Summary of risk management plan for Nustendi (Bempedoic acid/Ezetimibe)

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

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

This summary of the RMP for Nustendi 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 Nustendi's RMP.

I. The Medicine and What It Is Used For

Nustendi 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 Nustendi's benefits can be found in Nustendi'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/nustendi

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

Important risks of Nustendi, together with measures to minimize such risks and the proposed studies for learning more about Nustendi'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 (eg, 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 PBRER 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 Nustendi is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Nustendi 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 link with the use of Nustendi. 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 Drug interactions with substrates of OAT2
Missing information	Use in 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	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. 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 coadministered 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 (Moßhammer et al, 2014). 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. 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.
Risk factors and risk groups	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. 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) (Bruckert et al, 2005).
Risk minimization measures	<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 <u>Additional risk minimization measures</u>: None
Additional pharmacovigilance activities	Open-label extension to assess long-term safety and efficacy of bempedoic acid 180 mg See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Gout	
Evidence for linking the risk to the medicine	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.
Risk factors and risk groups	Patients with elevated uric acid and/or history of gout.
Risk minimization measures	Routine risk minimization measures SmPC Sections 4.4 and 4.8 PIL Section 4 Additional risk minimization measures None
Additional pharmacovigilance activities	Open-label extension to assess long-term safety and efficacy of bempedoic acid 180 mg 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 See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Drug Interactions With Substrates of OAT2	
Evidence for linking the risk to the medicine	In general, the evidence for a substantial clinical drug-drug interaction based on OAT2 inhibition is weak. No adverse effects due to OAT2 drug-drug interactions have been reported in the literature, with the possible exception of an interaction between theophylline and erythromycin, for which an OAT2 inhibitory mechanism is hypothesized but not demonstrated (Prince, et al, 1981). In in vitro studies of transporter-mediated uptake (RR 1002-500-071 and RR 1002-500-075), bempedoic acid inhibited OAT2 transport of uric acid and creatinine at clinically relevant concentrations and inhibited cyclic guanosine monophosphate (cGMP) at concentrations well above clinical relevance; thus, OAT inhibition by bempedoic acid is substrate dependent.
Risk factors and risk groups	Patients requiring long-term use of narrow therapeutic index drugs that might be impacted by OAT2 inhibition.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.5 Additional risk minimization measures: None
Additional pharmacovigilance activities	In vitro study to assess bempedoic acid inhibition of select human OAT2 substrates in MDCK-II cells expressing rat and monkey OAT2 ortholog (Oat2). In vitro study to assess bempedoic acid inhibition of select human OAT2 substrates in MDCK-II cells. In vitro study to assess bempedoic acid inhibition of select human OAT2 substrates in sandwich human hepatocyte culture. See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Use in Patients With Severe Renal Impairment and Patients With End-Stage Renal Disease Receiving Dialysis	
Risk minimization measures	Routine risk minimization measures SmPC Sections 4.2 and 5.2 PL Section 2 Additional risk minimization measures None
Additional pharmacovigilance activities	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. See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization 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 Nustendi.

II.C.2 Other Studies in Postauthorization 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: • To characterize the safety and tolerability of long-term administration of bempedoic acid 180 mg Secondary objective: • 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: • To assess the efficacy of FDC versus placebo on LDL-C lowering in subjects with T2DM treated for 12 weeks • To assess the efficacy of FDC versus ezetimibe on LDL-C lowering in subjects with T2DM treated for 12 weeks Secondary objectives: • To assess the efficacy of ezetimibe versus placebo on LDL-C lowering in subjects with T2DM treated for 12 weeks • To 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 weeks • To assess the effect of FDC, ezetimibe, and placebo on percent of subjects achieving LDL-C level <70 mg/dL • To assess the effect of the FDC, ezetimibe, and placebo on percent of subjects achieving LDL-C reduction ≥50% • To characterize the safety and tolerability of FDC, ezetimibe, and placebo in subjects with T2DM treated for 12 weeks Exploratory objective: • 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
Short Title	In vitro bempedoic acid inhibition of select human OAT2 substrates in MDCK-II cells expressing rat and monkey OAT2 ortholog (Oat2)
Purpose of the Study	Assess rat and monkey Oat2 for inhibition by bempedoic acid in vitro using a polarized MDCK-II cell model with clinical drugs that are human OAT2 substrates to assess the potential utility of these substrates in animal models to characterize OAT2-mediated drug-drug interactions. Safety concern addressed: drug interactions with substrates of OAT2

Short Title	In vitro bempedoic acid inhibition of select human OAT2 substrates in MDCK-II cells
Purpose of the Study	Screen a limited number of clinically relevant substrates at bempedoic acid concentrations equivalent to human C_{max} in vitro using an OAT2 polarized MDCK-II cell model. Further characterize bempedoic acid OAT2-mediated inhibition for drugs showing in vitro inhibition consistent with clinically relevant bempedoic acid concentrations. Safety concern addressed: drug interactions with substrates of OAT2
Short Title	In vitro bempedoic acid inhibition of select human OAT2 substrates in sandwich human hepatocyte culture
Purpose of the Study	Evaluate effect of bempedoic acid on the intrinsic clearance of two OAT2 substrates whose primary clearance mechanism is hepatic in sandwich hepatocyte culture. The identified substrates are warfarin (R- and S-enantiomers) and naproxen. Safety concern addressed: drug interactions with substrates of OAT2
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)