EU Risk Management Plan
For
Mevlyq 0.44 mg/mL solution for injection (eribulin mesylate)

RMP version to be assessed as part of this application:

RMP Version number: 1.1

Data lock point for this RMP: 31 July 2022

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorisation Holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

AE	Adverse Event
ANC	Absolute neutrophil count
ATC	Anatomical Therapeutic Chemical
DIC	Disseminated Intravascular Coagulation
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
STS	Soft Tissue Sarcoma

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

This risk management plan (RMP) is intended to support a generic product license for eribulin mesylate 0.44 mg/mL solution for injection, namely a Centralised procedure for Mevlyq 0.44 mg/mL solution for injection.

The reference product for this generic application is HALAVEN 0.44 mg/mL solution for injection approved by Eisai GmbH.

Active substance(s) **(International non-proprietary name or common name)**	Eribulin mesylate
Pharmacotherapeutic group(s) Anatomical Therapeutic Chemical (ATC) classification code	Other antineoplastic agents, ATC code: L01XX41
Marketing Authorisation Holder	YES Pharmaceutical Development Services GmbH
Medicinal products to which this RMP refers	1.
Invented name(s) in the European Economic Area (EEA)	Mevlyq 0.44 mg/mL solution for injection
Marketing authorisation procedure	Centralised, according to Article 10.1 generic of Directive 2001/83/EC Halaven, European Union (EU) originator.
Brief description of the product	Chemical class: Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.
	Summary of mode of action: Eribulin mesylate inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin mesylate exerts its effects via a tubulin-based antimitotic mechanism leading to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage.
	Important information about its composition: None.
Hyperlink to the Product Information	m1.3.1 Product Information

<table>
<tr><td>Indication(s) in the EEA</td><td>Current:

Eribulin mesylate is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease and for the unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.</td></tr>
<tr><td></td><td>Proposed (if applicable):

None.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

Posology:

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.

The recommended dose refers to the base of the active substance (eribulin). Calculation of the individual dose to be administered to a patient must be based on the strength of the ready to use solution that contains 0.44 mg/mL eribulin mesylate and the dose recommendation of 1.23 mg/m^2. The dose reduction recommendations shown below are also shown as the dose of eribulin to be administered based on the strength of the ready to use solution.

In the pivotal trials, the corresponding publications and in some other regions e.g., the United States and Switzerland, the recommended dose is based on the salt form (eribulin mesilate).

Patients may experience nausea or vomiting. Antiemetic prophylaxis including corticosteroids should be considered.

<u>Dose delays during therapy</u>

The administration of eribulin should be delayed on Day 1 or Day 8 for any of the following:

- Absolute neutrophil count (ANC) < 1 x 10^9/L

- Platelets < 75 x 10^9/L

- Grade 3 or 4 non-haematological toxicities.

<u>Dose reduction during therapy</u>

Dose reduction recommendations for retreatment are shown in the following table.

Dose reduction recommendations
<table>
<tr><th>Adverse reaction after previous eribulin administration</th><th>Recommended dose of eribulin</th></tr>
<tr><td>Haematological:</td><td></td></tr>
</table>
</td></tr>
</table>

ANC < 0.5 x 10^9/L lasting more than 7 days	0.97 mg/m^2
ANC < 1 x 10^9/L neutropenia complicated by fever or infection	
Platelets < 25 x 10^9/L thrombocytopenia	
Platelets < 50 x 10^9/L thrombocytopenia complicated by haemorrhage or requiring blood or platelet transfusion	
Non-haematological:	
Any Grade 3 or 4 in the previous cycle	
Reoccurrence of any haematological or non-haematological adverse reactions as specified above	
Despite reduction to 0.97 mg/m^2	0.62 mg/m^2
Despite reduction to 0.62 mg/m^2	Consider discontinuation

The dose of eribulin should not be re-escalated after it has been reduced.

Patients with hepatic impairment

Impaired liver function due to metastases

The recommended dose of eribulin in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of eribulin in patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Severe hepatic impairment (Child-Pugh C) has not been studied but it is expected that a more marked dose reduction is needed if eribulin is used in these patients.

Impaired liver function due to cirrhosis

This patient group has not been studied. The doses above may be used in mild and moderate impairment, but close monitoring is advised as the doses may need readjustment.

Patients with renal impairment

Some patients with moderately or severely impaired renal function (creatinine clearance <50 mL/min) may have increased eribulin exposure and may need a reduction of the dose. For all patients with renal impairment, caution and close safety monitoring is advised.

Elderly patients

	No specific dose adjustments are recommended based on the age of the patient. *Paediatric population* There is no relevant use of eribulin in children and adolescents for the indication of breast cancer. The safety and efficacy of eribulin in children from birth to 18 years of age have not yet been established in soft tissue sarcoma. No data are available. Method of administration: Eribulin is for intravenous use. The dose may be diluted in up to 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. It should not be diluted in glucose 5% infusion solution.
	Proposed (if applicable): None.
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection
	Proposed (if applicable): None
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

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

According to the Guideline on Good Pharmacovigilance Practices (GVP) – Module V (Rev 2) (European Medicines Agency [EMA]/838713/2011 Rev 2) this section is not applicable for generic medicinal products.

Part II: Module SII - Non-clinical part of the safety specification

According to the GVP – Module V (Rev 2) (EMA/838713/2011 Rev 2) this section is not applicable for generic medicinal products.

Part II: Module SIII - Clinical trial exposure

According to the GVP – Module V (Rev 2) (EMA/838713/2011 Rev 2) this section is not applicable for generic medicinal products.

Part II: Module SIV - Populations not studied in clinical trials

According to the GVP – Module V (Rev 2) (EMA/838713/2011 Rev 2) this section is not applicable for generic medicinal products.

Part II: Module SV - Post-authorisation experience

According to the GVP – Module V (Rev 2) (EMA/838713/2011 Rev 2) this section is not applicable for generic medicinal products.

Part II: Module SVI - Additional EU requirements for the safety specification

According to the GVP – Module V (Rev 2) (EMA/838713/2011 Rev 2) this section is not applicable for generic medicinal products.

Part II: Module SVII - Identified and potential risks

According to the GVP – Module V (Rev 2) (EMA/838713/2011 Rev 2) this section is not applicable for generic medicinal products if the originator product has an RMP or if the safety concerns are published on the Coordination Group for Mutual Recognition and Decentralised Procedures - Human website.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Tachycardia • Disseminated intravascular coagulation (DIC)
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal (GI) perforation
Missing information	• None

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

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are required to assess effectiveness of risk minimisation measures.

III.3 Summary Table of additional Pharmacovigilance activities

No ongoing or planned categories 1-3 safety studies have been conducted.

Part IV: Plans for post-authorisation efficacy studies

No planned and on-going imposed post-authorisation efficacy studies have been conducted.

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

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

No additional risk minimisation measures are warranted for any of the important identified. Routine risk minimisation in the form of appropriate product labelling and being available only on prescription is considered sufficient-at this time.

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Mevlyq (eribulin mesylate)

This is a summary of the RMP for Mevlyq 0.44 mg/mL solution for injection. The RMP details important risks of Mevlyq 0.44 mg/mL solution for injection, and how these risks can be minimised, and how more information will be obtained about Mevlyq 0.44 mg/mL solution for injection risks and uncertainties (missing information).

Mevlyq 0.44 mg/mL solution for injection SmPC and its package leaflet (PL) give essential information to healthcare professionals and patients on how Mevlyq 0.44 mg/mL solution for injection should be used.

This summary of the RMP for Mevlyq 0.44 mg/mL solution for injection 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 Mevlyq 0.44 mg/mL solution for injection RMP.

I. The medicine and what it is used for

Mevlyq 0.44 mg/mL solution for injection is authorised for the treatment in adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease and for the unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (See SmPC for the full indication). It contains eribulin mesylate as the active substance and it is given by intravenous route.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

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

Important risks of Mevlyq 0.44 mg/mL solution for injection, together with measures to minimise such risks and the proposed studies for learning more about Mevlyq 0.44 mg/mL solution for injection 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 PL 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 periodic safety update report assessment, 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 Mevlyq 0.44 mg/mL solution for injection 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 Mevlyq 0.44 mg/mL solution for injection. 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	• Tachycardia • Disseminated intravascular coagulation (DIC)
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal (GI) perforation
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 Mevlyq 0.44 mg/mL solution for injection.

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

There are no studies required for Mevlyq 0.44 mg/mL solution for injection.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not Applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not Applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not Applicable.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not Applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not Applicable.

Annex 7 - Other supporting data (including referenced material)

Not Applicable.

Annex 8 – Summary of changes to the risk management plan over time

Not Applicable.