Summary of risk management plan for Pretomanid FGK (pretomanid)

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

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

This summary of the RMP for Pretomanid FGK 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 Pretomanid FGK's RMP.

I. The medicine and what it is used for

Pretomanid FGK is authorised in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) (see SmPC for the full indication). It contains pretomanid as the active substance and it is given by mouth.

Further information about the evaluation of Pretomanid FGK's benefits can be found in Pretomanid FGK'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/pretomanid-fgk

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Pretomanid FGK, together with measures to minimise such risks and the proposed studies for learning more about Pretomanid FGK'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 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*.

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

II.A List of important risks and missing information

Important risks of Pretomanid FGK are risks that need special risk management activities to further investigate or minimise 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 Pretomanid FGK. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	QT prolongation
Important potential risks	Hepatotoxicity Testicular toxicity
Missing information	Use in pregnancy

II.B Summary of important risks

Important identified risk: QT prolongation	
Evidence for linking the risk to the medicine	Preclinical studies (hERG signal and QT prolongation in monkeys) indicated a potential for QT prolongation for pretomanid. QT prolongation is a known adverse reaction of bedaquiline. Bedaquiline in combination with pretomanid appears to result in a higher QT prolongation than expected with bedaquiline alone. However, the impact of pretomanid has not been fully characterized. In the Nix-TB study, no subjects were observed to have a treatment emergent QTcF exceeding 480 ms, and only one subject was observed to have a change from baseline of QTcF exceeding 60 ms. Six (6.4%) patients reported an event of QT prolongation, three of which were considered drug-related; all were clinically asymptomatic.
Risk factors and risk groups	The following may increase the risk for QT prolongation: • a history of Torsade de Pointes, • a personal or family history of congenital long QT syndrome, • a history of or ongoing hypothyroidism, • ongoing bradyarrhythmia, • heart failure or known structural heart disease,

	• QT-interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram) or • serum calcium, magnesium, or potassium levels below the lower limits of normal. The QT prolongation risk for the combination regimen has not been established at exposures higher than therapeutic levels. The risk may be increased if the systemic exposure of pretomanid is elevated.
Risk minimisation measures	Routine risk communication: SmPC sections 4.4, 4.8, 5.3 PL sections 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: An ECG should be obtained before initiation of treatment, and at least monthly during treatment with the combination regimen of pretomanid, bedaquiline, and linezolid (SmPC section 4.4). Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected (SmPC section 4.4). Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimisation measures: None

Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Hepatic enzyme increases have been seen in subjects treated with pretomanid, and were more frequent with pretomanid in combinations with various other medications during the clinical development program. Note, although hepatic events are of interest for pretomanid, they are also known to occur with bedaquiline (Sirturo® SmPC, 2019).
Risk factors and risk groups	• the presence of coexisting disease, • use of concomitant medications (including anti-retrovirals), • harmful alcohol use.
Risk minimisation measures	Routine risk minimisation measures

	SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: recommendation to avoid alcohol and other hepatotoxic medicinal products, other than those specified in the indication statement, is included in the SmPC section 4.4 recommendation for monitoring liver function, including for symptoms and signs of liver injury and laboratory tests, are included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study short name: NC-007-(B-Pa-L) (ZeNix): A Phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDRTB), pre-XDR-TB or treatment intolerant or non-responsive multidrug resistant tuberculosis (MDR TB). See section II.C of this summary for an overview of the post-authorisation development plan

Important potential risk: Testicular toxicity	
Evidence for linking the risk to the medicine	Testicular toxicity was observed in rats and mice without exposure margin to the maximum recommended human dose (MRHD). Decreased fertility to complete infertility was observed in male rats treated with oral pretomanid. There were no direct effects of pretomanid on reproductive organs in monkeys given oral pretomanid for 3-months and 9-months. Decreased sperm motility, total sperm count and increased abnormal sperm ratio were observed in monkeys, which were considered as effects of substantial decreases in food consumption and body weight at high dose levels. Based upon the preclinical data, rodents are susceptible to pretomanid-induced testicular injury. Serum levels of the male reproductive hormones are biomarkers that are altered in association with this injury. In the preclinical study of primates, no pretomanid-

	related alterations in testis or male reproductive hormones were observed. Studies of male reproductive hormones showed no evidence of treatment-associated testicular toxicity and no events of fertility disorders were reported in male patients in the Nix-TB study.
Risk factors and risk groups	Not known.
Risk minimisation measures	Routine risk communication: SmPC sections 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimization measures: None

Missing information: Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Pretomanid FGK.

II.C.2 Other studies in post-authorisation development plan

Study short name: NC-007-(B-Pa-L) (ZeNix): A Phase 3 partially-blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDRTB), pre-XDR-TB or treatment intolerant or non-responsive multidrug resistant tuberculosis (MDR-TB).

Purpose of the study: To evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB.