EU[redacted] Risk Management Plan

for

Trabectedin 0.25 mg powder for concentrate for solution for infusion
Trabectedin 1 mg powder for concentrate for solution for infusion
(trabectedin)

RMP version to be assessed as part of this application:

RMP Version number	1.1
Data lock point for this RMP	03-Jun-2024
Date of final sign off	19-Jun-2024

Rationale for submitting an updated RMP: The Risk Management Plan (RMP) has been updated as per CHMP Day 120 Assessment Report.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part II (SVII and SVIII), Part VI and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP: Not Applicable

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QPPV signature: (on behalf of QPPV)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ANC	Absolute Neutrophil Count
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CPK	Creatine Phosphokinase
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GGT	Gamma Glutamyl Transpeptidase
MAH	Marketing Authorization Holder
MDS	Myelodysplasia
PIL	Package Information Leaflet
PLD	Pegylated Liposomal Doxorubicin
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
ULN	Upper Limit of Normal

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Trabectedin
Pharmacotherapeutic group(s)(ATC Code)	Anti-neoplastic agent, ATC code: L01CX01
Marketing Authorisation Holder	Accord Healthcare S.L.U, Spain [redacted]
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)/ [redacted]	Trabectedin 0.25 mg powder for concentrate for solution for infusion Trabectedin 1 mg powder for concentrate for solution for infusion
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/006433) [redacted]
Brief description of the product	Chemical class: Alkylating agent
	Summary of mode of action: Trabectedin binds to the minor groove of deoxyribonucleic acid (DNA), bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.

	<u>Important information about its composition:</u> ***Trabectedin 0.25 mg*** Each vial of powder contains 0.25 mg of trabectedin. One ml of reconstituted solution contains 0.05 mg of trabectedin. *Excipients with known effect:* Each vial of powder contains 2 mg of potassium and 0.1 g of sucrose. ***Trabectedin 1 mg*** Each vial of powder contains 1 mg of trabectedin. One ml of reconstituted solution contains 0.05 mg of trabectedin. *Excipients with known effect:* Each vial of powder contains 8 mg of potassium and 0.4 g of sucrose.
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA	***Current*** Trabectedin is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.
Dosage in the EEA	***Current*** **<u>Posology</u>:** For the treatment of soft tissue sarcoma, the recommended dose is 1.5 mg/m^2 body surface area, administered as an intravenous

	infusion over 24 hours with a three-week interval between cycles. For the treatment of ovarian cancer trabectedin is administered every three weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1-hour period. All patients must receive corticosteroids e.g. 20 mg of dexamethasone intravenously 30 minutes prior to PLD (in combination therapy) or trabectedin (in monotherapy); not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed. The following criteria are required to allow treatment with trabectedin: • Absolute neutrophil count (ANC) ≥ 1,500/mm^3 • Platelet count ≥ 100,000/mm^3 • Bilirubin ≤ upper limit of normal (ULN) • Alkaline phosphatase ≤ 2.5 x ULN (consider hepatic isoenzymes 5-nucleotidase or gamma glutamyl transpeptidase (GGT), if the elevation could be osseous in origin). • Albumin ≥ 25 g/l • Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 2.5 x ULN • Creatinine clearance ≥ 30 ml/min (monotherapy), serum creatinine ≤ 1.5 mg/dl (≤ 132.6 µmol/l) or creatinine clearance ≥ 60 ml/min (combination therapy) • Creatine phosphokinase (CPK) ≤ 2.5 x ULN

	• Haemoglobin ≥ 9 g/dl The same criteria as above must be met prior to re-treatment. Otherwise treatment must be delayed for up to 3 weeks until the criteria are met. Additional monitoring of haematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles. The same dose should be given for all cycles provided that no grade 3-4 toxicities are seen and that the patient fulfils the re-treatment criteria **<u>Method of administration</u>:** Intravenous administration through a central venous line.
Pharmaceutical form(s) and strengths	***Current*** Powder for concentrate for solution for infusion 0.25 mg & 1 mg
Is the product subject to additional monitoring in the EU[redacted]?	No

Part II: Safety specification

Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU [redacted] requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been considered as per European Public Assessment Report (EPAR) – RMP summary of Yondelis (trabectedin) published on EMA website on 14-Apr-2021 and CHMP Day 120 Assessment Report.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2 Presentation of the missing information

Not applicable

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Injection site reactions
Important potential risks	• Acute Myeloid Leukaemia/ Myelodysplasia (AML/ MDS) • Cardiac Dysfunction • Pancreatitis, Lipase and/or Amylase increased
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the mentioned safety concerns.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Trabectedin 0.25/1 mg powder for concentrate for solution for infusion (Trabectedin).

This is a summary of the risk management plan (RMP) for Trabectedin 0.25/1 mg powder for concentrate for solution for infusion. The RMP details important risks of Trabectedin 0.25/1 mg powder for concentrate for solution for infusion, how these risks can be minimised, and how more information will be obtained about Trabectedin 0.25/1 mg powder for concentrate for solution for infusion's risks and uncertainties (missing information).

Trabectedin 0.25/1 mg powder for concentrate for solution for infusion's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Trabectedin 0.25/1 mg powder for concentrate for solution for infusion should be used.

This summary of the RMP for Trabectedin 0.25/1 mg powder for concentrate for solution for infusion 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 the future updates of Trabectedin 0.25/1 mg powder for concentrate for solution for infusion's RMP.

I. The medicine and what it is used for

Trabectedin 0.25/1 mg powder for concentrate for solution for infusion is indicated for the adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

It contains trabectedin as the active substance and it is given by intravenous route.

Further information about the evaluation of Trabectedin 0.25/1 mg powder for concentrate for solution for infusion's benefits can be found in Trabectedin 0.25/1 mg powder for concentrate for solution for infusion's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of Trabectedin 0.25/1 mg powder for concentrate for solution for infusion, together with measures to minimise such risks and, the proposed studies for learning more about Trabectedin 0.25/1 mg powder for concentrate for solution for infusion'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, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Trabectedin 0.25/1 mg powder for concentrate for solution for infusion 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 Trabectedin 0.25/1 mg powder for concentrate for solution for infusion. 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):

Important identified risks	• Injection site reactions
Important potential risks	• Acute Myeloid Leukaemia/ Myelodysplasia (AML/ MDS) • Cardiac Dysfunction • Pancreatitis, Lipase and/or Amylase increased
Missing information	• None

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

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 Trabectedin 0.25/1 mg powder for concentrate for solution for infusion.

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

There are no studies required for Trabectedin 0.25 mg powder for concentrate for solution for infusion. and Trabectedin 1 mg powder for concentrate for solution for infusion.