Summary of the Risk Management Plan for Xenleta (lefamulin)

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

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

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

I. The Medicine and What it is Used for

Xenleta is authorised for community-acquired bacterial pneumonia (CAP) (see SmPC for the full indication). It contains lefamulin as the active substance and it is given by infusion or orally.

Further information about the evaluation of Xenleta's benefits can be found in Xenleta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Xenleta, together with measures to minimise such risks and the proposed studies for learning more about Xenleta'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 Xenleta is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Xenleta 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 Xenleta. 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	• None
Important potential risks	• Severe Hepatotoxicity
Missing information	• Use in Patients with Severe Hepatic Impairment • Use in Pregnant and Lactating Women

II.B Summary of Important Risks

Important Potential Risk: Severe Hepatotoxicity	
Evidence for linking the risk to the medicine	In the nonclinical data, a direct effect of lefamulin on the liver cannot be entirely discounted. However, liver histopathology was limited to 1 animal and this finding occurred only at a non-tolerated dose level associated with significant local intolerance at the site of a surgically implanted catheter (thromboemboli which may have caused liver pathology), suggesting that significant hepatotoxicity as a direct result of lefamulin was unlikely. In the Phase 1 program, there were no clinically relevant changes in liver chemistry parameters. In the Phase 2 and Phase 3 studies, the incidence of liver chemistry findings reported as TEAEs was similar or lower in the lefamulin groups compared with the comparator groups. Across all studies (combined data), a TEAE indicative of increased hepatic enzymes was reported in 2.4% of lefamulin subjects compared with 2.8% of subjects receiving a comparator. Increased bilirubin was not reported as a TEAE in any lefamulin-treated subject and was reported in only 1 comparator-treated (moxifloxacin) subject. Among lefamulin subjects with baseline ALT within normal limits, 3.4% (17/495) developed ALT >3 x ULN, 1.6% (8/495) developed ALT >5 x ULN and 0.2% (1/495) developed ALT >10 x ULN. The corresponding proportions for moxifloxacin subjects were 2.9% (14/475), 0.4% (2/475), and 0.0% (0/475). Among lefamulin subjects with baseline ALT above normal but ≤3 x ULN, 16.4% (12/73) developed ALT >3 x ULN and 4.1% (3/73) developed ALT >5 x ULN. The corresponding proportions for moxifloxacin were 13.9% (14/101) and 4.0%

Important Potential Risk: Severe Hepatotoxicity	
	(4/101). Similar trends were observed for AST analyses.
Risk factors and risk groups	Since there is limited human experience with administration of systemic pleuromutilins, there are no potentially relevant data that might assist in assessing the risk that the transaminase increases may translate into severe hepatotoxicity. The actual risk of severe hepatotoxicity occurring cannot be predicted solely by comparing the rates for hepatic enzyme elevation, and elevation per se does not predict progression of drug induced liver injury.
Risk minimisation measures	**Routine risk minimisation measures:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Recommendation to prescribers to monitor transaminases as in the current product label. **Additional risk minimisation measures:** No risk minimisation measures.

Important Missing Information: Use in Patients with Severe Hepatic Impairment	
Risk minimisation measures	**Routine risk minimisation measures**: Section 4.4 Special warning and Precautions: Hepatic Impairment **Additional risk minimisation measures:** None

Important Missing Information: Use in Pregnant and Lactating Women	
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.6 Fertility, pregnancy and lactation **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 Xenleta.

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

There are no studies required for Xenleta.