Summary of the Risk Management Plan For Lurbinectedin

Active substance:	Lurbinectedin
Strength:	4 mg
Pharmaceutical form:	Lyophilised powder for concentrate for solution for infusion
Version number of current RMP:	1.1
Name of Marketing Authorization Holder:	Pharma Mar, S.A.
Date:	July 2023

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossiers for market approval of a medicinal product. The RMP summary contain information on the medicinal products' safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of lurbinectedin is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the content in the product information («Arzneimittelinformation») approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorizations. Please note that the reference document, which is valid and relevant for the effective and safe use of lurbinectedin in Switzerland, is the «Arzneimittelinformationen» (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Pharma Mar, S.A. is responsible for the accuracy and correctness of the content of the published summary RMP of lurbinectedin.

SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for lurbinectedin

This is a summary of the risk management plan (RMP) for lurbinectedin. The RMP details important risks of lurbinectedin, how these risks can be minimized, and how more information will be obtained about lurbinectedin's risks and uncertainties (missing information). Lurbinectedin's product information gives essential information to healthcare professionals and patients on how lurbinectedin should be used. This summary of the RMP for lurbinectedin should be read in the context of overall information. Important new concerns or changes to the current ones will be included in updates of lurbinectedin's RMP.

I. The medicine and what it is used for

Lurbinectedin is available for the treatment of adult patients with metastatic small cell lung cancer (SCLC) who have progressed after prior platinum-containing therapy with a subsequent chemotherapy- free interval (CTFI) ≥30 days and with no central nervous system (CNS) metastases.

It contains lurbinectedin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of lurbinectedin’s benefits can be found in the Medicinal Product Information.

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

Important risks of lurbinectedin, together with measures to minimise such risks and the proposed studies for learning more about lurbinectedin'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 product information 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 Periodic Safety Updated 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 lurbinectedin is not yet available, it is listed under ‘missing information’ below.

II.A: List of important risks and missing information

Important risks of lurbinectedin 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 lurbinectedin. 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	Myelosuppression Creatine Phosphokinase (CPK) elevations, including rhabdomyolysis
Important potential risks	Capillary leak syndrome (CLS) Acute Myeloid Leukaemia/ Myelodysplasia
Missing information	Use in patients with hepatic impairment

II.B: Summary of important risks

Important identified risk: Myelosuppression	
Evidence for linking the risk to the medicine	Reversible myelosuppression, a condition in which the activity of the bone marrow is decreased, is the main dose limiting toxicity for lurbinectedin. Myelosuppression results in fewer red blood cells, white blood cells and platelets (a cell involved in clotting) forming. In a clinical study in SCLC patients treated with lurbinectedin, anaemia (deficiency of red blood cells) occurred in 95.2% (100/105) of patients. Neutropenia (low number of a type of white blood cell (neutrophil) that helps fight infection) occurred in 71.4 % (75/105) of patients and thrombocytopenia (low platelets) occurred in 43.8% (46/105) of patients.
Risk factors and risk groups	Risk factors for myelosuppression include: radiotherapy, chemotherapy, exposure to toxic chemicals (e.g. pesticides, insecticides), certain drugs used to treat rheumatoid arthritis (gold compounds) and some antibiotics (chloramphenicol), autoimmune disorders, viral infections (e.g. Hepatitis, Epstein-Barr, cytomegalovirus, parvovirus B19 and HIV), blood diseases and pregnancy (rarely).
Risk minimisation measures	**Routine risk minimisation measures:** *Section Warnings and Precautions (Bone Marrow Suppression)* where it instructs to monitor full blood counts including differential blood cells and platelet count at baseline and prior to each cycle of lurbinectedin. It also recommends not to administered lurbinectedin to patients with baseline neutrophil counts of less than 1.5×10^9/L and platelet counts of less than 100×10^9/L. *Section Dosage/Administration* where advice is given not to administer lurbinectedin until neutrophils recover to greater than or equal to 1.5×10^9/L, platelet counts greater than or equal to 100×10^9/L and haemoglobin levels recover to greater than or equal to 9 g/dl for cycle 1 and 8 g/dl for subsequent cycles (with transfusion if necessary). Regarding dose-modifications, it instructs to withhold the dose of lurbinectedin if any of the following adverse reactions occurs: Grade 2 non haematological toxicity (until Grade ≤1 and resume at the same dose); ≥Grade 3 (severe) non haematological toxicity (until Grade ≤1 and resume at reduced dose), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding or Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3) (until platelet ≥100,000/mm^3 and resume at reduced dose), Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), Grade 3-4 febrile neutropenia (until Grade ≤1 and resume at reduced dose) or any grade neutropenia associated with infection/sepsis (reduce the dose of lurbinectedin). Once the dose is reduced, dose re-escalation is not allowed. **Additional risk minimisation measures:** *None*

Important identified risk: CPK elevations, including rhabdomyolysis	
Evidence for linking the risk to the medicine	Rare cases of rhabdomyolysis have been reported with post-marketing use of lurbinectedin.
Risk factors and risk groups	Direct muscular traumatism, excessive muscular activity, body-temperature extremes, muscle hypoxia, infections, metabolic and electrolyte disorders, endocrine disorders, connective tissue disorders, drugs like statins and toxins.
Risk minimisation measures	**Routine risk minimisation measures:** *Section Dosage/Administration* where it indicates to withhold the dose of lurbinectedin if Grade 2 rhabdomyolysis occurs until Grade ≤1 and resume at the same dose. If Grade ≥3 rhabdomyolysis occurs, lurbinectedin should be permanently discontinued. *Section Warnings and Precautions (Rhabdomyolysis)* advices that, if rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with lurbinectedin, since the risk of rhabdomyolysis may be increased. **Additional risk minimisation measures:** *None*

Important potential risk: CLS	
Evidence for linking the risk to the medicine	CLS has been categorized as important potential risk for lurbinectedin because this is an important identified risk for trabectedin which is a medicinal product of the same therapeutic class as lurbinectedin
Risk factors and risk groups	CLS can be idiopathic (Clarkson's disease) or secondary that is mostly due to malignant haematological diseases, viral infections, and treatments such as chemotherapies and therapeutic growth factors.
Risk minimisation measures	**Routine risk minimisation measures:** Insufficient evidence of risk to warrant Medicinal Product Information statement at present **Additional risk minimisation measures:** *None.*

Important potential risk: Acute Myeloid Leukaemia/ Myelodysplasia	
Evidence for linking the risk to the medicine	Acute myeloid leukaemia/ myelodysplasia has been categorized as important potential risk for lurbinectedin because this is also an important potential risk for trabectedin which is a medicinal product of the same therapeutic class as lurbinectedin
Risk factors and risk groups	Patients heavily pre-treated with chemotherapy and radiation. Other risk factors include smoking which can double or triple the risk of acute myeloid leukaemia, genetics, blood disorders such as myelodysplastic syndrome, autoimmune conditions such as rheumatoid arthritis.
Risk minimisation measures	**Routine risk minimisation measures:** Insufficient evidence of risk to warrant Medicinal Product Information statement at present **Additional risk minimisation measures:** *None.*

Missing information: Use in patients with hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures:** *Section Contraindications* according to which, the product is contraindicated in case of moderate or severe hepatic impairment. *Section Warnings and Precautions (Hepatotoxicity)* where it informs that lurbinectedin has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5×ULN and AST >3×ULN). *Section Dosage/Administration* where it instructs not to administer lurbinectedin to patients with AST or ALT greater than 3×ULN, total bilirubin greater than 1.5×ULN or direct bilirubin >ULN. **Additional risk minimisation measures:** *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pharmacokinetic study in varying degrees of hepatic impairment [PM1183-A-017-20]. 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

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

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

Pharmacokinetic (PK) study in varying degrees of hepatic impairment [PM1183-A-017-20]

Purpose of the study:

Lurbinectedin is mainly eliminated by the liver. Thus, hepatic impairment may alter the plasma concentrations of lurbinectedin. This study is designed to examine the PK and safety of an adjusted dose of lurbinectedin when administered to patients with hepatic impairment.