NEXLIZET®
(Bempedoic acid and Ezetimibe)

1. NAME OF THE MEDICINAL PRODUCT

Nexlizet 180 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 180 mg of bempedoic acid and 10 mg of ezetimibe.

Excipient(s) with known effect
Each 180 mg/10 mg film-coated tablet contains 71.6 mg of lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, oval, film-coated tablet of approximately 15.00 mm × 7.00 mm × 5.00 mm debossed with “818” on one side and “ESP” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia and mixed dyslipidaemia
Nexlizet 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 in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe (see sections 4.2, 4.3, and 4.4),
- 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
Nexlizet 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.

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 Nexlizet is one film-coated tablet of 180 mg/10 mg taken once daily.

Coadministration with bile acid sequestrants
Dosing of Nexlizet should occur either at least 2 hours before or at least 4 hours after administration of a bile acid sequestrant.

Concomitant simvastatin therapy
When Nexlizet 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 with bempedoic acid. Additional monitoring for adverse reactions may be warranted in these patients when Nexlizet is administered (see section 4.4).

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). Treatment with Nexlizet 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 (see section 4.4).

Paediatric population
The safety and efficacy of Nexlizet in children aged less than 18 years have not 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 substances 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).
- Nexlizet coadministered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.
- When Nexlizet is coadministered with a statin, please refer to the summary of product characteristics (SmPC) for that particular statin therapy.

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). 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. In postmarketing experience with ezetimibe, very rare cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe.

Patients receiving Nexlizet as adjunctive therapy to a statin should be monitored for adverse reactions that are associated with the use of high doses of statins. All patients receiving Nexlizet 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 Nexlizet and a statin, a lower maximum dose of the same statin or an alternative statin, or discontinuation of Nexlizet 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), Nexlizet 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 Nexlizet (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 Nexlizet 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. In controlled coadministration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥ 3× ULN) have been observed. Liver function tests should be performed at initiation of therapy. Treatment with Nexlizet should be discontinued if an increase in transaminases of > 3× ULN persists (see sections 4.3 and 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 with bempedoic acid (see section 5.2). Additional monitoring for adverse reactions may be warranted in these patients when Nexlizet 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), Nexlizet is not recommended in these patients (see section 5.2).

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established. If cholelithiasis is suspected in a patient receiving Nexlizet and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Ciclosporin

Caution should be exercised when initiating Nexlizet in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Nexlizet and ciclosporin (see section 4.5).

Anticoagulants

If Nexlizet is added to warfarin, other coumarin anticoagulants, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Contraception

Women of childbearing potential must use effective contraception during treatment. Patients should be advised to stop taking Nexlizet before stopping contraceptive measures if they plan to become pregnant.

Excipients

Nexlizet 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/10 mg film-coated tablet (daily dose), that is to say essentially 'sodium free'.

Patients at high risk of cardiovascular disease

Evidence for the use of the fixed combination medicinal product of bempedoic acid with ezetimibe in patients at high risk of cardiovascular disease is only available for the lipid-lowering effect in absence of any cardiovascular risk reduction estimation for ezetimibe in primary prevention patients (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

No specific pharmacokinetic drug interaction studies with Nexlizet have been conducted. Drug interactions that have been identified in studies with bempedoic acid or ezetimibe determine the interactions that may occur with Nexlizet.

Effects of other medicinal products on individual components of Nexlizet

Fibrates
Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold, respectively). Fenofibrate may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see section 5.3). A lithogenic risk associated with the therapeutic use of Nexlizet cannot be ruled out.

If cholelithiasis is suspected in a patient receiving Nexlizet and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see section 4.4).

Ciclosporin
In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, a single 10 mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold)

increase in the mean area under the curve (AUC) for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medicinal products demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of ciclosporin alone. A controlled study on the effect of coadministered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating Nexlizet in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Nexlizet and ciclosporin (see section 4.4).

Cholestyramine
Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe plus ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding Nexlizet to cholestyramine may be lessened by this interaction (see section 4.2).

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 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.

<u>Effects of individual components of Nexlizet on other medicinal products</u>

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).

No clinically significant pharmacokinetic interactions were seen when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

Transporter-mediated drug interactions
Bempedoic acid and its glucuronide weakly inhibit OATP1B1 and OATP1B3 at clinically relevant concentrations. Coadministration of Nexlizet 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.

Anticoagulants
Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been postmarketing reports of increased INR in patients who had ezetimibe added to warfarin or fluindione.

If Nexlizet is added to warfarin, other coumarin anticoagulants, or fluindione, INR should be appropriately monitored (see section 4.4).

Other interactions studied
Bempedoic acid had no effect on the pharmacokinetics of oral contraceptive norethindrone/ethinyl estradiol. In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of oral contraceptives ethinyl estradiol and levonorgestrel. Bempedoic acid had no effect on the pharmacokinetics or pharmacodynamics of metformin.

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide, or midazolam, during coadministration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Nexlizet is contraindicated during pregnancy (see section 4.3).

There are no or limited amount of data from the use of Nexlizet 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, Nexlizet may cause foetal harm when administered to pregnant women. Nexlizet 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 or ezetimibe/metabolites are excreted in human milk. Because of the potential for serious adverse reactions, women taking Nexlizet should not breast-feed their infants. Nexlizet is contraindicated during breast-feeding (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

Nexlizet 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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in Nexlizet were hyperuricaemia (4.7%) and constipation (4.7%).

In placebo-controlled phase 3 primary hyperlipidaemia studies (N=3,621) with bempedoic acid, 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) with bempedoic acid; (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 Nexlizet are displayed by system organ class and frequency in table 1. Any additional adverse reactions that have been reported with bempedoic acid (based on incidence rates from phase 3 primary hyperlipidaemia studies and exposure adjusted incidence rates from CLEAR Outcomes study), or ezetimibe have also been presented to provide a more comprehensive adverse reaction profile for Nexlizet.

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
Adverse reactions with Nexlizet		
Blood and lymphatic system disorders	Anaemia Decreased haemoglobin	Common
Metabolism and nutrition disorders	Hyperuricaemia[a]	Common
	Decreased appetite	Common
Nervous system disorders	Dizziness Headache	Common
Vascular disorders	Hypertension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Constipation Diarrhoea Abdominal pain Nausea Dry mouth Flatulence Gastritis	Common
Hepatobiliary disorders	Liver function test increased[b]	Common
Musculoskeletal and connective tissue disorders	Back pain Muscle spasms Myalgia Pain in extremity Arthralgia	Common
Renal and urinary disorders	Blood creatinine increased	Common
General disorders and administration site conditions	Fatigue Asthenia	Common

System organ class (SOC)	Adverse reactions	Frequency categories
Additional adverse reactions with bempedoic acid		
Metabolism and nutrition disorders	Gout	Common
	Weight decreased[d]	Uncommon
Hepatobiliary disorders	Aspartate aminotransferase increased	Common
	Alanine aminotransferase increased	Uncommon
Renal and urinary disorders	Glomerular filtration rate decreased	Common
	Blood urea increased	Uncommon
Additional adverse reactions with ezetimibe		
Blood and lymphatic system disorders	Thrombocytopaenia	Not known
Immune system disorders	Hypersensitivity, including rash, urticaria, anaphylaxis and angio-oedema	Not known
Psychiatric disorders	Depression	Not known
Nervous system disorders	Paraesthesia[c]	Not known
Vascular disorders	Hot flush	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known
Gastrointestinal disorders	Dyspepsia Gastrooesophageal reflux disease	Uncommon
	Pancreatitis	Not known
Hepatobiliary disorders	Aspartate aminotransferase increased Alanine aminotransferase increased Gammaglutamyltransferase increased	Uncommon
	Hepatitis Cholelithiasis Cholecystitis	Not known
Skin and subcutaneous tissue disorders	Pruritus[c]	Uncommon
	Erythema multiform	Not known
Musculoskeletal and connective tissue disorders	Blood CPK increased	Common
	Neck pain Muscular weakness[c]	Uncommon
	Myopathy/rhabdomyolysis	Not known
General disorders and administration site conditions	Chest pain Pain Oedema peripheral[c]	Uncommon

a. Hyperuricaemia includes hyperuricaemia and uric acid increased
b. Liver function test increased includes liver function test increased and liver function test abnormal
c. Adverse reactions with ezetimibe coadministered with a statin
d. (CLEAR Outcomes study) Weight decrease was observed only in patients with a baseline body mass index (BMI) of $\geq$ 30 kg/m^2, with a mean body weight reduction of -2.28 kg at month 36. Mean reduction in body weight was $\leq$0.5 kg in patients with a baseline BMI of 25 to <30 kg/m^2. Bempedoic acid was not associated with a mean change in body weight in patientswith a baseline BMI of < 25 kg/m^2

Description of selected adverse reactions

Increased serum uric acid

Nexlizet increases serum uric acid possibly due to inhibition of renal tubular OAT2 by bempedoic acid (see section 4.5). A mean increase of 35.7 micromole/L (0.6 mg/dL) in uric acid compared to baseline was observed with Nexlizet 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. There were no reports of gout with Nexlizet. In the phase 3 primary hyperlipidaemia studies of bempedoic acid, 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 (see section 4.4).

Effects on serum creatinine and blood urea nitrogen
Nexlizet increases serum creatinine and blood urea nitrogen (BUN). A mean increase of 1.8 micromole/L (0.02 mg/dL) in serum creatinine and a mean increase of 1.0 mmol/L (2.7 mg/dL) in BUN compared to baseline was observed with Nexlizet 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 therapy. 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 Nexlizet therapy, particularly in patients with medical conditions or receiving medicinal products that require monitoring of estimated creatinine clearance.

Hepatic enzyme elevations
Hepatic transaminase (AST and/or ALT) elevations of ≥ 3× ULN were reported in 2.4% of patients treated with Nexlizet compared with no patients on placebo. In four phase 3 primary hyperlipidaemia studies of bempedoic acid, the incidence of elevations (≥ 3× ULN) in hepatic transaminase levels (AST and/or ALT) was 0.7% for patients treated with bempedoic acid and 0.3% for placebo. In controlled clinical combination trials of ezetimibe initiated concurrently with a statin, the incidence of consecutive elevations (≥ 3× ULN) in hepatic transaminase levels was 1.3% for patients treated with ezetimibe administered with statins and 0.4% for patients treated with statins alone. 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%). The elevations in transaminases with bempedoic acid or ezetimibe were not associated with other evidence of liver dysfunction (see section 4.4).

Decreased haemoglobin
In the phase 3 primary hyperlipidaemia studies of bempedoic acid, 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 hyperlipidaemia 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 acidtreated patients (4.7%) compared to placebo-treated patients (3.9%).

4.9 Overdose

In the event of overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Bempedoic acid
Doses up to 240 mg/day (1.3 times the approved recommended dose) have been administered in clinical trials with no evidence of dose limiting toxicity. No adverse events were observed in animal studies at exposures up to 14-fold higher than those in patients treated with bempedoic acid at 180 mg once daily.

Ezetimibe
In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, did not result in an increase in the rate of adverse events. In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents in combination with other drugs, ATC code: C10BA10

Mechanism of action

Nexlizet contains bempedoic acid and ezetimibe, two LDL-C lowering compounds with complementary mechanisms of action. It reduces elevated LDL-C through dual inhibition of cholesterol synthesis in the liver and cholesterol absorption in the intestine.

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 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.

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.

Pharmacodynamic effects

Administration of bempedoic acid and ezetimibe 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), 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
A QT trial has been conducted for bempedoic acid. 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.

The effect of ezetimibe or the combination regimen bempedoic acid/ezetimibe on QT interval has not been evaluated.

Clinical efficacy and safety

Ezetimibe 10 mg has been shown to reduce the frequency of cardiovascular events.

Clinical efficacy and safety in primary hypercholesterolaemia and mixed dyslipidaemia
The efficacy of Nexlizet was assessed in a sensitivity analysis of 301 patients who received treatment in CLEAR Combo (Study 1002-053). This analysis excluded all data from 3 sites (81 patients) due to systematic patient non-compliance with all the four treatments. The study was a 4-arm, multi-centre, randomised, double-blind, parallel-group, 12-week trial in patients with high cardiovascular risk and hyperlipidaemia. Patients randomised 2:2:2:1, received either Nexlizet orally at a dose of 180 mg/10 mg per day (n=86), bempedoic acid 180 mg per day (n=88), ezetimibe 10 mg per day (n=86), or placebo once daily (n=41) as add-on to a maximum tolerated statin therapy. Maximum tolerated statin therapy could include statin regimens other than daily dosing or no statin. Patients were stratified by cardiovascular risk and baseline statin intensity. Patients on simvastatin 40 mg per day or higher were excluded from the trial.

Demographics and baseline disease characteristics were balanced between the treatment arms. Overall, the mean age at baseline was 64 years (range: 30 to 87 years), 50% were ≥ 65 years old,
50% were women, 81% were White, 17% were Black, 1% were Asian, and 1% were other. At the time of randomisation, 61% of patients on bempedoic acid/ezetimibe, 69% of patients on bempedoic acid, 63% of patients on ezetimibe and 66% of patients on placebo were receiving statin therapy; 36% of patients on bempedoic acid/ezetimibe, 35% of patients on bempedoic acid, 29% of patients on ezetimibe and 41% of patients on placebo were receiving high intensity statin therapy. The mean baseline LDL-C was 3.9 mmol/L (149.7 mg/dL). Most patients (94%) completed the study.

Nexlizet significantly reduced LDL-C from baseline to week 12 compared with placebo (-38.0%; 95% CI: -46.5%, -29.6%; $p < 0.001$). The maximum LDL-C lowering effects were observed as early as week 4 and efficacy was maintained throughout the trial. Nexlizet also significantly reduced non-HDL-C, apo B, and TC (see table 2).

Table 2: Treatment effects of Nexlizet on lipid parameters in patients with high cardiovascular risk and hyperlipidaemia on background statin regimens (mean % change from baseline to week 12)

	Nexlizet 180 mg/10 mg n=86	**Bempedoic acid 180 mg n=88**	**Ezetimibe 10 mg n=86**	**Placebo n=41**
LDL-C, n	86	88	86	41
LS Mean (SE)	-36.2 (2.6)	-17.2 (2.5)	-23.2 (2.2)	1.8 (3.5)
non-HDL-C, n	86	88	86	41
LS Mean (SE)	-31.9 (2.2)	-14.1 (2.2)	-19.9 (2.1)	1.8 (3.3)
apo B, n	82	85	84	38
LS Mean (SE)	-24.6 (2.4)	-11.8 (2.2)	-15.3 (2.0)	5.5 (3.0)
TC, n	86	88	86	41
LS Mean (SE)	-26.4 (1.9)	-12.1 (1.8)	-16.0 (1.6)	0.7 (2.5)

apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol, LDL C=low-density lipoprotein cholesterol; LS=least squares; TC=total cholesterol.
Background statin: atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin.

Administration of bempedoic acid on background ezetimibe therapy
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 bempedoic acid 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. Administration of bempedoic acid to patients on background ezetimibe therapy significantly reduced LDL-C from baseline to week 12 compared with placebo and ezetimibe ($p < 0.001$). Administration of bempedoic acid with background ezetimibe therapy also significantly reduced non-HDL-C, apo B, and TC (see table 3).

Table 3: Treatment effects of bempedoic acid compared with placebo in statin intolerant patients on back ground ezetimibe therapy (mean percent change from baseline to week 12)

	CLEAR Tranquility (Study 1002-048) (N=269)	
	Bempedoic acid 180 mg + Background Ezetimibe 10 mg n=181	**Placebo + Background Ezetimibe 10 mg n=88**
LDL-C[a], n	175	82
LS Mean	-23.5	5.0
non-HDL-C[a], n	175	82
LS Mean	-18.4	5.2
apo B[a], n	180	86
LS Mean	-14.6	4.7
TC[a], n	176	82
LS Mean	-15.1	2.9

apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL C=low-density lipoprotein cholesterol; LS=least squares; TC=total cholesterol.
Background statin: atorvastatin, simvastatin, rosuvastatin, pravastatin, lovastatin
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.

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 bempedoic acid 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 m2 (21%), and a mean body mass index 29.9 kg/m2. 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%).

Bempedoic acid 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). The point estimate for MACE-4 Hazard Ratio was 0.94 (95% CI: 0.74, 1.20) in the subgroup of patients using ezetimibe at baseline. For the limited subgroup of patients with ezetimibe use at baseline and at high cardiovascular risk (n=335), LDL-C reduction was -26.7% (95% CI; -30.9%, -22.4%), but cardiovascular risk reduction could not be estimated.

Impact of bempedoic acid on the individual components of the primary endpoint included a 27% reduction in the risk of non-fatal 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 bempedoic acid and placebo in mean percent change in LDL-C from baseline to month 6 was -20% (95% CI: -21%, -19%).

Table 4: Effect of Bempidoic acid 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
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

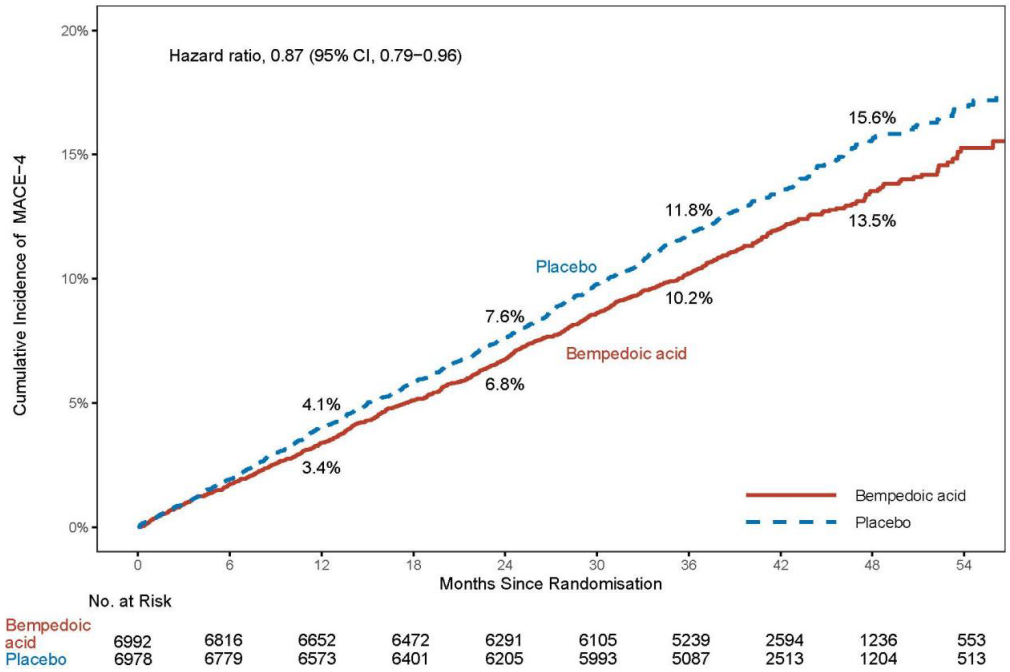
CI = confidence interval; MACE = major adverse cardiovascular event; NS=not significant

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

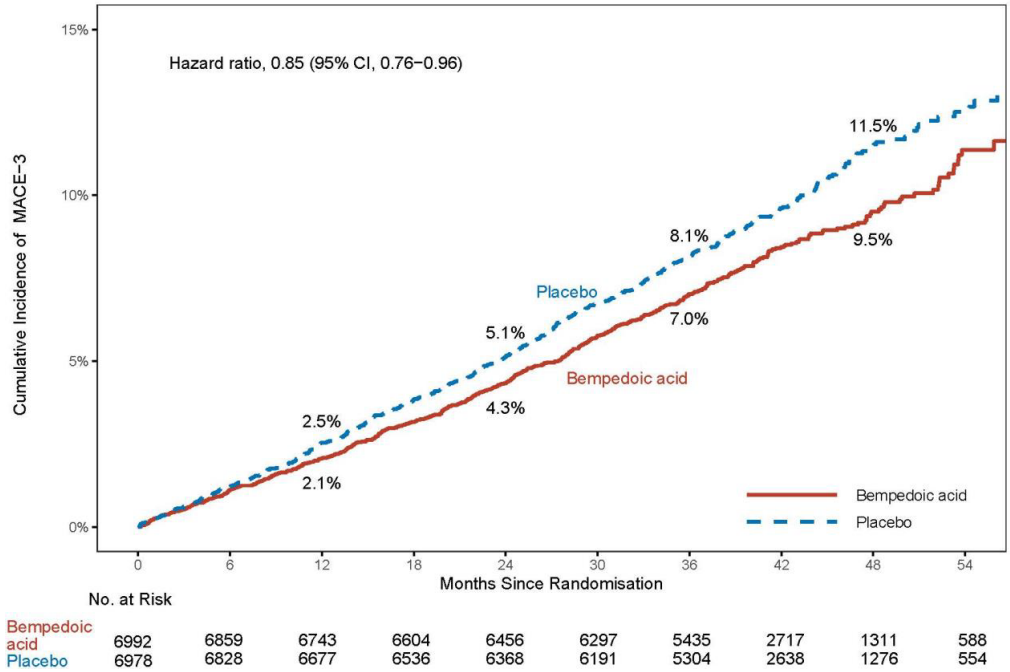
Figure 1: Kaplan-Meier Curve for Time to First Occurrence of MACE-4



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 waived the obligation to submit the results of studies with Nexlizet in all subsets of the paediatric population in the treatment of elevated cholesterol (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Nexlizet
The bioavailability of bempedoic acid/ezetimibe tablets was similar relative to that from the individual tablets, coadministered. C_{max} values for bempedoic acid and its active metabolite (ESP15228) were similar between formulations, but ezetimibe and ezetimibe glucuronide C_{max} values were approximately 13% and 22% lower, respectively, for bempedoic acid/ezetimibe relative to the individual tablets, coadministered. Given a similar overall extent of ezetimibe and ezetimibe glucuronide exposure (as measured by AUC), a 22% lower C_{max} is unlikely to be clinically significant.

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with bempedoic acid. 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 the AUC and C_{max} for ezetimibe were less than 20%.

Bempedoic acid
Pharmacokinetic data indicate that bempedoic acid is absorbed with a median time to maximum concentration of 3.5 hours when administered as Nexlizet 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.

Ezetimibe
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean C_{max} occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe undergoes extensive enterohepatic cycling, multiple peaks of ezetimibe can be observed.

Effect of food
After the administration of bempedoic acid/ezetimibe with a high-fat, high calorie breakfast in healthy subjects, the AUC for bempedoic acid and ezetimibe were comparable to the fasted state. Compared to the fasted state, the fed state resulted in 30% and 12% reductions in C_{max} of bempedoic acid and ezetimibe, respectively. Relative to the fasted state, the fed state resulted in 12% and 42% reductions in ezetimibe glucuronide AUC and C_{max}, respectively. This effect of food is not considered to be clinically meaningful.

Distribution

Bempedoic acid
The bempedoic acid apparent volume of distribution (V/F) was 18 L. Plasma protein binding of bempedoic acid, its glucuronide and its active metabolite, ESP15228, were 99.3%, 98.8% and 99.2%, respectively. Bempedoic acid does not partition into red blood cells.

Ezetimibe
Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88% to 92% to human plasma proteins, respectively.

Biotransformation

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

The primary route of elimination for bempedoic acid is through metabolism to the acyl glucuronide. Bempedoic acid is also reversibly converted to an active metabolite (ESP15228) based on aldo-keto reductase activity observed *in vitro* from human liver. Mean plasma AUC metabolite/parent drug ratio for ESP15228 following repeat-dose administration was 18% and remained constant over time. Both 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.

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.

Ezetimibe
In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. 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. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling.

Elimination

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

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

Ezetimibe
Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe and ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of

radioactivity in the plasma. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Special populations

Renal impairment

Bempedoic acid
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 Nexlizet did not include patients with ESRD on dialysis (see section 4.4).

Ezetimibe
After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 mL/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. An additional patient in this study (post-renal transplant and receiving multiple medicinal products, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Hepatic impairment
Nexlizet is not recommended in patients with moderate or severe hepatic impairment due to the unknown effects of increased exposure to ezetimibe.

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

Ezetimibe
After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh A), compared with healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh B), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared with healthy subjects.

Other special populations

Bempedoic acid
Of the 3,621 patients treated with bempedoic acid in the placebo-controlled studies, 2,098 (58%) were > 65 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

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.

Ezetimibe

Geriatrics
In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥ 65 years) healthy subjects compared to younger subjects. LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe.

Gender
Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

5.3 Preclinical safety data

Nexlizet

Coadministration of bempedoic acid with doses of ezetimibe in rats at systemic total exposures > 50 times the human clinical exposure did not alter the toxicologic profile of either bempedoic acid or ezetimibe. Bempedoic acid in combination with ezetimibe did not alter the effects on embryo-fetal development profile of bempedoic acid or ezetimibe.

Bempedoic acid

The standard battery of genotoxicity studies have 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.

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).

Ezetimibe

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study in dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

In coadministration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in coadministration therapy. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2,000 times the AUC level for the active metabolites).

In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or coadministered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1,000 mg/kg/day. The coadministration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The coadministration of ezetimibe with lovastatin resulted in embryolethal effects.

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)
Sodium laurilsulfate (E487)
Povidone (K30) (E1201)

Film-coating

Partially hydrolyzed poly(vinyl alcohol) (E1203)
Talc (E553b)
Titanium dioxide (E171)
Indigo Carmine Aluminium Lake (E132)
Glycerol monocaprylocaprate
Sodium laurilsulfate (E487)
Brilliant Blue FCF Aluminium Lake (E133)

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
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Polyvinyl chloride (PVC)/Aclar/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 Pharma Limited
Plot # 67-70 Sector II
Pithampur District Dhar
Madhya Pradesh 454 775 India

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

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