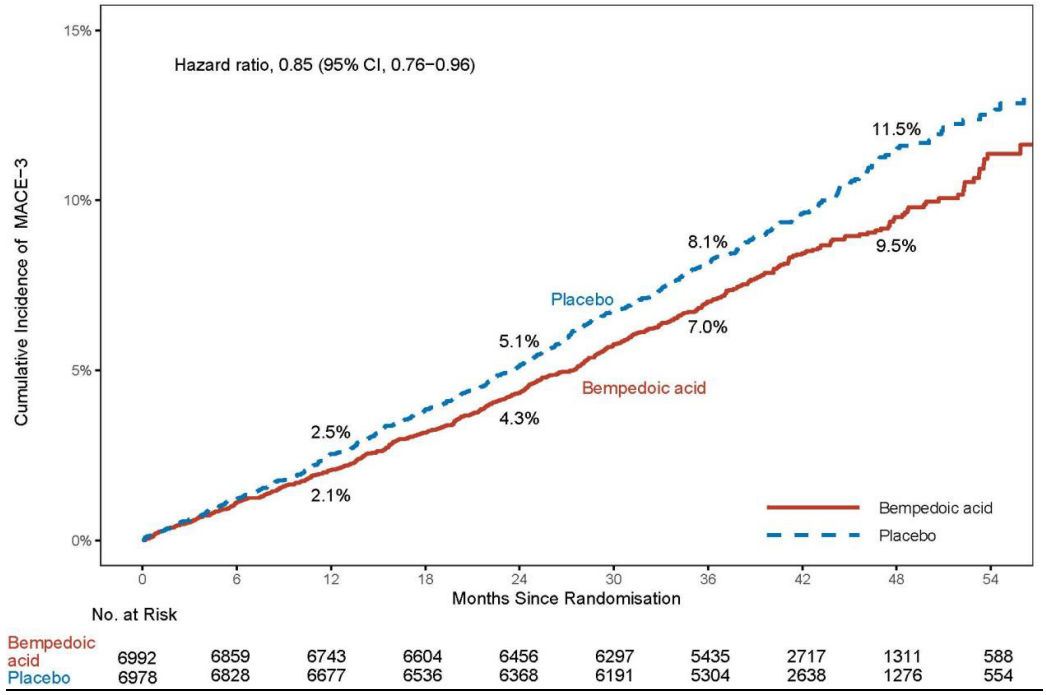
Figure 1: Kaplan-Meier Curve for Time to First Occurrence of MACE-4



MACE = major adverse cardiovascular event

Note: MACE-4 defined as the composite endpoint of CV death, non-fatal MI, non-fatal stroke, or coronary revascularization.

Figure 2: Kaplan-Meier Curve for Time to First Occurrence of MACE-3



MACE = major adverse cardiovascular event
Note: MACE-3 defined as the composite endpoint of CV death, non-fatal MI, or non-fatal stroke.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with bempedoic acid in paediatric population from 4 to less than 18 years of age in the treatment of elevated cholesterol. See section 4.2 for information on paediatric use.

5.2 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 Nexletol 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 Nexletol 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 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 $AUC_{0\text{-}48h}$ 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.

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.

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.

Special populations

Renal impairment
Pharmacokinetics of bempedoic acid was evaluated in a population PK analysis performed on 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 m^2) 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 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. 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.

5.3 Preclinical safety data

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 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.

No data are available on the effect of Nexletol 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose (E460)
Sodium starch glycolate (Type A grade)
Hydroxypropyl cellulose (E463)
Magnesium stearate (E470b)
Silica, colloidal anhydrous (E551)

Film-coating

Partially hydrolysed poly(vinyl alcohol) (E1203)
Talc (E553b)
Titanium dioxide (E171)
Macrogol/PEG (E1521)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Please refer to outer box

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Polyvinyl chloride (PVC)/aluminum blisters.
Pack sizes of 10 x 3 film-coated tablets in a carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Imported by:
DAIICHI SANKYO (THAILAND) LTD.
24th Fl., United Center Bldg.,
323, Silom Rd., Silom, Bangrak, Bangkok, 10500, Thailand
Tel.: +66 2631-2070-9 FAX: +66 2236-2656

Manufactured by:
Piramal Healthcare UK Limited
Whalton Road
Morpeth
Northumberland NE61 3YA
United Kingdom

Packaged by:
Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1
85276 Pfaffenhofen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

1C 15011/67 (NC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 February 2024
Date of latest renewal: NA

10. DATE OF REVISION OF THE TEXT

July 2024