Summary of the Risk Management Plan for Deltyba

This is a summary of the risk management plan (RMP) for Deltyba. The RMP details important risks of Deltyba, how these risks can be minimised.

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

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

I: The Medicine and What it is Used for

Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children, and infants with a body weight of at least (≥) 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see SmPC for more details). It contains delamanid as the active substance and it is given orally.

Further information about the evaluation of Deltyba's benefits can be found in Deltyba'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/deltyba

II: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Deltyba, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

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

II.A: A List of Important Risks and Missing Information

Important risks of Deltyba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Deltyba. 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.

II.A-1: List of Important Risks and Missing Information	
Important Identified Risks	QT interval prolongation
Important Potential Risks	Liver disorders Drug use during pregnancy Drug use during breastfeeding
Missing Information	None

II.B: Summary of Important Risks

II.B-1: Important Identified Risk: QT Interval Prolongation	
Evidence for linking the risk to the medicine	QT prolongation has been observed in patients treated with delamanid. This prolongation increases slowly over time in the first 6-10 weeks of treatment and remains stable thereafter. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively. In the placebo-controlled trial 242-07-204, in MDR-TB patients receiving 100 mg delamanid twice daily, the mean placebo corrected increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months. Three percent (3%) of patients experienced an increase of 60 ms or greater at some point during Trial 242-07-204, and 1 patient exhibited a QTcF interval >500 ms. In Trial 242-09-213, the maximum mean placebo corrected value for QTcF reached 5.9 msec. In Trial 242-12-232, a paediatric clinical study with 37 patients aged 0-17 years performed to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid (treatment duration 10 days), there were no clinically meaningful differences in the mean changes from baseline for the various ECG parameters across the age groups. The mean change from baseline for QTcF reached 4.4 ms at Day 10. Trial 242-12-233 (treatment duration of 6 months) is an open label extension of Trial 242-12-232 and is completed and analysed across all age groups (0-17 years). In Trial 242-12-233, the ECG assessment did not show clinically significant effects of delamanid on QT intervals. No subjects experienced new onset changes > 480 msec in QTcF and new onset changes > 450 msec in QTcF were experienced by 5/36 (13.8%) subjects. However, the small sample size of 37 patients between 0 to 17 years of age has to be considered, as well as the lack of a control group for comparison of relative QT effect.
Risk factors and risk groups	• Prolonged QTc interval, e. g. congenital long QT syndrome • Female sex; advanced age • Heart disease (bradycardia, cardiac arrhythmias congestive heart failure) • Hypokalaemia, hypomagnesaemia, hypocalcaemia • Combinations of drugs (QT prolonging drugs) • Severe hepatic impairment • Hypoalbuminaemia • Alcohol abuse • Advanced HIV infection

II.B-1: Important Identified Risk: QT Interval Prolongation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.5, 4.8 PIL Section 2 Recommendation for ECG before initiation of treatment and monthly during the full course of treatment with delamanid is included in SmPC Section 4.4. It is further recommended that treatment not be initiated in patients with specific cardiac risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks. Prescription only medicine. **Additional risk minimisation measures:** Educational materials for Healthcare Professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice The endTB study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients in the experimental arms with either QTc interval prolongation of ≥60 ms from baseline or QTc interval of >500 ms at 73 weeks to that in the control arm as a secondary endpoint. See section II.C of this summary for an overview of the post-authorisation development plan.

II.B-2: Important Potential Risk: Liver Disorders	
Evidence for linking the risk to the medicine	Liver disorders are well known complications of TB, and several drugs used as part of the MDR-TB treatment regimens have well-established hepatic side effects. The overall frequency of adverse events related to or indicating liver disorders in the clinical studies with delamanid was very low, with no indication of difference from placebo or of any dose response relationship. Furthermore, there has been no non-clinical evidence for a hepatotoxic effect, nor have there been any signal in laboratory indicators of liver cell injury or cholestatic disease. In cases with adverse events involving hepatic function in which a causal relation with delamanid cannot fully be ruled out, there were other factors, including the underlying disease and concomitant medication, which may have played a causative role in the events. The clinical and non-clinical data do not provide any evidence that would support the plausibility of delamanid as culprit for the findings. In Trial 242-09-213, TEAEs referring to hepatobiliary disorders were similar across treatment groups. The lab values pertaining to liver function tests retrieved during this trial also did not show any significant differences across treatment groups.

II.B-2: Important Potential Risk: Liver Disorders	
	The frequency of liver disorders in the Phase 1, open-label, multidose, paediatric trial (Study 242-12-232) of 37 patients aged 0-17 years was low with a single occurrence in 1 patient (1/37, 2.7%) in Group 4 (ages 0 to 2 years). Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed across all age groups (0-17 years). Occurrences included 1 event each of activated partial thromboplastin time prolonged, alanine aminotransferase increased, hepatic enzyme increased; and 3 events each of liver function test increased and prothrombin time prolonged.
Risk factors and risk groups	Despite a multi-drug regimen resulting in drug-induced liver injury, advanced age, hypoalbuminaemia and alcohol consumption, along with advanced disease state, have been shown to be independent risk factors for liver disorders (specifically drug induced liver disease) in pulmonary tuberculosis patients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 PIL Section 4 Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice. The endTB study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients with AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm as a secondary endpoint. See section II.C of this summary for an overview of the post-authorisation development plan.

II.B-3: Important Potential Risk: Drug Use During Pregnancy	
Evidence for linking the risk to the medicine	Experience regarding delamanid administration during pregnancy is very limited. Rat and rabbit embryo-foetal development studies did not suggest teratogenicity at the maximal feasible doses of 300 mg/kg in rats and 10 mg/kg in rabbits. Except for a slight increase in the incidence of early reabsorption noted at the maternal toxic dose of 10 mg/kg in rabbits, no evident developmental toxicity was noted in either species. The rat fertility-embryonic development study showed no toxic effect on parent animals, fertility, or early embryonic development at the maximal feasible dose of 300 mg/kg. For metabolite DM-6705, the no observable adverse effect level (NOAEL) was 10 mg/kg/day for reproductive function of dams, and 10 mg/kg/day for embryo-foetal development. The NOAEL of (S)-DM-6718 was 3 mg/kg/day for general toxicity and reproductive function of dams, and 0.5 mg/kg/day for embryo-foetal development.

II.B-3: Important Potential Risk: Drug Use During Pregnancy	
Risk factors and risk groups	Female TB patients of childbearing potential not using contraception or not practicing abstention from sexual intercourse.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.6, 5.3 PIL Section 2 Prescription only medicine. **Additional risk minimisation measures:** Educational materials for Healthcare Professionals and Patients
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice See section II.C of this summary for an overview of the post-authorisation development plan.

II.B-4: Important Potential Risk: Drug Use During Breastfeeding	
Evidence for linking the risk to the medicine	Pharmacokinetic data in animals have shown excretion of delamanid and its metabolites in milk. In lactating rats the Cmax for delamanid in milk was 4-fold higher than that of the blood. It is not known whether delamanid is excreted in human milk. No clinical data are available to estimate potential hazards to infants who might be exposed to delamanid via breast milk. However, if excretion in human milk were similar to that observed in animals, it may be assumed that only a small fraction (< 1%) of the maternal daily dose would be ingested by the infant, due to the large volume of distribution of the drug.
Risk factors and risk groups	Female TB patients during lactation
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.6, 5.3 PIL Section 2 Prescription only medicine. **Additional risk minimisation measures:** Educational materials for Healthcare Professionals and Patients
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice See section II.C of this summary for an overview of the post-authorisation development plan.

II.C: Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

endTB - Evaluating Newly approved Drugs for multidrug-resistant TB

Description: In order to further investigate the use of delamanid in different combination treatment regimens as well as safety, the MAH should submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III trial in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières, including an additional analysis of the data with a focus on the evaluation of delamanid based on an agreed statistical analysis plan.

Due Date: Q2 2024

Delamanid In-vitro HFS Study - Delamanid PK/PD Studies

Description: In order to further characterise the PK/PD relationship of delamanid, the MAH should conduct and submit the results of an in vitro study using the HFS-TB model

Due Date: Q4 2019

Completion date: 09 Apr 2021 (EMEA/H/C/002552/II/0045)

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

EU PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice

Summary

Study short name and title: EU PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice

Rationale and study objectives:

Deltyba received a conditional marketing authorisation within the EU as of 28 April 2014 based on a favourable benefit-risk ratio assessment derived from Phase II data. The benefits of the treatment with Deltyba were shown for patients with MDR-TB affecting the lung. The safety profile was considered manageable, and several measures were introduced to minimise the risks. This included an EU-wide PASS to monitor usage of the product, to assess treatment outcomes and to obtain further information on safety.

Consequently, EU PASS 242-12-402 is a non-interventional treatment registry for Deltyba in routine medical practice and aims 1) to assess compliance with the recommendations in the authorised product information; 2) to collect further information

on safety; and 3) to collect further information on treatment outcomes as assessed per WHO definition and / or national guidelines.

All safety concerns will be evaluated through the data analysis of this study; of special interest: 1) Cardiac disorders (including QT prolongation) and 2) Suspected delamanid resistance (including lack of delamanid effect)

Study design: 242-12-402 is an EU-wide, multicentre, non-interventional study of MDR-TB patients prescribed Deltyba. The total duration of the study per patient is up to 30 months after receiving first dose of Deltyba or until completion of MDR-TB treatment. The total duration of the Deltyba PASS is planned to be 6.5 years (4 years enrolment). The ACR will be designed by the treating physician. Treatment, all assessments and patient monitoring will be performed according to the existing practices and / or treatment centre's local / national tuberculosis programme (NTP).

Study population: It is planned that 250 patients with MDR-TB, prescribed Deltyba and treated at specialised centres in the EU will be included in PASS 242-12-402.

Milestones:

- Protocol Submission: 16 MAY 2014
- Registration in the EU PAS Register: Q3 2015
- Start of Data Collection: Q4 2015
- End of Data Collection: Q1 2022
- Annual Study Progress Report(s): Q2 2017 and yearly afterwards
- Final Report Submission: Q3 2022