Summary of Risk Management Plan for SIRTURO (Bedaquiline)

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

SIRTURO's summary of product characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how SIRTURO should be used.

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

I. The Medicine and What it is Used For

SIRTURO is authorized for use as part of an appropriate combination regimen for pulmonary multidrug-resistant (MDR) tuberculosis (TB) in adults and adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see SmPC for the full indication). It contains bedaquiline as the active substance and it is given as oral tablets (100 mg of bedaquiline).

Further information about the evaluation of SIRTURO’s benefits can be found in SIRTURO’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002614/human_med_001730.jsp&mid=WC0b01ac058001d124

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

Important risks of SIRTURO, together with measures to minimize such risks and the proposed studies for learning more about SIRTURO'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 PL 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 Periodic Safety Update Report (PSUR) 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 SIRTURO is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of SIRTURO 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 SIRTURO. 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 Risks and Missing Information	
Important identified risks	Electrocardiogram QT prolonged Increased transaminases
Important potential risks	Severe hepatotoxicity Pancreatitis Myopathy Myocardial injury
Missing information	Long-term effects of bedaquiline treatment on mortality Use in patients using potent inhibitors of drug-metabolizing enzymes Prolonged treatment duration

II.B. Summary of Important Risks

Important Identified Risk: Electrocardiogram QT prolonged	
Evidence for linking the risk to the medicine	In vitro data indicated that bedaquiline and *N*-monodesmethyl metabolite (M2) have the potential to inhibit the human ether-à-go-go-related gene (hERG) channel. In vivo, QT interval corrected for heart rate (QTc) prolongation was seen in a 6-month repeated-dose study in dogs given 40 mg/kg/day up to 2 months and disappeared after lowering the dose to 20 mg/kg/day. A direct relationship between bedaquiline or M2 plasma concentration and QT interval corrected for heart rate according to Fridericia (QTcF) prolongation has not been found based on the results from the Phase 2b trials in adult subjects.

	QTcF prolongation in association with bedaquiline has been reported during the clinical development program and was identified as an adverse drug reaction (ADR). This ADR is described in the SmPC for SIRTURO.
Risk factors and risk groups	Risk factors include a history of heart failure, a QT interval >450 msec, as confirmed by repeat electrocardiogram (ECG), a personal or family history of congenital QT prolongation, a history of or ongoing hypothyroidism, a history of or ongoing bradyarrhythmia, a history of Torsade de Pointes or hypokalemia. Concomitant administration of bedaquiline with fluoroquinolone antibiotics that have a potential for significant QT prolongation (gatifloxacin, moxifloxacin, and sparfloxacin) is also considered a risk factor for QT prolongation. There is limited information available on the potential for a pharmacodynamic interaction between bedaquiline and medicinal products that prolong the QTc interval (including delamanid and levofloxacin).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.5; • SmPC Section 4.8; • PL Section 4; • Recommendations for ECG monitoring, the use of SIRTURO in patients with 1 or more risk factors for QT interval prolongation, and the monitoring of electrolytes are included in SmPC Section 4.4; • Advice on the use of SIRTURO in patients developing clinically significant ventricular arrhythmia or a QTcF interval of >500 ms (confirmed by repeat ECG) is included in SmPC Section 4.4; • Recommendation to obtain an ECG if syncope occurs is included in SmPC Section 4.4; • Warnings regarding coadministration of SIRTURO with medicinal products that prolong the QT interval are included in SmPC Sections 4.4 and 4.5; • Recommendations for ECG (QT interval) monitoring in case of deliberate or accidental overdose are included in SmPC Section 4.9; • Warnings for patients who have had an abnormal heart reading (ECG) or heart failure, who have a personal or family history of a heart problem called “congenital long QT syndrome”, or who faint are included in PL Sections 2 and 4; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None.

	Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Increased transaminases	
Evidence for linking the risk to the medicine	Increased transaminases, such as increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were reported during the clinical development program and were identified as ADRs. These ADRs are described in the SmPC for SIRTURO.
Risk factors and risk groups	Potential risk factors for anti-TB drug-induced hepatotoxicity include advanced age, female sex, low body mass index or malnutrition, human immunodeficiency virus (HIV), pre-existing liver disease, genetic factors, and alcoholism. In the published literature, factors associated with hepatotoxicity include elevated baseline transaminases (ALT, AST) and/or bilirubin and renal insufficiency.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.8; • SmPC Section 5.3; • PL Section 4; • Recommendations regarding the use of SIRTURO, including dose adjustments, in patients with mild, moderate, or severe hepatic impairment are included in SmPC Sections 4.2 and 5.2; • Warnings regarding coadministration of SIRTURO with other hepatotoxic medicinal products and alcohol are included in SmPC Section 4.4; • Recommendation for liver function monitoring is provided in SmPC Section 4.4; • Recommendation on evaluation and actions to be taken in case of increased transaminases is provided in SmPC Section 4.4; • A warning for patients who have liver disease or drink alcohol on a regular basis is included in PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Severe hepatotoxicity	
Evidence for linking the risk to the medicine	Liver histopathological changes were seen in mice, rats, and dogs which were associated with relevant increases in liver biomarkers (ALT, AST, alkaline phosphatase [ALP], and/or gamma-glutamyltransferase [GGT]). The observed liver histopathological changes did not include evidence of cholestasis and no elevation of bilirubin was seen. Liver-related adverse events including increases in hepatic enzyme levels (eg, ALT increased, AST increased, transaminases increased, hepatic enzyme increased) were reported during the clinical development program. These events have been identified as ADRs and are described in the SmPC for SIRTURO.
Risk factors and risk groups	Potential risk factors for anti-TB drug-induced hepatotoxicity include advanced age, female sex, low body mass index or malnutrition, HIV, pre-existing liver disease, genetic factors, and alcoholism. In the published literature, factors associated with hepatotoxicity include elevated baseline transaminases (ALT, AST) and/or bilirubin and renal insufficiency.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.8; • SmPC Section 5.3; • PL Section 4; • Recommendations regarding the use of SIRTURO, including dose adjustments, in patients with mild, moderate, or severe hepatic impairment are included in SmPC Sections 4.2 and 5.2; • Warnings regarding coadministration of SIRTURO with other hepatotoxic medicinal products and alcohol are included in SmPC Section 4.4; • Recommendation for liver function monitoring is provided in SmPC Section 4.4;

	• Recommendation on evaluation and actions to be taken in case of increased transaminases is provided in SmPC Section 4.4; • A warning for patients who have liver disease or drink alcohol on a regular basis is included in PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Pancreatitis	
Evidence for linking the risk to the medicine	Changes in the pancreas were observed in dogs and consisted of focal to multifocal chronic pancreatitis. Microvacuolation of acinar cells sometimes associated with minimal single acinar cell necrosis was observed in mice. Changes were associated with increases in amylase and lipase in mice, whereas there were no relevant changes in amylase, lipase, or trypsin-like immunoreactivity in dogs. The risk for pancreatitis, based on nonclinical findings, is described in the SmPC for SIRTURO.
Risk factors and risk groups	Pancreatic involvement in TB is more common among subjects who are coinfected with HIV. Among pancreatic TB cases, 23% occur in subjects who are HIV-positive. The prevalence of pancreatitis in the general population is higher for alcoholics than for nonalcoholics, 19.9 versus 17.7 per 100,000, respectively.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.3; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Myopathy	
Evidence for linking the risk to the medicine	Degenerative/necrotic lesions in skeletal muscle were noted in mice, rats, and dogs. These changes were accompanied by increases in AST, total creatine kinase, and myoglobin. This myopathy only occurred after prolonged or high dose administration and was usually reversible after treatment cessation or a decrease in dose. Myalgia was reported during the clinical development program and has been identified as an ADR. This ADR is described in the SmPC for SIRTURO.
Risk factors and risk groups	None known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8; • SmPC Section 5.3; • PL Section 4; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Myocardial injury	
Evidence for linking the risk to the medicine	Myocardial degeneration was seen in dogs after administration of bedaquiline for 6 months at high dose (40 mg/kg/day). Cardiac lesions consisted of minimal multifocal lymphohistiocytic infiltrates with degeneration of cardiomyocytes and/or minimal to slight endocardial fibrosis. The changes were associated with elevated levels of total creatine kinase and increase in cardiac troponin I. Myocardial injury-related laboratory abnormalities were reported during the clinical development program; however, in the randomized blinded trials population the frequencies of the observed abnormalities were similar for bedaquiline-treated subjects and placebo-treated subjects with MDR-TB. The risk for myocardial injury, based on nonclinical findings, is described in the SmPC for SIRTURO.
Risk factors and risk groups	Subjects with TB myocarditis typically suffer from disseminated disease. It is unknown whether age or the presence of other symptoms are linked to the likelihood of development of disseminated disease. In the general population, elevated C-reactive protein and creatine kinase concentrations, decreased left ventricular ejection fraction, and intraventricular conduction disturbances have been found to be associated with the risk of fulminant acute myocarditis. Risk factors for pericarditis include an immune-compromised state and cardiac surgery.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.3; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Long-term effects of bedaquiline treatment on mortality	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.1; • SmPC Section 4.4; • SmPC Section 5.1; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Use in patients using potent inhibitors of drug-metabolizing enzymes	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.5; • PL Section 2; • Warnings regarding coadministration of SIRTURO with moderate or strong cytochrome P450 (CYP)3A4 inhibitors are included in SmPC Section 4.4; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Prolonged treatment duration	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • PL Section 3 • Recommendations regarding the initiation and monitoring of SIRTURO treatment by a physician experienced in the management of MDR-TB are included in SmPC Section 4.2; • Recommendation regarding posology is included in SmPC Section 4.2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020. See section II.C of this summary for an overview of the post-authorization development plan.

II.C. Post-authorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

Confirmatory Phase 3 study STREAM Stage 2 - The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB.

Purpose of the study: To investigate the efficacy and safety, including mortality, of the adapted 'Bangladesh' regimen and of bedaquiline in combination with the BR followed by a treatment-free follow-up.

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

Multi-Country MDR-TB Disease Registry (TBC4002) - A multi-country prospective multi-drug resistant tuberculosis patient registry to monitor bedaquiline safety, utilization, and emergence of resistance.

Purpose of the study: To investigate the effectiveness, safety, including mortality, and drug resistance of bedaquiline in combination with the BR in MDR-TB patients followed by a treatment-free follow-up.