SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Halaven (eribulin)

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

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

This summary of the RMP for Halaven 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 the RMP for Halaven.

I. The medicine and what it is used for

Halaven (also known as eribulin) is authorised as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer that has progressed after at least one chemotherapy treatment for advanced disease, and for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease. Eribulin has also been shown to improve overall survival (OS) in patients with soft tissue sarcoma (STS). It contains eribulin mesilate as the active substance and it is given intravenously (IV) on Days 1 and 8 of every 21-day cycle.

Further information about the evaluation of the benefits of Halaven can be found in the EPAR, including a plain-language summary, available on the EMA website under the medicine's webpage (web link to be provided by EMA).

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

Important risks of Halaven, together with measures to minimise such risks and the proposed study for learning more about the risks of Halaven 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 medicine's legal status – the way a medicine is supplied to the patient. .

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 Halaven is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Halaven 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 Halaven. 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 (eg, on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Peripheral neuropathy • Tachycardia • Disseminated intravascular coagulation
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal perforation
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Peripheral neuropathy	
Evidence for linking the risk to the medicine	Evidence from clinical studies. Integrated Safety Analysis completed breast cancer and STS studies. Eribulin is an anti-tubulin agent, peripheral neuropathy is a common adverse event for this class of agents.
Risk factors and risk groups	In the breast cancer clinical program about a third of patients had some sort of neuropathy (peripheral) during treatment with eribulin. This is not unexpected, since peripheral neuropathy is a common adverse effect with anti-tubulin agents, such as docetaxel, paclitaxel, ixabepilone, or vincristine, and is a DLT in most cases. Patients were eligible for enrolment in Eisai clinical studies with pre-existing peripheral neuropathy up to Grade 2. Patients with pre-existing neuropathy Grade >2 were not eligible for the studies. There were no notable differences in the overall incidence of AEs by neuropathy grade, in any of the populations. Patients with pre-existing neuropathy Grade ≥2 did not exhibit an unacceptable level of neuropathy adverse events, demonstrating that eribulin is acceptable to use in breast cancer and STS subjects without regard to pre-existing neuropathy. Development of severe peripheral neuropathy was infrequent. In clinical trials, patients with pre-existing neuropathy were no more likely to develop new or worsening symptoms than those who entered the study without the condition
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 warning to monitor patients for signs of peripheral and sensory neuropathy. • PL section 4 No additional risk minimisation measures

Important Identified Risk: Peripheral neuropathy	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study E7839-M044-504: Incidence and Resolution of Eribulin-induced peripheral Neuropathy (IRENE). See section II.C of this summary for an overview of the post-authorisation development plan

Important Identified Risk: Tachycardia	
Evidence for linking the risk to the medicine	Evidence from Clinical Studies. Integrated Safety Analysis completed breast cancer and STS studies 201, 206, 207, 209, 211, 217, 221, 224, 301, 305, 309 (June 2015)
Risk factors and risk groups	Cardiac events are common in the indicated population, especially in subjects who have previously received anthracyclines or have underlying pulmonary, cardiac disease or anemia.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Identified Risk: Disseminated intravascular coagulation	
Evidence for linking the risk to the medicine	Post-marketing reports of DIC in association with eribulin have been received.
Risk factors and risk groups	Malignancy and sepsis are key risk factors for DIC.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.8 • PL section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Important Potential Risk: Adverse pregnancy outcomes	
Evidence for linking the risk to the medicine	Preclinical data, there is insufficient clinical data to exclude a risk.
Risk factors and risk groups	Fertile men and women of child bearing potential are advised to take adequate precautions.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.6, which has a Warning to avoid eribulin in pregnancy unless benefit outweighs the risks • PL section 4 No additional risk minimisation measures

Important Potential Risk: Adverse pregnancy outcomes	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Potential Risk: Male infertility	
Evidence for linking the risk to the medicine	Preclinical data, there is insufficient clinical data to exclude a risk.
Risk factors and risk groups (not missing information)	Men considering therapy with eribulin are advised to take adequate precautions
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.6 provides information on testicular toxicity and advice to male patients to conserve sperm prior to treatment • PL section 2 No additional risk minimisation measures

Important Potential Risk: Gastrointestinal perforation	
Evidence for linking the risk to the medicine	A small number of events of gastrointestinal perforation in patients treated with eribulin were reported in clinical trials. The perforations were attributed to complications of their underlying disease, however gastrointestinal perforation is a known effect associated with other anti-tubuline agents.
Risk factors and risk groups	Perforation of a malignancy primary or secondary and delayed post-operative complications of abdominal surgery e.g. clip placement or adhesions are key risk factors for GI perforation in the Halaven –treated population
Risk minimisation measures	Routine risk minimisation measures: • SmPC: Appropriate actions e.g. labeling updates will be taken as applicable. No additional risk minimisation measures

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 Halaven.

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

Study Short Name	Purpose of the Study
E7839-M044-504: Incidence and Resolution of Eribulin-induced peripheral Neuropathy (IRENE)	Safety concerns addressed: important identified risk of peripheral neuropathy, continue to characterise/ confirm Study is currently being conducted to capture data on frequency of and time to resolution of eribulin-induced or aggravated peripheral neuropathy