



Summary of risk management plan for NILEMDO (Bempedoic acid)

**Daiichi Sankyo (Schweiz) AG
Vulkanstrasse 106
8048 Zürich**

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of NILEMDO is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of NILEMDO in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Daiichi Sankyo (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of NILEMDO.

Nilemdo (bempedoic acid 180mg) tablet for oral use

Summary of risk management plan for Nilemdo (Bempedoic acid)

This is a summary of the risk management plan (RMP) for Nilemdo. The RMP details important risks of Nilemdo, how these risks can be minimized, and how more information will be obtained about Nilemdo's risks and uncertainties (missing information).

Nilemdo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nilemdo should be used.

This summary of the RMP for Nilemdo should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Nilemdo's RMP.

I. The Medicine and What It Is Used For

Nilemdo is authorized for treatment of primary hypercholesterolemia in adults, as an adjunct to diet (see SmPC for the full indication). It contains bempedoic acid as the active substance and it is given by mouth.

Further information about the evaluation of Nilemdo's benefits can be found in Nilemdo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <https://www.ema.europa.eu/en/medicines/human/EPAR/nilemdo>.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Nilemdo, together with measures to minimize such risks and the proposed studies for learning more about Nilemdo's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size—the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status—the way a medicine is supplied to the patient (e.g, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PBREER assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Nilemdo is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Nilemdo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a

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link with the use of Nilemdo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Identified and Potential Risks and Missing Information	
Important identified risk	Not applicable
Important potential risks	Myopathy with concomitant use of statins Gout
Missing information	Use in patients with patients with severe renal impairment and patients with end-stage renal disease receiving dialysis

II.B Summary of Important Risks

Important Potential Risk: Myopathy with Concomitant Use of Statins	
Evidence for linking the risk to the medicine	<p>Serious muscle toxicity risk has been associated with coadministration of statins with drugs that raise statin plasma concentrations, especially when either multiple pathways of statin elimination are affected, eg, inhibition of CYP3A or CYP2C8 (eg, atorvastatin, cerivastatin) and/or transporters (eg, simvastatin acid and atorvastatin) are impacted.</p> <p>Bempedoic acid interacts weakly with simvastatin lactone (parent compound), rosuvastatin, atorvastatin, and pravastatin, with 1.2- to 1.5-fold increases in statin AUC when co-administered with steady-state bempedoic acid at a dose of 180 mg QD (Module 2.7.2, Section 4.5). Simvastatin hydroxyl acid (metabolite) was increased approximately 2-fold. PK alterations that increase simvastatin systemic exposure are one of the significant identified risk factors.</p> <p>The magnitude of bempedoic acid effects on each statin studied are small relative to the theoretical maximum fold increase for each statin through its major mechanisms of elimination and with exposures from disposition factors associated with statin risk of myopathy. Therefore, the risk of statin-induced myopathy as a result of a PK interaction from bempedoic acid, with the exception of simvastatin at doses ≥ 40 mg, is considered to be low. The lack of significant effects on rates of myalgia, muscle weakness, and CK elevation in the bempedoic acid development program is consistent with the lack of a clinically significant PK interaction between bempedoic acid and statins.</p> <p>Simvastatin ≥ 40 mg in combination with bempedoic acid was not fully studied in the long-term Phase 3 studies. Therefore, an impact on increase in the risk of myopathy with the combination with simvastatin in that dose range cannot be ruled out. Based on the potential exposure differences, simvastatin dose-proportional PK, and the safety issues present with the simvastatin 80 mg daily dose, coadministration of bempedoic acid with simvastatin doses >40 mg/day is contraindicated in the SmPC; the maximum recommended dose regimen for simvastatin is 20 mg daily (or 40 mg daily for patients with severe hypercholesterolemia and high risk for CV complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks) when administered with bempedoic acid.</p>
Risk factors and risk groups	<p>Patients with hypercholesterolemia and taking statins for reduction of LDL-C would be at risk. Risk factors also include concomitant therapies that are independently associated with myopathy or those that increase statin exposure, such as female sex, diabetes, and age > 80 years.</p> <p>An observational survey of patients taking high-dose statin therapy found that the strongest predictors for muscular symptoms were personal history of muscle pain during lipid-lowering therapy (OR 10.12, 95% CI 8.23, 12.45; $p < 0.0001$), unexplained cramps (OR 4.14; 95% CI 3.46, 4.95; $p < 0.0001$), and history of CK elevation (OR 2.04, 95% CI 1.55, 2.68; $p < 0.0001$).</p>

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Risk minimization measures	<p><u>Routine risk minimization measures:</u> SmPC Section 4.2 (simvastatin only), 4.3 (simvastatin only), Section 4.4, Section 4.5 PIL Section 2</p> <p><u>Additional risk minimization measures:</u> None</p>
Additional pharmacovigilance activities	<p>Open-label extension to assess long-term safety and efficacy of bempedoic acid 180 mg</p> <p>See Section II.C of this summary for an overview of the postauthorization development plan.</p>
Important Potential Risk: Gout	
Evidence for linking the risk to the medicine	<p>Mean increases in serum uric acid were observed in bempedoic acid clinical studies. Uric acid increased is considered an adverse reaction of bempedoic acid that appears to be causally associated with shift in levels due to OAT2 inhibition. It is unclear whether the increased uric acid puts patients at increased risk for gout; however, its association with potential risk of gout or worsening of gout cannot be ruled out. Thus, gout is considered an important potential risk of bempedoic acid.</p>
Risk factors and risk groups	<p>Patients with elevated uric acid and/or history of gout.</p>
Risk minimization measures	<p><u>Routine risk minimization measures</u> SmPC Sections 4.4 and 4.8 PIL Section 2 and 4</p> <p><u>Additional risk minimization measures</u> None</p>
Additional pharmacovigilance activities	<p>Open-label extension to assess long-term safety and efficacy of bempedoic acid 180 mg</p> <p>Study to evaluate the efficacy and safety of bempedoic acid 180 mg + ezetimibe 10 mg fixed dose combination (FDC) in subjects with T2DM and elevated LDL-C</p> <p>See Section II.C of this summary for an overview of the post-authorization development plan.</p>
Missing Information: Use in Patients with Severe Renal Impairment and in Patients With End-Stage Renal Disease Receiving Dialysis	
Risk minimization measures	<p><u>Routine risk minimization measures</u> SmPC Sections 4.4 and 5.2 PIL Section 2</p> <p><u>Additional risk minimization measures</u> None</p>
Additional pharmacovigilance activities	<p>Phase 1, open-label, single-dose, parallel-group study to evaluate the effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid.</p> <p>See Section II.C of this summary for an overview of the post-authorization development plan.</p>

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II.C. Post-authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation for Nilemdo.

II.C.2 Other Studies in Post-authorization Development Plan

Short Title	Open-label extension to assess long-term safety and efficacy of bempedoic acid 180 mg
Purpose of the Study	Primary objective: <ul style="list-style-type: none">To characterize the safety and tolerability of long-term administration of bempedoic acid 180 mg Secondary objective: <ul style="list-style-type: none">To characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in LDL-C, high HDL-C, non-HDL-C, apo B, TC, TGs, and hsCRP in patients with hyperlipidemia Safety concerns addressed: myopathy with concomitant use of statins, gout
Short Title	Study to evaluate the efficacy and safety of bempedoic acid 180 mg + ezetimibe 10 mg FDC in subjects with T2DM and elevated LDL-C
Purpose of the Study	Primary objectives: <ul style="list-style-type: none">To assess the efficacy of FDC versus placebo on LDL-C lowering in subjects with T2DM treated for 12 weeksTo assess the efficacy of FDC versus ezetimibe on LDL-C lowering in subjects with T2DM treated for 12 weeks Secondary objectives: <ul style="list-style-type: none">To assess the efficacy of ezetimibe versus placebo on LDL-C lowering in subjects with T2DM treated for 12 weeksTo assess the efficacy of FDC versus placebo, FDC versus ezetimibe, and ezetimibe versus placebo on hsCRP, non-HDL-C, TC, apo B, TGs, and HDL-C in subjects with T2DM treated for 12 weeksTo assess the effect of FDC, ezetimibe, and placebo on percent of subjects achieving LDL-C level <70 mg/dLTo assess the effect of the FDC, ezetimibe, and placebo on percent of subjects achieving LDL-C reduction $\geq 50\%$To characterize the safety and tolerability of FDC, ezetimibe, and placebo in subjects with T2DM treated for 12 weeks Exploratory objective: <ul style="list-style-type: none">To assess the effect of FDC versus placebo and ezetimibe on HbA_{1c}, fasting glucose, fasting fructosamine, fasting insulin, C-peptide, homeostatic model assessment of insulin sensitivity (HOMA-IR) and beta cell function (HOMA-%B) indices, and 2-hour postprandial glucose in subjects with T2DM treated for 12 weeks. Safety concerns addressed: Gout

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Short Title

Effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid

Purpose of the Study

Primary objectives:

- To characterize the PK of ETC-1002, ESP15228, and ETC-1002-glucuronide in subjects with normal renal function, ESRD, and ESRD requiring dialysis following single-dose bempedoic acid administration

Secondary objectives:

- To evaluate the safety and tolerability of a single dose of bempedoic acid 180 mg in subjects with normal renal function, ESRD, and ESRD requiring dialysis.

Safety concern addressed: use in patients with severe renal impairment and in patients with ESRD receiving dialysis (note: only part of the safety concern, patients with severe ESRD and ESRD requiring dialysis, is addressed by this study)