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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Nilemdo

International non-proprietary name: acidum bempedoicum

Pharmaceutical form: tablet

Dosage strength: 180 mg

Route(s) of administration: oral

Marketing Authorisation Holder: PharmaContext GmbH

Marketing Authorisation No.: 67583

Decision and Decision date: approved on 14 December 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

About Swissmedic

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- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
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- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
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- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ACL	Adenosine triphosphate citrate lyase
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HDL	High density lipoprotein
HeFH	Heterozygous familial hypercholesterolaemia
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QD	Once a day
RMP	Risk Management Plan
SREBP2	Sterol response element binding protein 2
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
VLDL	Very low density lipoprotein

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance bempedoic acid of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Nilemdo is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) 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 or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The effect of Nilemdo on cardiovascular morbidity and mortality has not yet been determined.

2.2.2 Approved Indication

Nilemdo is indicated as an adjunct to diet and in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies for the treatment of adults with clinical manifestations of atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolaemia who need additional LDL-C lowering.

The effect of Nilemdo on cardiovascular morbidity and mortality has not yet been determined.

2.2.3 Requested Dosage

The recommended dose of Nilemdo is one tablet (180 mg) taken once daily.

Concomitant Simvastatin Therapy

When Nilemdo is coadministered with simvastatin, limit simvastatin dosage 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). Refer to the simvastatin summary of product characteristics for simvastatin dosing recommendations.

Special populations

Elderly patients

No dose adjustment is necessary in elderly patients

Patients with renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment.

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Paediatric population

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

Method of administration

Each tablet should be taken orally with or without food.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	27 May 2019
Formal control completed	20 June 2019
List of Questions (LoQ)	18 October 2019
Answers to LoQ	13 April 2020
Predecision	15 July 2020
Answers to Predecision	15 September 2020
Final Decision	14 December 2020
Decision	approval

3 Medical Context

Hyperlipidaemia is the diverse group of disorders characterised by an excess of different lipid entities (i.e., triglycerides, cholesterol and phospholipids) in the blood. Hypercholesterolaemia refers to the high levels of cholesterol in the bloodstream, and primary hypercholesterolaemia is any hypercholesterolaemia caused by a familial or nonfamilial disorder in lipid metabolism. Part of this disorder is heterozygous familial hypercholesterolaemia (HeFH), which affects between 1:200 and 1:500 individuals globally. Cholesterol levels are elevated in affected individuals, and lowering cholesterol has been proven to reduce the risk of cardiovascular disease (CVD) in this population.

CVD remains the leading cause of death among Americans, Europeans, and other populations around the world (World Health Organization (WHO), 2015). CVD risk factors are well established and include hypercholesterolaemia, hypertension, smoking, diabetes, physical inactivity, obesity, and increasing age; the first three are the key risk factors. Across the European region, CVD causes more than half of all deaths (WHO, 2018).

Cholesterol reduction was the leading factor contributing to the decline in CVD mortality. Current international guidelines emphasise the importance of targeting cholesterol reduction for both primary and secondary prevention of reducing CV events. If the prevalence of elevated LDL-C were more widely reduced, this would lead to even greater declines in morbidity and mortality associated with atherosclerotic cardiovascular disease (ASCVD). Since current international guidelines and recommendations recognise that LDL-C goals are not always achievable with current lipid-lowering therapies, there remains an unmet medical need to provide additional LDL-C-lowering therapies for patients with elevated LDL-C.

4 Quality Aspects

4.1 Drug Substance

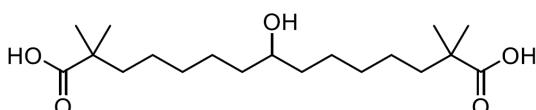
INN: bempedoic acid

Chemical name: 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid

Molecular formula: C₁₉H₃₆O₅

Molecular mass: 344.49

Molecular structure:



Physico-chemical properties: White to off-white, crystalline powder. One crystalline form (Type A) of bempedoic acid has been identified. The solubility of the drug substance is pH-dependent.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

Specification: The active substance specifications include tests for appearance, identification (FTIR, HPLC), assay (HPLC) and impurities (HPLC), residual solvents (GC), elemental impurities (ICP), residue on ignition, particle size distribution, water content (KF) and microbial quality. The specifications conform to the requirements outlined in ICH guideline Q6A and are considered appropriate in order to ensure a consistent drug substance quality.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug Product

Description and composition: Nilemdo film-coated tablets are presented as immediate release film-coated tablets containing 180 mg bempedoic acid. The white to off-white, oval, film-coated tablets are debossed with '180' on one side and 'ESP' on the other side.

The tablet cores consist of the pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, hydroxypropyl cellulose, colloidal silicon dioxide, sodium starch glycolate and magnesium stearate. The tablets are film-coated with a mixture of partially hydrolysed polyvinyl alcohol, titanium dioxide, polyethylene glycol (PEG) and talc.

Pharmaceutical development: Suitable pharmaceutical development data have been provided for the drug product composition and manufacturing process, including establishment of the Quality Target Product Profile (Q TPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).

Manufacture: The manufacturing process consists of dry mixing, wet granulation, wet milling, drying and dry milling, blending, lubrication, tablet compression and film coating. Process parameters and in-process controls are defined in order to ensure a consistent quality of the tablets.

Specification: For the control of the drug product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters appearance, tablet dimensions, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution, water content (KF) and microbial purity. The corresponding test procedures have been adequately validated, as appropriate.

Container-Closure System: Nilemdo film-coated tablets are packaged in PVC/aluminium blisters.

Stability: Drug product stability studies have been conducted with three primary stability batches and five supportive stability batches according to the recommendations of the relevant ICH guidelines. Based on these studies, a shelf-life of 36 months has been established for Nilemdo film-coated tablets. The storage recommendation is "Do not store above 30 °C".

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical Aspects

Bempedoic acid (ETC-1002) is an inhibitor of adenosine triphosphate (ATP) citrate lyase (ACL), a cytoplasmic enzyme that generates acetyl-Coenzyme A for the *de novo* synthesis of cholesterol and fatty acids.

The nonclinical testing strategy for the development of bempedoic acid followed the recommendations in the ICH M3 (R2) guideline. Pivotal toxicity and safety pharmacology studies were conducted in accordance with GLP regulations.

5.1 Pharmacology

Bempedoic acid (ETC-1002) is a prodrug activated by very long-chain acyl-Coenzyme A synthetase 1 (ACSVL1) in the liver to the active form ETC-1002-CoA (ETC-1002-CoA). In a cell-free system, ETC-1002-CoA dose-dependently inhibited recombinant human ACL ($K_i = 2 \mu\text{M}$), while bempedoic acid was inactive. In rat hepatocytes, bempedoic acid caused a dose-dependent reduction of metabolites downstream of ACL (Acetyl-Co-A, Malonyl-CoA, and HMG-CoA ($IC_{50} 3-10 \mu\text{M}$)), with a concomitant increase in the ACL substrate (citrate). In primary human hepatocytes, inhibition of lipid synthesis by bempedoic acid correlated with increased low-density lipoprotein receptor (LDLR) activity and increased LDLR mRNA levels, suggesting enhanced LDL-cholesterol (LDL-C) particle clearance from plasma and upregulation of sterol response element binding protein 2 (SREBP2) dependent gene transcription. In contrast to statins, bempedoic acid had no effect on ATP levels or the viability of primary human myotubes, which is consistent with the lack of ACSVL1 expression in muscle tissue. Consequently, bempedoic acid did not induce reduction of ATP levels, cytotoxicity or caspase 3/7 activation in primary human myotubes. In addition, ETC-1002-CoA also activated AMP-activated protein kinase (AMPK), a heterotrimeric complex that stimulates fatty acid degradation and reduces glucose levels, immune response, protein synthesis, and cell growth. However, while the specific AMPK isoform activated by ETC-1002-CoA is highly expressed in rodent liver, its expression in human liver is very low. Therefore, the contribution of the AMPK pathway to the pharmacologic effects of bempedoic acid in human is expected to be minimal, if any.

Bempedoic acid inhibited lipid synthesis in mouse and hamster models with normal lipid metabolism and in diet-induced models of hyperlipidaemia. In obese Zucker rats given up to 100 mg/kg/day, bempedoic acid induced dose-dependent decreases in body weight, VLDL-C and LDL-C (up to 80%), triglycerides (up to 90%), and an increase in HDL-C. In addition, a dose-dependent increase in serum β -hydroxybutyrate (β -HBA) was observed in these animals 1 and 2 weeks after treatment at ≥ 10 mg/kg/day, suggesting that bempedoic acid may increase fatty acid oxidation. Similar results were observed in normally fed Sprague Dawley rats, hyperlipidaemic mice, and golden Syrian hamsters. The effect on the prevention of atherosclerosis was shown in rodent models with aberrant lipid metabolism, triglyceride overproduction, hypercholesterolaemia, and atherosclerosis ((*ApoE*^{−/−} mice), and in Yucatan minipigs (LDLR^{+/−} and LDLR^{−/−})).

Similarly to bempedoic acid, the major human metabolite (ESP 15228) dose-dependently inhibited the fatty acid and sterol synthesis in primary rat hepatocytes ($IC_{50} < 3 \mu\text{M}$), and similarly regulated fatty acid and carbohydrate metabolism. The other two major human metabolites, acyl ETC-1002 and ESP15228 glucuronides, did not inhibit lipid synthesis in mouse hepatocytes. Bempedoic acid did not inhibit (>50%) various human receptors, ion channels, transporters, or enzymes. Unlike statins, bempedoic acid and ETC-1002-CoA did not inhibit HMG-CoA reductase, as shown using partially purified rodent enzyme. Concerning AMPK signalling, it was demonstrated that ETC-1002-CoA activates recombinant human AMPK $\alpha\beta$ by binding to the $\beta 1$ subunit. Since human liver predominately expresses AMPK $\beta 2$ -containing complexes, the potential for relevant effects of bempedoic acid in this organ is considered low. Bempedoic acid increased levels of AMPK phosphorylation in human macrophages, which coincided with reduced activity of MAP kinases and decreased production of pro-inflammatory cytokines, chemokines (TNF α , IL-1 b , IL-6, IL-8, CCL2, CXCL10, CCL5, CCL1) and adhesion molecules (ICAM1, CD40L, MIP1 b , C5a). In addition, bempedoic acid attenuated homing of leukocytes into inflammatory sites and inhibited adipose tissue inflammation in a mouse model of diet-induced obesity.

Both bempedoic acid and ESP15288 weakly activated human PPAR α and PPAR γ at concentrations $\geq 100\mu\text{M}$.

In addition, in the toxicity studies in rats and monkeys the activity of hepatic enzymes CYP4A1 and acyl-Coenzyme A oxidase (ACOX) was markedly increased in rats (at $\geq 10 \text{ mg/kg/day}$) and minimally increased in monkeys (at $\geq 3 \text{ mg/kg/day}$), which correlated with liver changes and PPAR/peroxisome activation.

Safety pharmacology studies showed no effect of bempedoic acid on the central nervous system in rats, no effect on the cardiovascular parameters in monkeys, and no adverse effects on respiratory function in rats. Bempedoic acid had no *in vitro* effect on hERG current up to 300 μM (104 $\mu\text{g/mL}$), which is >100 fold the C_{\max} of unbound bempedoic acid at the maximum recommended human dose of 180 mg. No elevation of troponin was recorded in the repeated-dose toxicity study in monkeys.

5.2 Pharmacokinetics

Bempedoic acid has a low solubility, but is highly permeable. The absorption of bempedoic acid in monkeys and rats was faster (T_{\max} 0.5- 2 h) than in rabbits (4 h) and humans (T_{\max} 3.5 h).

Blood/plasma ratios were similar across the species (0.4-0.6), indicating that bempedoic acid does not preferentially partition into red blood cells. Elimination ($t_{1/2}$) from plasma and blood in intact rats and monkeys (18-27 h) was similar to $t_{1/2}$ in humans (19 h). In rabbits and in bile-cannulated rats, elimination was faster (10-12.5 h and approx. 5 h, respectively). Bempedoic acid undergoes enterohepatic recirculation (39%).

Plasma protein binding of bempedoic acid and its metabolites (ETC-1002, ESP15228, ETC-1002-glucuronide) was similar across the nonclinical species and humans, and ranged between 86-98%. In albino rats, bempedoic acid-related radioactivity was widely distributed following oral administration of 10 mg/kg, reaching peak concentration in tissues after 2 h. The highest concentration of radioactivity was observed in the gastrointestinal tract (stomach, small intestine), followed by the liver, kidney cortex, blood, lung, kidney medulla, and tooth pulp. In most of the tissues, drug-related radioactivity was not detectable after 72 h; in kidney, liver and gastrointestinal tract, radioactivity persisted until 168 h postdose. There was no evidence of retention in melanin-containing tissues.

The major routes of bempedoic acid metabolism in all species was via direct acyl glucuronidation and glycerol conjugation. *In vitro*, metabolism in human, mouse, rat and cynomolgus monkey hepatocytes was similar. The metabolite ETC-1002 acyl glucuronide (M11) was detected in hepatocytes of all species, but in different quantities (50-98% humans; 39% monkeys, 27% male rats, 10% female rats, 47% mice). Metabolite M15 (acyl glucuronide ESP15228) was the second major metabolite in human (5%), monkey (10%), and male rat (2%) hepatocytes, but not in female rat and mouse hepatocytes. *In vivo*, the active metabolite ESP15228 (M1) was present in similar quantities in the plasma of rats and cynomolgus monkeys. However, the two acyl glucuronides M11 and M15 were either not present (rat) or were present at lower levels (cynomolgus monkeys) compared to human plasma.

In rats, biliary/faecal excretion was the major route of clearance. In monkeys, similarly as in humans, urinary excretion was the primary route of elimination. Excretion in milk was not evaluated.

After repeated dose administration, exposure (AUC and C_{\max}) to bempedoic acid in nonclinical species increased approximately proportional to dose or more than dose proportionally at higher concentrations (in rabbits and monkeys). Systemic exposure to bempedoic acid was substantially higher (12- to 20-fold) than that of ESP15228 and, in rodents, mainly decreased following repeated administration of ETC-1002, meaning that the exposure is lower at steady state than after a single dose. Mean exposure of ESP15228 increased with increasing dose in a greater than dose proportional manner. There were no clear gender-related differences. Accumulation of bempedoic acid and ESP15228 was observed in monkeys and rabbits following repeated administration of bempedoic acid (up to 2.8-fold). Toxicokinetics in pregnant and in juvenile rats was similar to that in adult animals.

The combination of atorvastatin (40 mg/kg) and bempedoic acid (10 mg/kg) did not mutually influence their toxicokinetic parameters in cynomolgus monkeys.

5.3 Toxicology

Studies to characterise the toxicological profile of bempedoic acid were conducted in rats, monkeys, and rabbits. The toxicology species selection is considered adequate, although the monkey is considered closer to humans based on the metabolism similarities and lipoprotein profile. The duration of the studies supports the long-term use of bempedoic acid.

In the repeated-dose studies, rats and monkeys received bempedoic acid at doses up to 100 mg/kg and 60 mg/kg for up to 26 and 52 weeks, respectively. The most common observations were decreased food consumption and body weight, and clinical signs of morbidity/mortality at high doses. Mortality was caused by the interference of bempedoic acid in glucose and fatty acid metabolic pathways at the exposure levels not relevant for humans (>10). No risk for humans was observed in clinical studies.

The main target organs were liver and kidney. Dose-dependent hepatotoxicity observed in both species was considered the cause of morbidity/mortality at high doses. Increases in liver weight correlated with increased transaminase (ALT, AST) values, decreases in alkaline phosphatase, and histopathology findings. In rats, hepatocyte necrosis and minimal to moderate centrilobular to panlobular hepatocellular hypertrophy and minimal periportal vacuolation were observed. In monkeys, increases in liver weight correlated with centrilobular hepatocellular hypertrophy and periportal hepatocellular vacuolation. Increased intensity of Oil Red O-positive droplets predominantly in periportal hepatocytes was noted at the 30 and 60 mg/kg/day doses. Examination of the monkeys given 30 mg/kg/day by transmission electron microscope revealed lipid accumulation, prominent rough endoplasmic reticulum, and an increased number of structures consistent with peroxisomes in the periportal hepatocytes. Increases in urea nitrogen and creatinine were occasionally associated with renal tubular degeneration and necrosis. Although changes in liver and kidneys were reversible, or showed a tendency to reverse, during treatment-free recovery periods, the findings are considered of human relevance due to the proposed long-term treatment. Other findings included reversible decreases in red cell mass (erythrocytes, haemoglobin and haematocrit), occasional increases in leukocytes (in rats), and decreases in coagulation parameters.

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.

The highest dose combination of bempedoic acid/atorvastatin (60/40 mg/kg) given resulted in excessive toxicity (gastrointestinal tract, hepatotoxicity). The observed toxicities were attributed either to bempedoic acid or to the known toxicities of atorvastatin. The potential synergistic effect cannot be excluded. There is no safety margin.

Bempedoic acid is not genotoxic according to the standard test battery. Carcinogenicity studies in rats and mice revealed increased incidences of hepatocellular adenoma and thyroid follicular cell adenoma. However, these tumours are considered species-specific related to PPAR alpha activation and not relevant for humans. In rats, bempedoic acid had no adverse effects on male and female reproductive organs or fertility. However, treatment of female rats prior to mating and through gestation day 7 with bempedoic acid led to decreased corpora lutea, implantation sites, viable embryos, and increased pre-implantation loss at ≥ 30 mg/kg/day (4 times the clinical exposure at the human dose). In males, decreases in sperm count were observed at 60 mg/kg/day (9 times clinical exposure at the human dose) without an effect on fertility.

Bempedoic acid induced malformations in rats, but not in rabbits. 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 showed adverse maternal effects at ≥ 20 mg/kg/day and reductions in the numbers of live pups and pup survival, pup growth and learning and memory at ≥ 10 mg/kg/day. There is no safety margin. Bempedoic acid is contraindicated in pregnancy and lactation.

There were no juvenile-specific findings. Local tolerance studies were not conducted as it is intended for oral use.

There are no concerns regarding impurities. The submitted RMP includes a description of the key safety findings from nonclinical studies and their relevance to humans. According to the environmental risk assessment, no significant risk for the environment is anticipated.

5.4 Nonclinical Conclusions

Overall, bemedoic acid is considered well characterised within the nonclinical documentation and sufficient to support the clinical use of Nilemdo from the nonclinical point of view. The safety margins are considered to be sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Bempedoic acid is a prodrug, which is activated in hepatocytes to bempedoic acid -Coenzyme A, which subsequently inhibits the pharmacological target adenosine triphosphate citrate lyase (ACL).

Besides bempedoic acid, also an oxidized metabolite (ESP15228) is likely activated in hepatocytes by conjugation with CoA and has inhibitory activity for ACL.

Both active forms, bempedoic acid-CoA and ESP15228-CoA, were not detected in plasma.

Pharmacokinetics

Pharmacokinetics of bempedoic acid and its relevant metabolite ESP15228 have been characterised following single and multiple doses in healthy subjects and the intended patient population.

ADME of bempedoic acid

Absorption

Following administration of single doses of bempedoic acid (2.5 – 250 mg) under fasting conditions, C_{max} of bempedoic acid was observed at a median time of 1-2 h at the lower dose levels and at 3.0 – 3.5 h at the higher dose levels.

Following multiple QD doses of 20 - 120 mg or 140 - 220 mg, bempedoic acid reached maximal concentrations at median values of 2 - 3.5 h. Steady-state was reached by Day 8 and bempedoic acid accumulated ~2.3 - 2.8-fold.

The absolute bioavailability of bempedoic acid has not been determined, but was estimated to be at least 62% based on renal recovery in an ADME study.

Food effect

Intake of a 180 mg bempedoic acid tablet with a high-fat, high calorie meal, had no effect on bempedoic acid AUC or median t_{max} , while C_{max} was slightly decreased to 0.875-fold. There was no food effect on the metabolite ESP15228. Administration irrespective of food is acceptable.

Dose linearity

Following single doses, bempedoic acid C_{max} and exposure (AUC_{0-t} and AUC_{0-inf}) increased in a more than dose-proportional manner with increasing dose (2.5- to 250-mg dose range).

At steady-state, bempedoic acid C_{max} and AUC_{0-24h} increased in a more than dose-proportional manner at doses <120 mg but behaved approximately dose-proportionally at doses >120 mg.

Distribution

Bempedoic acid plasma protein binding was ~97-98%. The blood/plasma ratio was ~0.5 - 0.6, indicating minimal distribution of bempedoic acid into erythrocytes. The apparent volume of distribution of bempedoic acid was 18 L.

Metabolism and elimination

Bempedoic acid was primarily cleared by metabolism. Bempedoic acid was oxidized to ESP15228 by an aldo-keto reductase that has not been further characterised. In addition, bempedoic acid and ESP15228 were conjugated to acyl glucuronides by UGT2B7.

Following administration of a single 240 mg radioactive dose of bempedoic acid, the parent compound, bempedoic acid, accounted for 37.31 - 67.84%, the acyl glucuronide of bempedoic acid

accounted for 20.68 - 35.63%, metabolite ESP15228 accounted for 4.1 - 13.4% and the acyl glucuronide of ESP15228 accounted for 1.81 - 17.96% of total radioactivity in plasma. Seven additional metabolites, resulting from oxidation, taurine conjugation, cysteine sulphonic acid conjugation and sulphation were detected in faeces. There was a high inter-individual variability in the relative contribution of the various metabolites to excretion.

Both, bempedoic acid and ESP15228 are thought to be activated intracellularly by conjugation with Coenzyme A, but the CoA-conjugated forms have not been detected in plasma.

The mean terminal half-life of bempedoic acid was 19-26 h without apparent dose dependency. Renal clearance of unchanged bempedoic acid was 0.06 ml/min and only ~3% of the dose administered, was recovered in urine.

Following administration of a single 240 mg radioactive dose of bempedoic acid, 62.1% of the radioactive dose was recovered in urine and 25.4% was recovered in faeces.

In urine, besides the parent compound 32 - 41.5% of the administered radioactive dose was excreted as acyl glucuronide of bempedoic acid and 10 – 14% was excreted as an acyl glucuronide of ESP15228.

Nine radioactive species were recovered in faeces, without any clear major species. Bempedoic acid and ESP15228 were detected in faeces but accounted for less than 2% of the administered radioactive dose.

ADME of active metabolite ESP15228

Absorption

Following administration of single doses of bempedoic acid from 2.5 – 250 mg under fasting conditions, C_{max} of ESP15228 was observed at a median time of 6-10 h across dose groups.

Following multiple QD doses of 20-120 mg or 140 - 220 mg of bempedoic acid, metabolite ESP15228, reached maximal concentrations at median times of 6-7 h. ESP15228 reached steady-state by Day 8 and accumulated ~2.5 to 2.7-fold.

Dose-proportionality

Following single doses in the range of 2.5 - 250 mg, ESP15228 exposure (AUC_{0-t} and AUC_{0-inf}) increased in a more than dose-proportional manner with the dose, while C_{max} increased approximately dose- proportionally. Under steady-state conditions (20 – 220 mg QD) C_{max} and $AUC_{0-24,ss}$ of ESP15228 increased in a roughly dose - proportional manner.

Metabolite ratio

The ratio of metabolite ESP15228 / bempedoic acid was dose dependent with values up to 40% at lower doses (<100 - 140 mg) and ~20% at doses > 100 - 140 mg.

Distribution

ESP15228 plasma protein binding was > 98%.

Elimination

The mean terminal half-life of ESP15228 was 21-33 h. Details on ESP15228 metabolism and excretion are included above in the respective sections for bempedoic acid.

Special Populations

Renal impairment

Renal impairment had mild to moderate effects on the exposure of bempedoic acid and its metabolite ESP15228. The AUC_{inf} metabolite ratio (ESP15228/ bempedoic acid) was similar among renal function cohorts, suggesting that the extent of ESP15228 formation did not change substantially as a function of renal insufficiency. The effect of end-stage renal disease has not been investigated.

Mean terminal half-life and relative (-fold) changes in mean PK parameters compared to control

	renal function	normal CrCl) ≥90 mL/min	mild impairment eGFR ≥60-89 mL/min/1.73 m ²	moderate impairment eGFR >30-59 mL/min/1.73 m ²	severe impairment eGFR ≤30 mL/min/1.73 m ²
bempedoic acid	AUC _{inf}		1.18	1.76	1.9
	C _{max}		1.23	1.15	0.97
	terminal t _{1/2}	17.5 h	18.5 h	48.2 h	30.0 h
ESP15228	AUC _{inf}		1.15	1.87	2.26
	C _{max}		1.06	1.16	1.2
	terminal t _{1/2}	28.2 h	27.7 h	68.1 h	40.5 h
	metabolite ratio	19.5%	18.4%	21.6%	22.8%

The information for healthcare professionals cites the effects of renal impairment observed in a PopPK analysis. These have been consistent with the effects observed in the dedicated PK study (presented above).

Hepatic impairment

Mild and moderate hepatic impairment had only mild effects on the exposure of bempedoic acid and its metabolite ESP15228. The effect of severe hepatic impairment has not been investigated.

Mean terminal half-life and relative (-fold) changes in mean PK parameters compared to control

	hepatic function	normal	mild impairment	moderate impairment
bempedoic acid	AUC _{inf}		0.8	0.84
	C _{max}		0.89	0.86
	Fu	3.0%	2.8%	4.9%
	AUC _{inf, u}		0.74	1.31
	terminal t _{1/2}	27.2 h	25.3 h	20.7 h
ESP15228	AUC _{inf}		0.77	0.64
	C _{max}		0.87	0.77
	Fu	undetectable in 13/24 patients		
	terminal t _{1/2}	31.2 h	29.2 h	30.1 h
	metabolite ratio	18%	18%	14.5%

In a PopPK analysis, several demographic covariates had statistically significant effects on the bempedoic acid PK. However, these covariate effects on bempedoic acid exposure were only mild, and no dose adjustments based on age, weight, gender or ethnic background are required.

Interactions

Detailed information on the interaction potential of bempedoic acid and recommendations with regard to concomitant medications are provided in the attached information for healthcare professionals (see Chapter 7.1 of this report).

The clinically most relevant interaction arose from the OATP1B1/1B3 inhibitory activity of bempedoic acid and its acid -glucuronide: *In vitro*, bempedoic acid and bempedoic acid -glucuronide inhibited OATP1B1 and OATP1B3. Accordingly, the interaction effect of bempedoic acid on statins has been

investigated extensively for various statins at high and low statin doses. Increases in exposure of ~1.5-fold to 2-fold have been observed for various statins and their metabolites. In consequence, a maximal dose of 20 mg (or 40 mg in exceptional cases) simvastatin is recommended, while simvastatin doses >40 mg are contraindicated. For pravastatin, a maximal dose of 40 mg is recommended but not dose adjustments are required for atorvastatin, pravastatin or rosuvastatin.

Pharmacodynamics

Mechanism of Action and primary Pharmacology

Bempedoic acid is a prodrug that is activated in the liver to bempedoic acid -Coenzyme A, which subsequently inhibits the pharmacological target adenosine triphosphate citrate lyase (ACL). Besides bempedoic acid, an oxidized metabolite, produced by aldo-keto reductase activity and referred to as ESP15228, is also activated by conjugation with CoA and has inhibitory activity for ACL.

ACL is an enzyme in the cholesterol biosynthesis pathway and bempedoic acid is claimed to lower LDL-C by inhibition of cholesterol synthesis in the liver and subsequent upregulation of LDL-receptors.

As a proof of concept, the effect of bempedoic acid on fasting lipids was characterised after multiple doses of 20 mg – 220 mg QD for 15 days. At Day 15, dose-related reductions of fasting LDL-C and total cholesterol compared to baseline were observed at doses <60 mg. No consistent or dose-related effects on other fasting lipid parameters (HDL-C and triglycerides) were observed.

Relationship between Plasma Concentration and Effect

The relationship between bempedoic acid exposure and LDL-C reduction was modelled by combining a PopPK model with an indirect response PD Model. The estimate of bempedoic acid IC₅₀ from the model was 3.06 µg/mL and I_{max} was 32.6%.

The predicted effects of bempedoic acid dose on LDL-C reduction over the dose range in Phase 3 studies indicated that the applied clinical dose fell well within the flat range of the exposure response curve. Statin and ezetimibe use were significant covariates on the bempedoic I_{max}.

Secondary Pharmacology (Safety)

The potential effect of bempedoic acid on the QT interval was investigated in a thorough QT/QTc study. Intake of a single dose of 240 mg bempedoic acid caused no prolongation of the QT interval (upper bound of the 95% CI of ΔΔQTcF was <10 msec at all postdose timepoints).

In the categorical analysis, the QTcF interval did not exceed 450 msec at any time points in the bempedoic acid arm.

Change of QTcF over Baseline > 30 msec was observed at two timepoints in the bempedoic acid arm, at six time points in the moxifloxacin arm, but at none in the placebo arm. A change > 60 msec was observed at one timepoint in the moxifloxacin arm but not in the other two arms.

6.2 Dose Finding and Dose Recommendation

Bempedoic acid was investigated at the fixed oral doses of 2.5 to 250 mg in healthy volunteers and patients with hyperlipidaemia. A pooled analysis of the data from six phase 2 clinical studies in 580 patients demonstrated a dose-dependent LDL-C-lowering effect up to the 180 mg QD dose of bempedoic acid. Higher doses than the 180 mg QD dose of bempedoic acid did not provide an additional LDL-C-lowering effect versus placebo. Therefore, the 180 mg QD dosing regimen was selected for further evaluation in phase 3 clinical studies.

6.3 Efficacy

The efficacy of bempedoic acid as monocomponent was demonstrated in two multi-centre, randomised (2:1), double-blind, placebo controlled clinical studies. Both clinical studies enrolled 3009 (first study: n=779; second study: n=2230) adult patients on maximally tolerated lipid-lowering therapy with HeFH or established atherosclerotic cardiovascular disease. By risk classification, study participants had a high to very high CV risk. In both studies, the maximally tolerated lipid-lowering therapy was defined as a maximally tolerated statin dose alone or in combination with other lipid-lowering therapies. Patients were stratified by presence of HeFH and baseline statin intensity. Patients on simvastatin 40 mg/day or higher were excluded from both studies. Overall, the baseline characteristics of the bempedoic acid and placebo groups in both studies were balanced and comparable.

The maximum LDL-C-lowering effects occurred at Week 4 in both studies, and the results were consistent across all subgroups studied, including age, gender, diabetes history, baseline LDL-C, body mass index, HeFH status.

The primary efficacy endpoint in both studies was the percent change from baseline to week 12 in LDL-C. The primary analysis demonstrated that, in patients on maximally tolerated statin therapy, the reduction from baseline in LDL-C at week 12 for bempedoic acid compared to placebo was -17 % (95% CI: -21%, -14%; p < 0.001) in the first study and -18% (95% CI: -20%, -16%; p < 0.001) in the second study. The LDL-C reduction persisted through week 52 in both studies.

6.4 Safety

In the pivotal clinical studies, the discontinuation rates due to adverse events was higher in the bempedoic acid group, at 11% compared to 8% for placebo. The most common reasons for treatment discontinuation in the bempedoic acid group were muscle spasms (0.5% versus 0.3% for placebo) and diarrhoea (0.4% versus 0.1% for placebo). In different pooled safety analyses, the following adverse events ($\geq 1\%$ difference) were more common in the bempedoic acid group than in the placebo group: arthralgia, muscle cramps, dizziness, back pain, pain in the extremities, high blood pressure, increased blood uric acid, musculoskeletal pain and sinusitis.

An increased incidence of muscle disorders was observed in study participants using the maximally tolerated statin dose. This is most likely driven by the bempedoic acid-induced increased exposure of statins as identified in two dedicated PK studies. Overall, the clinical database is sufficient to characterise the safety profile of bempedoic acid, although long-term data is still limited.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Bempedoic acid as an adenosine triphosphate citrate lyase (ACL) inhibitor (corresponds to a first-in-class mechanism of action) inhibits cholesterol synthesis in the liver. Bempedoic acid was submitted with the indication for LDL-C reduction in patients with primary hypercholesterolaemia (heterozygous familial and non-familial).

In parallel to Nilemdo as a monopreparation with bempedoic acid, the dossier on Nustendi as a fixed dose combination (FDC) of bempedoic acid and ezetimibe has been submitted.

Bempedoic acid was approved by the EMA with the product name Nilemdo on April 1st, 2020 and by the FDA with the product name Nexletol on February 21st, 2020.

Beneficial Effects

The pharmacokinetics of bempedoic acid and its major metabolite were characterised comprehensively. Mild and moderate renal or hepatic impairment had only mild effects on the exposure of bempedoic acid. Drug–drug interactions were generally mild and do not require dose adjustments upon concomitant use of other drugs (except for the interactions with simvastatin and pravastatin).

Bempedoic acid at a dose of 180 mg QD produced an LDL-C reduction at 12 weeks from -17% to -18% as compared to placebo on top of maximum tolerated statin therapy. The LDL-C-lowering effect of bempedoic acid was consistent across the main subgroups, i.e. age, gender, race, ethnicity, region, diabetes history, baseline LDL-C, body mass index, HeFH status and background therapies.

Additional support for the clinical relevance of the primary efficacy results comes from secondary endpoints that reached statistical significance ($p < 0.001$ for all phase 3 studies) and were all tested using a hierarchical approach. A sustained effect of LDL-C reduction has been demonstrated up to 52 weeks in the two placebo-controlled studies.

Uncertainties about the beneficial effects

LDL-C reduction is an established surrogate marker for cardiovascular disease, and bempedoic acid has demonstrated the capability to reduce the LDL-C level. However, its effect on cardiovascular morbidity and mortality has not yet been determined. Long-term efficacy data beyond one year of treatment of bempedoic acid are still limited.

Unfavourable effects

Bempedoic acid is an inhibitor of the hepatic uptake transporters OATP1B1/3. These transporters are relevant for the hepatic uptake of statins and other drugs. Although bempedoic acid inhibits these transporters only to a mild extent, this inhibition is clinically relevant in case of certain statins (simvastatin and pravastatin), and warrants dose adjustments and a contraindication for high simvastatin doses.

In different pooled safety analyses, the following adverse events ($\geq 1\%$ difference) were more common in the bempedoic acid group than in the placebo group: arthralgia, muscle cramps, dizziness, back pain, pain in the extremities, high blood pressure, increased blood uric acid, musculoskeletal pain and sinusitis.

The evaluated safety signals and adverse events are summarised in the updated product information under the headings "Warnings and precautions" and "Adverse effects".

Uncertainties about the unfavourable effects

There are no data available on the pharmacokinetics, efficiency or safety of bempedoic acid in patients with end-stage renal disease under dialysis or in patients with severe hepatic impairment. In consequence, no dosing recommendations can be given for these patient populations.

Long-term safety data beyond one year of treatment of bempedoic acid are still limited.

Benefit Risk Conclusion

Overall, the benefit-risk ratio for bempedoic acid at a dose of 180 mg QD is positive for the following indication:

"Nilemdipine is indicated as an adjunct to diet and in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies for the treatment of adults with clinical manifestations of atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who need additional LDL-C lowering."

The effect of Nilemdipine on cardiovascular morbidity and mortality has not yet been determined."

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nilemdo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Nilemdo 180 mg film-coated tablets

Composition

Active substances

Bempedoic acid

Excipients

Tablet core:

Lactose monohydrate 30 mg; cellulose, microcrystalline; sodium starch glycolate (type A); hydroxypropyl cellulose; magnesium stearate; silica, colloidal anhydrous.

Film-coating:

Poly(vinyl alcohol), talc, titanium dioxide, macrogol.

1 film-coated tablet contains 0.97 mg of sodium.

Pharmaceutical form and active substance quantity per unit

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

White to off-white, oval, film-coated tablet debossed with "180" on one side and "ESP" on the other side.

Indications/Uses

Nilemdo is indicated as an adjunct to diet and in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies for the treatment of adults with clinical manifestations of atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolaemia who need additional LDL-C lowering.

The effect of Nilemdo on cardiovascular morbidity and mortality has not yet been determined.

Dosage/Administration

Posology

Usual dosage

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

Dose adjustment in the event of concomitant treatments

For dosage recommendations in the event of concomitant treatments, see section “Interactions”.

Concomitant simvastatin therapy

When Nilemdo is coadministered with simvastatin, simvastatin dose should be limited to 20 mg daily (or 40 mg daily for patients who can tolerate simvastatin 80 mg daily longterm without any signs of muscle toxicity) (see sections “Warnings and precautions” and “Interactions”).

Special populations

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 disorder (see sections “Warnings and precautions” and “Pharmacokinetics”).

Patients with renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. There are limited data available in patients with severe renal impairment (defined as estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²), and patients with end-stage renal disease (ESRD) on dialysis have not been studied. Additional monitoring for adverse reactions may be warranted in these patients when Nilemdo is administered (see sections “Warnings and precautions” and “Pharmacokinetics”).

Elderly patients

No dose adjustment is necessary in elderly patients (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Nilemdo in children and adolescents aged less than 18 years have not been established. No data are available.

Mode of administration

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

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.
- Pregnancy and breast-feeding (see section “Pregnancy, lactation”).
- Concomitant use with simvastatin > 40 mg daily (see sections “Dosage/Administration”, “Warnings and precautions”, and “Interactions”)

Warnings and precautions

Tendon rupture

Tendon rupture has occurred. Nilemdo should be discontinued at the first sign of tendon rupture. Nilemdo should be avoided in patients who have a history of tendon disorders or tendon rupture.

Potential risk of myopathy with concomitant use of statins

Bempedoic acid increases plasma concentrations of statins (see section “Indications”). Patients receiving Nilemdo 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 Nilemdo 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 Nilemdo and a statin, a lower dose of the same statin or an alternative statin, or discontinuation of Nilemdo 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), Nilemdo 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 Nilemdo (see sections “Dosage/Administration” and “Contraindications”).

Concomitant administration of Nilemdo with pravastatin doses more than 40 mg daily should be avoided (see section “Interactions”).

Increased serum uric acid

Elevations in serum uric acid have occurred. Bempedoic acid may raise 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 “Undesirable effects”). Uric acid levels should be assessed periodically as clinically indicated. Patients should be monitored for signs and symptoms of hyperuricemia and treated with urate-lowering drugs as appropriate. Treatment with Nilemdo should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.

Elevated liver enzymes

In clinical trials, elevations of $> 3\times$ 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 $\geq 2\times$ 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 Nilemdo should be discontinued if an increase in transaminases of $> 3\times$ ULN persists (see section “Undesirable effects”).

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section “Pharmacokinetics”). Periodic liver function tests should be considered for patients with severe hepatic impairment.

Renal impairment

There is limited experience with Nilemdo in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m²), and patients with ESRD requiring dialysis have not been studied (see section “Pharmacokinetics”). Additional monitoring for adverse reactions may be warranted in these patients when Nilemdo is administered.

Excipients

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

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

Interactions

Effect of Nilemdo 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.

Simvastatin: 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. When Nilemdo is coadministered with simvastatin, limit simvastatin dosage to 20 mg daily (or 40 mg daily for patients who can tolerate simvastatin 80 mg daily longterm without any signs of muscle toxicity) (see section “Warnings and precautions”). Refer to the simvastatin product information for healthcare professionals for simvastatin dosing recommendations.

Pravastatin: Administration of pravastatin 80 mg with steady-state bempedoic acid 180 mg in healthy subjects resulted in 46% (1.5-fold) and 36%(1.4-fold) increases in pravastatin area under the curve (AUC) and maximum plasma concentration (C_{max}), respectively. Administration of pravastatin 40 mg with steady-state bempedoic acid 240 mg in healthy subjects resulted in 99% (2-fold) and 104% (2-fold) increases in pravastatin acid AUC and C_{max} , respectively. In the event of concomitant administration of Nilemdo and pravastatin, pravastatin doses more than 40 mg daily should be avoided.

Atorvastatin and rosuvastatin: Elevations of 1.4-fold to 1.5-fold in AUC of atorvastatin and rosuvastatin (administered as single doses) and/or their major metabolites were observed when coadministered with bempedoic acid 180 mg. Higher elevations have been observed when these statins were coadministered with a supratherapeutic 240 mg dose of bempedoic acid.

Transporter-mediated drug interactions

Bempedoic acid and its glucuronide weakly inhibit OATP1B1 and OATP1B3 at clinically relevant concentrations. Coadministration of bempedoic acid with medicinal products that are substrates of OATP1B1 or OATP1B3 (i.e., bosentan, fimasartan, asunaprevir, glecaprevir, grazoprevir, voxilaprevir, and statins such as atorvastatin, pravastatin, fluvastatin, pitavastatin, rosuvastatin, and simvastatin) may result in increased plasma concentrations of these medicinal products.

Bempedoic acid inhibits OAT2 *in vitro*, which may be the mechanism responsible for minor elevations in serum creatinine and uric acid (see section “Undesirable effects”). 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

Increases in AUC and C_{max} for ezetimibe were less than 20% when a single dose of ezetimibe was taken with steady-state 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. 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. These elevations are not clinically meaningful and do not impact dosing recommendations.

Warfarin

In vitro studies indicate that bempedoic acid is not an inhibitor or inducer of CYP2C9. Because warfarin is primarily eliminated through CYP2C9, its pharmacokinetics is not expected to be altered by bempedoic acid; however, it is recommended to appropriately monitor international normalized ratio (INR) if bempedoic acid is coadministered with warfarin, another coumarin anticoagulant or fluindione.

Other interactions

Bempedoic acid had no effect on the pharmacokinetics or pharmacodynamics of metformin or the pharmacokinetics of oral contraceptive norethindrone/ethynodiol (an active substance combination not authorised in Switzerland). The effect of bempedoic acid on other contraceptives has not been studied.

Effect of other medicinal products on Nilemdo

Bile acid sequestrants (such as cholestyramine)

The effects of bile acid sequestrants such as cholestyramine on bempedoic acid exposure has not been studied. It is anticipated that bile acid sequestrants may reduce bempedoic acid bioavailability. Concomitant administration with bempedoic acid is therefore not recommended.

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 characterized 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- and a 1.2-fold increase in bempedoic acid AUC and C_{max}, respectively. AUC and C_{max} for bempedoic acid active metabolite (ESP15228) were increased 1.9- and 1.5-fold, respectively. These elevations are not clinically meaningful and do not impact dosing recommendations.

Cytochrome P450 Substrates

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 interact with cytochrome P450 enzymes.

Pregnancy, lactation

Pregnancy

Nilemdo is contraindicated during pregnancy (see section “Contraindications”).

There are no or limited amount of data from the use of Nilemdo in pregnant women. Studies in animals with bempedoic acid monotherapy have shown reproductive toxicity (see section “Preclinical data”).

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

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment.

Lactation

It is unknown whether bempedoic acid/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Because of the potential for serious adverse reactions, women taking Nilemdo should not breast-feed their infants. Nilemdo is contraindicated during breast-feeding.

Fertility

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

Effects on ability to drive and use machines

Nilemdo has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The safety profile of Nilemdo has been studied in 4 controlled phase 3 clinical studies (N=3621) including patients with hypercholesterolemia on maximum tolerated statin dose (2 studies; n=3008) and patients whose maximally tolerated statin dose was the lowest approved dose or less (2 studies; n=613). The most commonly reported adverse reactions with Nilemdo during pivotal trials were hyperuricaemia (3.8%), pain in extremity (3.1%), and anaemia (2.5%). More patients on Nilemdo compared to placebo discontinued treatment due to muscle spasms (0.7% versus 0.3%), diarrhoea (0.5% versus <0.1%), pain in extremity (0.4% versus 0), and nausea (0.3% versus 0.2%), although differences between bempedoic acid and placebo were not significant.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled placebo-controlled clinical studies (N=3621) are displayed by system organ class and frequency below.

Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$).

Infections and infestations

Common: upper respiratory tract infection, bronchitis

Blood and lymphatic system disorders

Common: anaemia

Uncommon: haemoglobin decreased

Rare thrombocytosis, leukopenia

Metabolism and nutrition disorders

Common: gout, hyperuricaemia^a

Cardiac disorders

Common: atrial fibrillation

Gastrointestinal disorders

Common: abdominal pain or discomfort^b

Hepatobiliary disorders

Common: aspartate aminotransferase increased

Uncommon: alanine aminotransferase increased, liver function test increased

Musculoskeletal and connective tissue disorders

Common: pain in extremity, back pain, muscle spasms, blood CPK increased

Uncommon tendon rupture

Renal and urinary disorders

Uncommon: blood creatinine increased, blood urea increased, glomerular filtration rate decreased

Reproductive system and breast disorders

Uncommon: benign prostatic hyperplasia

- a. Hyperuricaemia includes hyperuricaemia and blood uric acid increased
- b. Abdominal pain or discomfort includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

Description of selected undesirable effects

Tendon rupture

Nilemdo is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.2% of patients treated with Nilemdo versus 0% of placebo-treated patients and involved the rotator cuff (the shoulder), biceps tendon, or Achilles tendon. Tendon rupture occurred within weeks to months of starting Nilemdo. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders.

Nilemdo should be discontinued immediately if the patient experiences rupture of a tendon.

Discontinuing Nilemdo should be considered if the patient experiences joint pain, swelling, or inflammation. Patients should be advised to rest at the first sign of tendinitis or tendon rupture and to contact their healthcare provider if tendinitis or tendon rupture symptoms occur. Alternative therapy should be considered in patients with a history of tendon disorders or tendon rupture.

Benign prostatic hyperplasia

Nilemdo was associated with an increased risk of benign prostatic hyperplasia (BPH) or prostatomegaly in men with no reported history of BPH, occurring in 1.1% of Nilemdo-treated patients versus 0.1% of placebo-treated patients. The clinical significance is unknown.

Atrial fibrillation

Nilemdo was associated with an imbalance in atrial fibrillation, occurring in 1.4% of Nilemdo-treated patients versus 0.9% of placebo-treated patients.

Hepatic enzyme elevations

Increases in serum transaminases (AST and/or ALT) have been reported with Nilemdo. In controlled clinical studies, the incidence of elevations ($\geq 3\times$ ULN) in hepatic transaminase levels was 0.7% for patients treated with Nilemdo and 0.3% for placebo. These elevations in transaminases were generally asymptomatic, not associated with elevations $\geq 2\times$ ULN in bilirubin or cholestasis, and returned to baseline with continued treatment or after discontinuation of therapy.

Increased serum uric acid

Increases in serum uric acid were observed in clinical trials with Nilemdo likely due to inhibition of renal tubular OAT2 (see section “Interactions”). In the pooled placebo-controlled trials, a mean increase of 0.8 mg/dL (47.6 micromole/L) in uric acid compared to baseline was observed with Nilemdo at week 12. The elevations in serum uric acid usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation of treatment. Gout was reported in 1.4% of patients treated with Nilemdo and 0.4% of patients treated with placebo (see section “Warnings and precautions”). 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 (BUN)

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

The observed elevations in serum creatinine may be associated with bempedoic acid inhibition of OAT2-dependent renal tubular secretion of creatinine (see section “Interactions”), 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 Nilemdo 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 Nilemdo. In the pooled placebo-controlled trials, a decrease in haemoglobin from baseline of ≥ 2 g/dL and < lower limit of normal (LLN) was observed in 4.6% of patients in the Nilemdo group compared with 1.9% of patients

on placebo. Greater than 5 g/dL and < LLN decreases in haemoglobin were reported at similar rates in Nilemdo 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 Nilemdo group and 0.4% in the placebo group experienced haemoglobin values below LLN while on treatment. Anaemia was reported in 2.5% of patients treated with Nilemdo and 1.6% of patients treated with placebo.

Increase in platelet count

Approximately 9.5% of patients (versus 4.1% placebo) had increases in platelet counts of $100 \times 10^9/L$ or more on one or more occasion. Platelet count increase was asymptomatic, did not result in increased risk for thromboembolic events, and did not require medical intervention.

Decrease in leucocytes

Approximately 8.7% of Nilemdo-treated patients with normal baseline leucocyte count had a decrease to less than the lower limit of normal on one or more occasion (versus 6.2% placebo). Leucocyte decrease was generally asymptomatic and did not require medical intervention. In clinical trials, there was a small imbalance in skin or soft tissue infections, including cellulitis (0.7% versus 0.3%), but there was no imbalance in other infections.

Increase in creatine kinase

Approximately 1.0% of patients (versus 0.5% placebo) had elevations of CK levels of 5 or more times the normal value on one or more occasions, and 0.4% of patients (versus 0.2% placebo) had elevations of CK levels of 10 or more times.

Elderly population

Of the 3621 patients treated in the bemedoic acid placebo-controlled studies, 2098 (58%) were > 65 years old. No overall difference in safety was observed between elderly and the younger population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIVIS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no clinical experience with Nilemdo 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 effects were observed in animal studies at exposures up to 14-fold higher than those in patients treated with Nilemdo at 180 mg once daily.

Treatment

There is no specific treatment for a Nilemdo overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Properties/Effects

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.

Pharmacodynamics

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 high-sensitivity C-reactive protein (hsCRP) in patients with hypercholesterolaemia.

Because patients with diabetes are at elevated risk for atherosclerotic cardiovascular disease, the clinical trials of Nilemdo 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 Nilemdo 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

The efficacy of Nilemdo was investigated in two 52-week, multi-centre, randomised, double-blind, placebo-controlled trials involving 3009 adult patients with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease, with 2010 patients randomised to Nilemdo. All patients received Nilemdo 180 mg or placebo orally once daily. Ninety seven percent (97%) of patients took a lipid-modifying background therapy consisting of a maximum tolerated dose of statins with or without further lipid-modifying therapies and had a high or very high cardiovascular risk.

In both 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 both trials, including age, gender, race, ethnicity, region, history of diabetes, baseline LDL-C, body mass index (BMI), HeFH status, and background therapies.

Combination therapy with statins

Study 1002-047 was a multi-centre, randomised, double-blind, placebo-controlled, 52-week trial in patients with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolaemia (HeFH). Efficacy of Nilemdo was evaluated at week 12. The trial included 779 patients randomised 2:1 to receive either Nilemdo (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% women, 94% White, 5% were Black, and 1% Asian. The mean baseline LDL-C was 120.4 mg/dL (3.1 mmol/L) and the median baseline hsCRP was 1.7 mg/L. At the time of randomisation, 91% of patients were receiving statin therapy and 53% were receiving high-intensity statin therapy. The

difference between Nilemدو and placebo in mean percent change in LDL-C from baseline to Week 12 was -17% (95% CI: -21%, -14%; p < 0.001).

Study 1002-040 was a multi-centre, randomised, double-blind, placebo-controlled 52-week trial evaluating safety and efficacy of bempedoic acid in patients with ASCVD and/or HeFH. Efficacy of Nilemدو was evaluated at week 12. The trial included 2230 patients randomised 2:1 to receive either Nilemدو (n=1488) 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% women, 96% White, 3% were Black, and 1% Asian. The mean baseline LDL-C was 103.2 mg/dL (2.7 mmol/L) and the median baseline hsCRP was 1.5 mg/L. At the time of randomisation, all patients were receiving statin therapy and 50% were receiving high-intensity statin therapy. The difference between Nilemدو and placebo in mean percent change in LDL-C from baseline to Week 12 was -18% (95% CI: -20%, -16%; p < 0.001). A significantly higher proportion of patients achieved an LDL-C of < 70 mg/dL (< 1.81 mmol/L) in the Nilemدو group as compared with placebo at week 12 (32% versus 9%, P < 0.001),

Safety and efficacy in paediatric patients

Swissmedic has deferred the obligation to submit the results of studies with Nilemدو in paediatric population from 4 to less than 18 years of age in the treatment of elevated cholesterol. See section “Dosage/administration” for information on paediatric use.

Pharmacokinetics

Absorption

Pharmacokinetic data indicate that bempedoic acid is absorbed with a median time to maximum plasma concentrations (C_{max}) of 3.5 hours when administered orally as Nilemدو 180 mg tablets. Bempedoic acid pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Bempedoic acid is a prodrug that is activated intracellularly by ACSVL1 to ETC-1002-CoA. The bempedoic acid 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 dosage, 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 Nilemdo 180 mg tablets.

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.

Metabolism

The primary route of elimination for bempedoic acid is through metabolism to the acyl glucuronide. Bempedoic acid is also reversibly converted to an active metabolite (ESP15228) based on aldo-keto reductase activity. 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_{0-48h} and its glucuronide being the next most prevalent (30%). ESP15228 and its glucuronide represented 10% and 11% of the plasma AUC_{0-48h}, respectively.

The steady-state C_{max} and AUC of the equipotent active metabolite (ESP15228) of bempedoic acid in patients with 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 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.

Kinetics in specific patient groups

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.

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

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 "Warnings and Precautions").

There is limited information in patients with severe renal impairment; in a single dose study, the bempedoic acid AUC was increased by 2.4-fold in patients (n=5) with severe renal impairment (eGFR < 30 mL/min/1.73 m²) compared to those with normal renal function. Clinical studies of Nilemido did not include patients with ESRD on dialysis (see section "Warnings and Precautions").

Age, weight, gender and race

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.

Preclinical data

Repeat dose toxicity

Deaths occurred in repeat-dose studies within the first 2 weeks of treatment in rats at exposures ≥ 9 times and in monkeys at exposures ≥ 15 times the systemic exposure in humans at 180 mg. Severely reduced blood glucose occurred within hours of dosing and preceded toxic effects at high doses leading to moribundity when untreated. Increased liver weight and hepatocellular hypertrophy were observed in rats 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, nonadverse changes in laboratory parameters indicative of these hepatic effects, and decreases in red blood cell, urea nitrogen, creatinine and coagulation parameters were observed in animals at doses lower than those associated with mortality. 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.

Mutagenicity

The standard battery of genotoxicity studies has not identified any mutagenic or clastogenic potential of bempedoic acid.

Carcinogenicity

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.

Reproductive toxicity

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).

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C. Keep out of the reach of children.

Authorisation number

67583 (Swissmedic)

Packs

Packs with 28 and 98 film-coated tablets. [B]

Marketing authorisation holder

Daiichi Sankyo (Schweiz) AG, Zurich

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