Taiwan Food and Drug Administration

Assessment Report

Trade Name：寧脂德膜衣錠 180 毫克 /
Nilemdo F.C. Tablets 180 mg

Active Ingredient：Bempedoic acid

License Number： MOHW-PI 028817

Applicant：台灣第一三共股份有限公司

Approval Date：113/11/05

Indication：

適用於患有異合子家族性或非家族性之原發性高膽固醇血症、或混合型血脂異常的成人病人，作為飲食的輔助治療以降低低密度脂蛋白膽固醇(LDL-C)：

- **與 statin 類藥品併用、或併用於 statin 合併其他降血脂療法，治療已接受最大耐受劑量 statin 仍無法達到低密度脂蛋白膽固醇目標值的病人，或，**
- **單獨或與其他降血脂療法併用，治療無法耐受 statin 或禁用 statin 的病人。**

Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet：

(1) 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,

(2) alone or in combination with other lipid lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.

Background Information

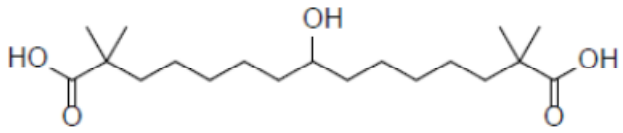
Trade Name	寧脂德膜衣錠 180 毫克 / Nilemdo F.C. Tablets 180 mg
Active Ingredient(s)	Bempedoic acid
Applicant	台灣第一三共股份有限公司
Dosage Form & Strengths	膜衣錠 180mg/tablet
Indication	適用於患有異合子家族性或非家族性之原發性高膽固醇血症、或混合型血脂異常的成人病人，作為飲食的輔助治療以降低低密度脂蛋白膽固醇(LDL-C)： ● 與 statin 類藥品併用、或併用於 statin 合併其他降血脂療法，治療已接受最大耐受劑量 statin 仍無法達到低密度脂蛋白膽固醇目標值的病人，或， ● 單獨或與其他降血脂療法併用，治療無法耐受 statin 或禁用 statin 的病人。 Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet： (1) 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, (2) alone or in combination with other lipid lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.
Posology	詳如仿單
Pharmacological Category **ATC Code**	C10AX15

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, bempedoic acid, is chemically designated as 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid and has the following structure:



It is a white to off-white crystalline powder. The molecular formula and the molecular weight are $C_{19}H_{36}O_5$ and 344.49 Daltons, respectively.

Adequate information of characterization of the drug substance has been provided. The structure of bempedoic acid is confirmed by ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, infrared spectroscopy, mass spectrometry, elemental analysis, UV spectroscopy and single crystal X-ray diffraction. The specification for the drug substance includes tests for appearance, identification, assay, impurities, residual solvents, elemental impurities, residue on ignition, water content, particle size distribution, microbial examination and Escherichia coli. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

Bempedoic acid has been developed for commercialization as white to off-white, oval, film-coated tablets, 180 mg, for oral administration. The primary packaging is polyvinyl chloride (PVC)/ aluminum blisters.

The specification for the drug product includes description, dimensions, identification, assay, related substances, dissolution, uniformity of dosage units, water content and microbial limits. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated. Stability studies of drug product under long term condition (30°C/75% RH and 25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 48 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of drug product can be granted for 48 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Bempedoic acid is a prodrug that requires activation in the liver to ETC-1002-Coenzyme A (ETC-1002-CoA), which mediates competitive inhibition of ACL and thus inhibits cholesterol

synthesis. Inhibition of cholesterol synthesis results in upregulation of hepatic LDLR protein expression and increased LDLR clearance of LDL-C from plasma. Pharmacology data demonstrated that bempedoic acid has been shown to attenuate diet-induced progression of atherosclerosis in several normal and low lipid metabolism, triglyceride overproduction, hypercholesterolemia, and atherosclerosis rodent models. Secondary pharmacodynamic studies demonstrated that bempedoic acid improved glycemic control, reduced serum and hepatic lipids, and prevented development of atherosclerosis in cholesterol-fed LDLR-knockout mice.

In addition, bempedoic acid improved hypertriglyceridemia, hepatic steatosis, and glycemic control in insulin-resistant mice, DIO mice, and fructose-fed hamsters. Bempedoic acid also exhibited anti-inflammatory effects in vitro and in vivo. Bempedoic acid did not demonstrate any significant off-target binding in vitro to isolated receptors, ion channels, enzymes, or transporters. Safety pharmacology studies demonstrated that bempedoic acid was not associated with adverse effects on CNS, pulmonary, or cardiovascular function.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies included a 26-week study in rats and a 52-week study in monkeys. Targets and target organs of toxicity were RBC mass (reduced RBC mass, including decreases in Hgb, Hct, mean corpuscular volume, and mean cell Hgb), the liver (minimal hepatocyte necrosis, bile duct hyperplasia, minimal subcapsular necrosis and minimal to severe centrilobular vacuolation) and the kidney (nonadverse minimal to mild brown tubular pigment) in rats. Bempedoic acid was well tolerated in monkeys. Safety margins are 0.2~1.4 fold of rats and 12~14 fold based on the AUC at the human dose of 180 mg daily. Bempedoic acid was considered to be non-genotoxic.

In carcinogenicity studies, increases in the incidence of hepatocellular adenomas and carcinomas in male mice at ≥75 mg/kg/day and increases in the incidence of hepatocellular adenoma and thyroid follicular cell adenomas in male rats at 30 mg/kg/day occur by mechanisms that are not relevant in humans. Reproductive and developmental studies indicate that bempedoic acid did not affect fertility in rats, caused effects on embryo-fetal development (skeletal malformations and variations) occurred in rats but not in rabbits, and effects on pre/postnatal development in rats. No additive or synergistic effects on target organs of either bempedoic acid or atorvastatin or toxicokinetic interactions were observed when both test articles were administered to monkeys at clinically tolerated dose levels

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

After administration of multiple doses of Nilemdo 180 mg tablets, T_{max} was reached 3.5 hours

after dosing. The steady-state C_{max} and AUC were 24.8 (6.9) µg/mL and 348 (120) µg·h/mL respectively. Bempedoic acid steady-state pharmacokinetics were generally linear over a range of 120 mg to 220 mg and the steady state was achieved after 7 days. The mean accumulation ratio of bempedoic acid was approximately 2.3-fold. Food administration had no effect on the oral bioavailability of bempedoic acid following administering Nilemdo 180 mg tablets, and thus bempedoic acid can be taken with or without food.

The apparent volume of distribution of bempedoic acid is 18 L. Plasma protein binding of bempedoic acid and its equivalent potency active metabolite, ESP15228, were 99.3% and 99.2%, respectively. In humans mass balance study, bempedoic acid accounted for 46% of the total AUC and its glucuronide (inactive), formed by UGT2B7-mediated glucuronidation, is the main metabolite (30% of the total AUC). The active metabolite, ESP15228, formed reversibly by aldo-keto reductase, and its glucuronide represented 10% and 11% of the plasma AUC, respectively.

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 feces. Less than 5% of the administered dose was excreted as unchanged bempedoic acid in feces and urine combined. 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.

2.3.2 Interaction Studies

In Vitro, UGT2B7 was identified as the only UGT enzyme responsible for glucuronidation of bempedoic acid and ESP15228. Bempedoic acid is a weak inhibitor of OAT3, OAT2, OATP1B1, and OATP1B3.

In clinical, a dedicated DDI study to evaluate potential effects of steady-state bempedoic acid on the PK of single doses of atorvastatin 80 mg, simvastatin 40 mg, pravastatin 80 mg, or rosuvastatin 40 mg was conducted. Co-administration of simvastatin 40 mg with steady-state bempedoic acid resulted in a 20% (1.2-fold) increase in simvastatin AUC and a 96% (2-fold) increase in simvastatin acid AUC. A weak interaction (1.25 to <2-fold increase in AUC) for atorvastatin, pravastatin, and rosuvastatin (administered as single doses) were observed.

Weak drug-drug interaction was also observed in the following DDI clinical trials, incluing single administration of Ortho-Novum 1/35 with bempedoic acid at steady state, single

administration of ezetimibe with steady-state bempedoic acid, co-administration of metformin with bempedoic acid, and single administration of bempedoic acid with steady-state probenecid. Therefore, no dose adjustment is recommended.

2.3.3 Special Populations

Based on population PK analysis, the pharmacokinetics of bempedoic acid were not affected by age, gender, or race except body weight. A 30% increase in steady-state AUC was predicted in the lowest quartile of body weight (< 73 kg) from the population PK analysis and this magnitude of effect was not expected to be clinically meaningful.

In renal impairment study, the mean AUC increase was approximately 48%, 131% and 137% greater in subjects with mild, moderate, or severe renal impairment, respectively, than in subjects with normal renal function. No dose adjustment is needed in patients with mild or moderate renal impairment.

In hepatic impairment study, bempedoic acid AUC decreased 22% in the subjects with mild hepatic impairment and 16% in the subjects with moderate hepatic impairment relative to the subjects with normal hepatic function. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Four Phase 3 double-blind, placebo-controlled, randomized (2:1 ratio of bempedoic acid: placebo), parallel-group studies (1002-040, 1002-046, 1002-047, and 1002-048) were reviewed to evaluate the efficacy of bempedoic acid 180 mg QD as a treatment for hyperlipidemia. In each study, mean percent change in LDL-C at Week 12 was the primary efficacy endpoint. The studies also each had the same key secondary endpoints (non-HDL-C, TC, apo B, and hsCRP).

Studies 1002-047 and 1002-040 enrolled patients at high and very high risk for cardiovascular (CV) events (heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular disease [ASCVD]) with hyperlipidemia receiving a maximally tolerated statin therapy as part of their lipid-modifying therapy (LMT). Treatment with bempedoic acid resulted in greater reductions from baseline for LS means in LDL-C compared with placebo: -16.5% vs 1.6%, respectively, in Study 1002-040 and -15.07% vs 2.35%, respectively, in Study 1002-047. The difference from placebo for LS means was statistically significant ($p < 0.001$) in Study 1002-040 (-18.1%; 95% CI: -20.0%, -16.1%) and in Study 1002-047 (-17.4%; 95% CI: -21.0%, -13.9%).

Studies 1002-046 and 1002-048 enrolled patients with statin intolerance whose maximally tolerated statin was no more than the lowest approved starting dose (Study 1002-048) or less than the lowest approved starting dose (Study 1002-046). Treatment with bempedoic acid resulted in greater reductions from baseline for LS means in LDL-C compared with placebo: -22.6% vs -1.2%, respectively in Study 1002-046 and -23.5% vs 5.0%, respectively in Study 1002-048. The difference from placebo for LS means was statistically significant ($p < 0.001$) in Study 1002-046 (-21.4%; 95% CI: -25.1%, -17.7%) and in Study 1002-048 (-28.5%; 95% CI: -34.4%, -22.5%).

The lipid-lowering treatment benefit of bempedoic acid was also observed across all key secondary efficacy endpoints in all 4 studies.

2.4.2 Safety Results

Main TEAEs included muscle spasm, hyperuricemia, back pain, abdominal discomfort/pain, pain of extremities, anemia and elevated liver enzymes.

In phase III clinical trials, subjects with AST or ALT > 2 X ULN would be excluded from studies and subjects with AST or ALT > 3 X ULN during clinical trials would be withdrawn form study drugs; hence the safety profile of hepatotoxicity could not be extrapolated to real world. Such limitation should be described in label.

Bempedoic acid was associated with an increased risk of tendon rupture; tendon rupture occurred in 0.5% of patients treated with bempedoic acid versus 0% of placebo treated patients

2.5 Bridging Study Evaluation

PK characteristic is comparable between East Asian and Western healthy subjects following single dose and multiple dose administration of 180 mg bempedoic acid. From PK's perspective, there was no significant ethnic concern.

The sponsor provided the results of Study 1002-079, a phase 2 randomized control trial done in South Korea, as bridging data; eligible subjects were randomized to bempedoic acid 180 QD (n=64) or placebo (n=32). The limited East Asian data disclosed efficacy and safety was consistent with that of global trials.

2.6 Conclusion

The efficacy was demonstrated and safety profile was acceptable. Approval of NILEMDO is recommended.

3. Post-Marketing Requirements

(1) Due to limited East Asian data (64 Korean subjects in Study 1002-079), the results of two Japanese trials, NCT04784442 and NCT05683340, should be submitted after approval of this NDA.

(2) Due to limited data of combination therapy of bempedoic acid, statin and other lipid lowering agents, post-marketing experience of above combination of long-term use should be provided.