EU Risk Management Plan for Halaven (Eribulin)

RMP version number:	8.0
Data lock point for this RMP	01 Jun 2022
Date of final sign off:	02 Jun 2023
Procedure number:	EMEA/H/C/002084
Summary of significant changes in RMP Version 8.0:	
Part II: Identified and Potential Risks Part III: Pharmacovigilance Plan	Based on the CHMP/PRAC Rapporteur's Assessment Report, the Important Identiifed Risk of Peripheral neuropathy is considered well characterised; therefore, Peripheral neuropathy is removed as a safety concern. Updated for completed Study E7389-M044-504 (final report)
Details of the currently approved RMP:	
Version number:	7.0
Approved with procedure:	EMEA/H/C/002084/IB/0064
Date of approval (opinion date):	04 May 2022
QPPV name:	Angela Schmidt-Mertens
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.	

TABLE OF CONTENTS

List of Tables

LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransaminase
ANC	absolute neutrophil count
AST	aspartate aminotransaminase
AUC	area under the plasma concentration-time curve
CCDS	company Core Data Sheet
CrCl	creatinine clearance
CTC	Common Toxicity Criteria
CYP450	cytochrome P450
DCIS	ductal carcinoma in situ
DHPC	Direct Healthcare Professional Communication
DIC	disseminated intravascular coagulation
DLT	dose limiting toxicity
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
E7389	eribulin, ER-086526, B1939, NSC-707389
ECOG	Eastern Cooperative Oncology Group
EU-RMP	European Union - Risk Management Plan
GCSF	granulocyte cell-stimulating factor
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go related gene
HLT	high level term
HRT	hormone replacement therapy
i.v., IV	intravenous
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
MRP	multidrug resistant proteins
MTD	maximum tolerated dose
NCI	National Cancer Institute
OATP	organic anion-transporting proteins
PD	pharmacodynamic

P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PLT	platelets
QTcF	Fridericia corrected QT interval
QTcNi	individually corrected QT interval
SAE	serious adverse event (s)
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SUSARS	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TPC	treatment of physician's choice
ULN	upper limit of normal
UKACR	United Kingdom Association of Cancer Registries

PART I: PRODUCT OVERVIEW

Active substance (INN or common name)	Eribulin
Pharmacotherapeutic group (ATC Code)	L01XX41
Marketing Authorisation <Holder> <Applicant>	Eisai GmbH.
Medicinal products to which this RMP refers	1
Invented names in the European Economic Area (EEA)	Eribulin (INN), Eribulin mesilate (INNM, JAN), Halaven (Trade name)
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Antineoplastic agent
	Summary of mode of action: Eribulin mesilate is a non-taxane microtubule dynamics inhibitor.
	Important information about its composition: Eribulin is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.
Hyperlink to the Product Information	The Summary of Product Characteristics (SmPC) is included in Module 1.3.1.
Indication(s) in the EEA	Current: Eribulin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments. Eribulin is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.
	Proposed: Not applicable

Dosage in the EEA	Current: The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2, which should be administered intravenously over 2-5 minutes on Days 1 and 8 of every 21-day cycle.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection Each 2 mL vial contains eribulin mesilate equivalent to 0.88 mg eribulin Each 3 mL vial contains eribulin mesilate equivalent to 1.32 mg eribulin
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

Indication: Breast cancer

Brand Name of Concerned Product (with this Indication): Halaven

For the purpose of this RMP, Halaven will be referred to by its generic name, eribulin, in accordance with the terminology used in the nonclinical and pivotal Phase 3 studies.

Incidence:

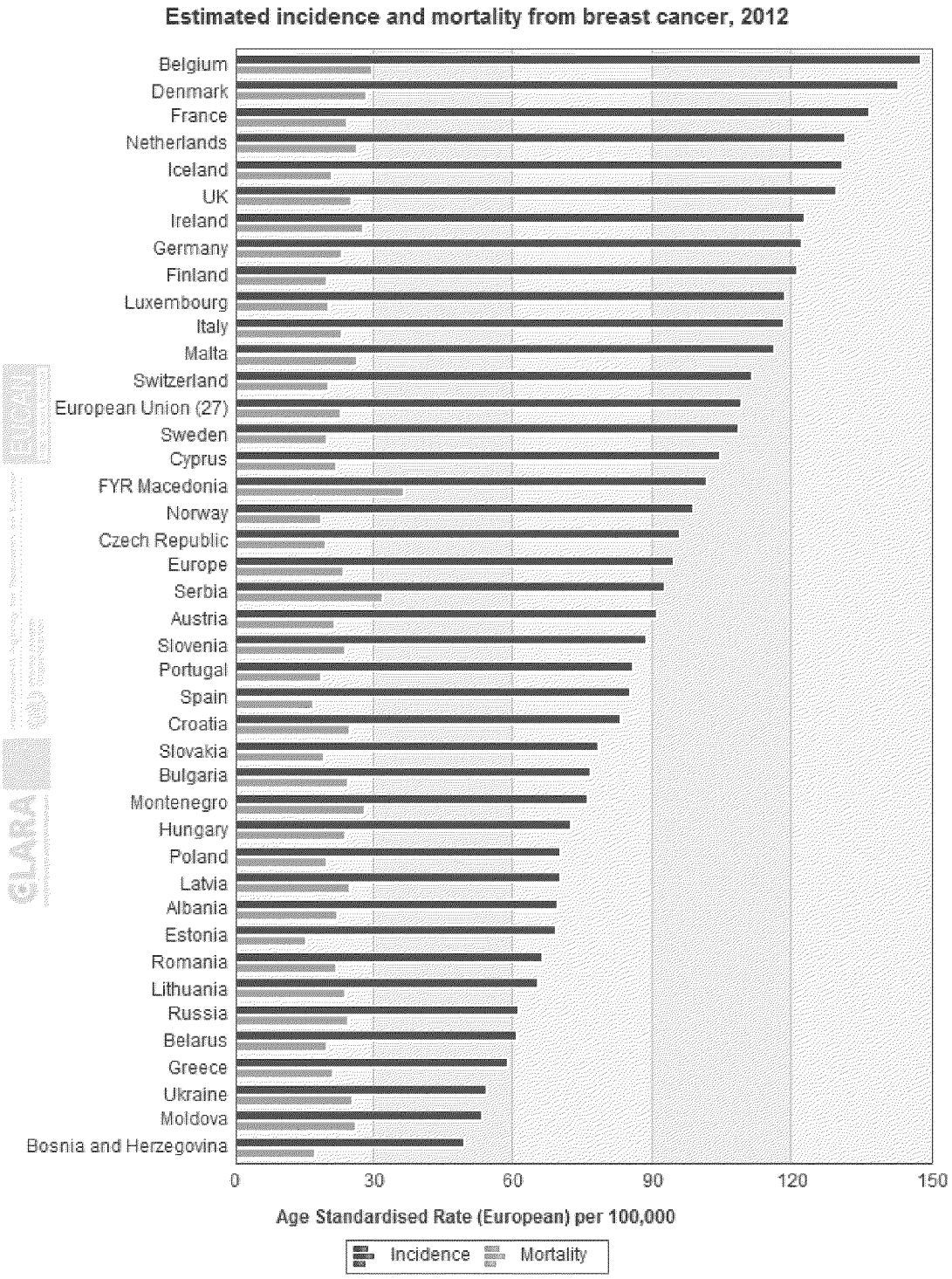
Worldwide, breast cancer is the most common cancer in women representing 16% of all female cancers. The highest incidence rates are observed in North America, whereas the lowest risk of breast cancer is observed in Asia and Africa (Parkin et al., 2001). The rate is more than twice that of colorectal cancer and cervical cancer and about three times that of lung cancer. Male breast cancer is uncommon; 1,970 new cases were estimated to be diagnosed in the United States in 2010 (American Cancer Society, 2010).

The incidence of breast cancer varies greatly around the world, and within Europe, being lower in less-developed countries and greatest in the more-developed countries. In the 12 world regions, the annual age-standardized incidence rates per 100,000 women are as

follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90 (Stewart and Kleihues, 2003).

The American Cancer Society estimated nearly 1.4 million new cases of invasive breast cancer worldwide in the year 2008. Female breast cancer incidence rate varied internationally by more than 13-fold in 2008, ranging from 8.0 cases per 100,000 in Mongolia and Bhutan to 109.4 per 100,000 in Belgium. Over the past 25 years, breast cancer incidence rates have risen globally, with the highest rates occurring in the westernized countries. Reasons for this trend include change in reproductive patterns, increased screening, dietary changes, and decreased activity. Although breast cancer incidence is on the rise globally, breast cancer mortality has been decreasing, especially in industrialized countries (American Cancer Society, 2011).

Breast cancer is also the most common cancer in women in Europe. It is estimated that in the year 2000 there were 350,000 new breast cancer cases in Europe, while the number of deaths from breast cancer was estimated at 130,000. Breast cancer is responsible for 26.5% of all new cancer cases among women in Europe, and 17.5% of cancer deaths (Data cited by Tyczynski et al, 2002). The International Agency for Research on Cancer has also published their estimates of incidence, prevalence and mortality data for women with breast cancer in Europe in 2012, presented by country below:



Reproduced from International Agency for Research on Cancer website
http://eco.iarc.fr/EUCAN/CancerOne.aspx?Cancer=46&Gender=2

Considering Europe specifically, increasing trends of breast cancer mortality were observed in European countries in the 1950s and 1960s. Deceleration of the increase in mortality or the beginning of a decline was observed in the 1970s and 1980s in several Western European countries (and also in the United States, Canada, and Australia; Hermon and Beral, 1996).

After two decades of increasing incidence rates described above, the number of new female breast cancers decreased by 2.2% per year from 1999 to 2005. This decrease is thought to reflect reduced use of hormone replacement therapy (HRT) following the publication of the Women's Health Initiative in 2002, which linked HRT use to an increased risk of heart disease and breast cancer. In addition to invasive breast cancer, 62,280 new cases of in situ breast cancer were expected to occur among women in 2009. Approximately 85% of these were expected to be ductal carcinoma in situ (DCIS). Rates of DCIS have stabilized since 2000 (American Cancer Society, 2009).

The current lifetime risk of breast cancer in the US is estimated at 12.7% (~ 1 in 8) for all women, 13.3% for non-Hispanic whites, and 9.98% for African American women. Overall, the annual incidence rates in African American women (119.4 out of every 100,000) and Hispanic/Latina women (89.9 out of every 100,000) have been stable since the early 1990s and are lower than the annual incidence of breast cancer in white women (141.1 out of every 100,000). However, African American women are more likely than white women to be diagnosed with larger, advanced stage tumors (> 5 cm). Incidence rates among Asian and Pacific Islander women have continued to increase at 1.5% per year (89 out of every 100,000) but are still significantly lower than white women (Jemal et al. 2009). Among the presenting patients with breast cancer, 3%-6% already have metastatic disease; a further 50%-70% of patients with initially localized breast cancer will suffer a systemic relapse. Approximately 75% of relapses occur within the first 5 years, but can occur up to 30 years later (Weiss et al, 2003).

Prevalence:

Regarding prevalence, on January 1, 2006, in the US there were approximately 2,533,193 women alive who had a history of breast cancer. This includes any person alive on January 1, 2006 who had been diagnosed with breast cancer at any point prior to January 1, 2006 and includes persons with active disease and those who are cured of their disease.

Considering Europe specifically, the average 5-year survival of women diagnosed with breast cancer increased in Europe between the end of the 1970s and the end of the 1980s (Berrino et al., 1999). However, there were substantial differences in survival among countries in Europe, with survival in cases diagnosed during 1985-1989 ranging from 81% in Swedish women to 58% in Slovakia and Poland (Berrino et al., 1999). The highest survival is in young women aged 40-49 years (Sant et al., 1998). Unsurprisingly, survival depends strongly on stage at diagnosis and treatment.

Age-standardized incidence of male breast cancer increased slightly from 1975 to 2000 (~1%-4%/year) and seemed to plateau or decrease slightly from 2000-2005. Recent epidemiological studies indicate that male breast cancer incidence is rising (Stang and

Thomssen, 2008). United Kingdom Association of Cancer Registries (UKACR) database identified a parallel trend, with the incidence of male breast cancer rising steadily between 1985 and 2004 (Speirs and Shaaban, 2009). Male breast cancer accounts for 0.8% of all breast cancers and for < 1% of all cases of cancer in men. The prevalence of male breast cancer increases with age, and 15%-20% of male breast cancer patients have a positive family history (Goss et al, 1999; Cutuli et al, 1995; Hill et al, 1999; Freidman et al, 1981; Salvadori et al, 1994).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Approximately 77% of breast cancer cases occur in women over 50 years of age. The older a woman is, the greater her chances of developing breast cancer. While breast cancer is less common at a young age (ie, in their thirties), younger women tend to have more aggressive breast cancers than older women, which may explain why survival rates are lower among younger women.

Male breast cancer is rare before the age of 30 years, and the average age at diagnosis is ~60 years, which is ~10 years older than in females with the disease (Devesa et al, 1995; Horm et al, 1984; Crishlow, 1972; Erlichman et al, 1984; Ribeiro et al, 1996; Ying et al, 2005). The median age at diagnosis is 68 years compared with 63 years in women (Crishlow, 1972); however, the disease has been reported in males ranging from 5 to 93 years of age (Ewertz et al, 1989). The bimodal age distribution seen in women is absent in men; the incidence increases exponentially with age (Amir et al, 1996) with a peak at age 71 years (Anderson et al, 2004). Estrogen receptors are positive in 65%-85% male breast cancer cases (Cutuli et al, 1995; Bezwoda et al, 1987; Gupta et al, 1980; Fox et al, 1992; Friedman et al, 1997; Chung et al, 1991).

Risk factors

There are several aetiological factors that are associated with occurrence of breast cancer, such as: age at menarche and menopause, childbearing, breastfeeding, hormonal status, consumption of alcohol and type of diet, obesity, radiation, and genetic susceptibility. Mammographic screening can reduce mortality from breast cancer.

The main existing treatment options:

The treatment of breast cancer is the subject of numerous text books and journals and is governed by factors including patient, payer and clinical guideline needs. The reader may, for example, wish to review the European Society of Medical Oncology clinical practice guidelines (Aebi et al, 2011) on breast cancer for detailed guidance on how the disease may be treated within the European Union. The following is highly summarized to provide an indicative background.

The type of breast cancer treatment recommended for any patient will depend on the size of the tumor, the extent of the disease, and the presence of the human epidermal growth factor

receptor 2 (HER2) oncogene and endocrine receptors (estrogen and progesterone receptors). Age, menstrual status, underlying health issues, and personal preferences play a role in this decision making process as well.

Breast cancer treatments are local or systemic. Local treatments are used to remove or destroy the disease within the breast and surrounding regions, such as lymph nodes. These include surgery, either mastectomy or lumpectomy, ie, "breast-conserving" therapy. There are various surgical approaches to mastectomy and lumpectomy. Additionally or alternatively, radiation therapy may be used.

Systemic treatments are used to destroy or control cancer cells all over the body and include, for example, chemotherapy, endocrine therapy, and biological therapies targeting specific receptors. All treatment modalities have side effects associated with them which are well recognized by clinicians and familiar to many patients, for example, alopecia with some chemotherapy agents.

Systemic therapy may be given after local treatment (adjuvant therapy) or before (neoadjuvant therapy). Adjuvant therapy is used after local treatments to kill any remaining cancer cells that are undetectable.

The particular treatment/regimen recommended for any breast cancer patient will depend on multiple factors as described above. Eribulin is indicated "*for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.*" (Summary of Product Characteristics.) Thus, patients considered for eribulin already have advanced cancers which have progressed despite prior chemotherapy for advanced cancer.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In 2004, breast cancer caused 519,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths) (WHO, 2006). In the US, death rates from breast cancer have steadily decreased in women since 1990. An estimated 40,610 breast cancer deaths (40,170 women, 440 men) are expected in 2009. The largest decrease in mortality has been seen in women younger than 50 years (3.3% per year) versus those aged 50 years and older (2.0% per year). The decrease in breast cancer death rates is thought to represent progress in both earlier detection and improved treatment modalities. (Jemal et al, 2009)

The median survival for women with metastatic breast cancer was found to be improved from 436 days in 1991 to 661 days in 1999-2001. (Chia et al, 2007). The 5-year survival rate for localized breast cancer is 99%, 85% for regional disease, and 26% for distant-stage disease (Howlader et al, 2015).

The median survival for patients with stage IV breast cancer is 18 to 24 months, although the range extends from only a few months to many years (Lee et al, 1992; Vogel et al, 1992)

Conversely, there exists a subset of women with metastatic breast cancer who have limited systemic tumor burden and biologically indolent disease.

Between 5% and 10% of patients with stage IV disease survive five or more years, and <2% to 5% become long-term survivors, possibly cured of their disease. (Greenberg et al, 1996; Falkson et al, 1990). These long-term survivors tend to be young, with an excellent performance status, and limited metastatic (sometimes referred to as oligometastatic) disease.

Patients with untreated metastatic breast cancer have a heterogeneous clinical course. The median overall survival of these patients is 9 to 12 months. Some have slowly progressive disease generally limited to bone and soft tissue, and may live >10 years, whereas those with rapidly progressive disease and visceral metastasis die within a few months (Dizdar and Altundag, 2009).

390 men are estimated to have died of breast cancer in the US in 2010 (American Cancer Society, 2010). As in women, axillary lymph node status, tumor size, histologic grade, and hormone receptor status have been shown to be significant prognostic factors in male breast cancer. Clinical outcome for men with breast cancer is similar to that for women.

Important co-morbidities:

The target population are women, usually (but not exclusively) elderly who have received prior chemotherapy regimes, including an anthracycline and a taxane. This population is likely to have reduced bone marrow reserves (due to prior therapy) and possibly suffers from concomitant medical problems as a consequence of their age (if elderly) and their advanced disease (particularly bone, lung and liver complications). Due to their prior cytotoxic drug exposure, these patients may also be more prone to cardiac disease (due to prior anthracycline and, if Her2 positive, trastuzumab use) and neuropathy (due to prior taxane and possibly, vinca and platinum agents) complications. Additionally, review of the studies conducted by Eisai suggests that a proportion of patients will also have depression; diabetes and/or osteoporosis at baseline, which are common conditions in the general population. (Reference – see Annex 12, Table 13)

Indication: Soft Tissue Sarcoma

Incidence:

Soft tissue sarcomas (STS) are a rare group of heterogeneous mesenchymal cancers. There are more than 50 histologic subtypes of STS, many of which are associated with distinct clinical profiles, response to individual therapies, and prognosis. In the past, all subtypes of STS were grouped together for the purposes of treatment, however consensus is now emerging that treatment selection should be governed by histology, particularly in the setting of advanced disease.

Soft tissue sarcomas account for less than 1% of all adult solid tumors (Burningham, et al., 2012) and the international annual incidence of STS is reported to range from 1.8 to 5/100,000 per year (Wibmer, et al., 2010). Adult soft tissue sarcomas are rare tumors in Europe, with an estimated incidence averaging 4–5/100,000/year. (ESMO 2014). Age-

standardised incidence of soft tissue sarcomas ranges from highest in Northern, Central and Southern Europe (4.5–4.7 per 100,000), lower in the UK and Ireland (3.8) and lowest in Eastern Europe (3.3) (Stiller et al, 2013).

Prevalence:

It is estimated that 11,930 people will be diagnosed with STS in the United States in 2015 and 4,870 deaths are expected to occur as a result of the disease. Based on SEER 2010-2012 data, approximately 0.3 percent of men and women in the U.S. will be diagnosed with STS at some point during their lifetime (SEER Stat Fact Sheets 2015).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Many of the STS subtypes can occur at any age and are not restricted to a specific location of the body. The rarity of the disease combined with the diverse number of subtypes can make STS very difficult to analyze.

Generally, an increase in the rate of soft tissue sarcomas occurs in new born babies and young children, until they reach the age of 5. Young adults experience the lowest incidence of soft tissue sarcomas, but occurrence steadily increases until the age of 50. At ages greater 50 years and above, incidence of soft tissue sarcomas increases much more dramatically (Burningham, et al., 2012). Based on current statistics provided by the National Center for Health Statistics and SEER data, the mean age at diagnosis for adult soft tissue sarcomas is 59 years of age. The mean age at death for STS is 65 years of age (SEER Stat Fact Sheets 2015).

The overall gender predilection by the National Cancer Data Base demonstrated that soft tissue sarcomas are more common in males than in females, by a 1.23 to 1.00 ratio in the U.S. (Corey, et al., 2014). As per the RARECARE project report, STS had slightly higher incidence in females (5.0) than in males (4.4) in the EU. This was due to rates among females of 1.0 per 100,000 for sarcomas of the uterus and 0.4 per 100,000 for sarcomas of the breast, whereas paratesticular sarcomas had a rate of only 0.1 per 100,000 in males (Stiller et al, 2013).

Race distribution includes 78% White, 10% Black, 6% Hispanic, 2.5% Asian/Pacific islander. The most common anatomic site where STS are diagnosed is the lower limb and hip (Corey, et al., 2014).

Risk factors

Risks for sarcoma development can be divided into environmental exposures and genetic susceptibility (Burningham, et al., 2012). Radiation exposure from radiotherapy has been strongly associated with secondary sarcoma development in certain cancer patients. Damage or removal of lymph nodes during previous cancer treatments may also increase the risk for developing STS. Occupational factors such as exposures to phenoxyacetic acid in herbicides and chlorophenols in wood preservative have been suggested as risk factors for sarcomas. Exposure to chemicals such as vinyl chloride (used in making plastics) and dioxin (formed

during the burning of household and industrial waste) can increase the risk of developing soft tissue sarcomas (Sarcoma Alliance 2015).

Genetic abnormalities and chromosome mutations are studied as possible causes for soft tissue sarcoma. People with certain inherited diseases such as Von Recklinghausen disease, Li-Fraumeni syndrome, Gardner syndrome, hereditary retinoblastoma, Werner syndrome, Gorlin syndrome, and tuberous sclerosis (NIH-NCI 2015).

The main existing treatment options:

Surgery, chemotherapy and radiotherapy are used in the treatment of STS. Surgery is the main line of treatment. In particular, radical surgery is a basic treatment option for localized sarcoma (Stages I through III) where it does not metastasize. However, even when radical surgery is performed, about 50% of the time, cases of high-grade sarcoma develop metastases which lead to death (Delaney, et al., 1991). For this reason, chemotherapy and radiotherapy are provided frequently as adjuvants to surgery.

While the majority of patients receive first line chemotherapy for advanced STS, with doxorubicin alone or in combination with ifosfamide being the usual choice, the rate of delivery of later lines of therapy falls after failure of first line therapy. Of those patients receiving adjuvant or first line chemotherapy, approximately half will receive a 2nd-line regimen (Minchom, 2010). There is limited clinical data to support the selection of the best treatment options in second-line or further treatment setting. Options for second line therapy include the use of standard-dose ifosfamide (or high-dose ifosfamide in patients who have already received standard dose (Minchom, 2010), trabectedin, and gemcitabine (either alone or in combination with docetaxel), dacarbazine, pazopanib (in patients with selective subtypes of advanced STS) or best supportive care. There is however, limited evidence-based data available to support improved survival with the use of any of these options. In general the choice of agent depends on several factors, such as histology, performance status, co-morbidities and patient preference (Minchom, 2010).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Unlike many other cancers, sarcoma is a disease of young and old alike. Over *a* fifth of soft tissue sarcomas are diagnosed in people under the age of 35, compared to less than 4 percent of all cancers, and thus the the person-years lost to deaths from sarcoma are disproportionately large (Sarcoma Alliance 2015). The median survival time in patients with metastatic STS is 11 to 15 months, and only a small subgroup of these patients achieve long term survival (Billingsley, et al., 1999; Van Glabbeke, et al., 1999). In the U.S., 15% of STS patients already have metastatic disease at diagnosis. The 5-year survival rate for localized STS is 57%, 59.5% for regional disease, and 17.3% for distant-stage disease (SEER Stat Fact Sheets 2015). The 5-year survival in Europe for adult STS (excluding visceral STS) averages 60%, with Eastern European countries tending to have lower survival rates (Storm, 1998). Based on the RARECARE project report, it was 54% in Eastern Europe and the UK and Ireland and 59–61% in the Northern, Central and Southern European regions. Survival rates

were generally similar for males and females. Survival was consistently lower for persons aged 65+ than for younger age groups. (Stiller et al, 2013)

Important co-morbidities:

The target population consists of adult men and women, who have received prior chemotherapy regimes, including an anthracycline, or alkylating agent, such as ifosfamide or darcabazine. This population is likely to have reduced bone marrow reserves (due to prior therapy) and possibly suffers from concomitant medical problems as a consequence of their age (if elderly) and their advanced disease (particularly bone, lung and liver complications). Due to their prior cytotoxic drug exposure, these patients may also be more prone to cardiac disease (due to prior anthracycline) and secondary malignancy (due to prior alkylating agents) complications. Patients may also be more susceptible to wound-healing complications as a result of locoregional management (eg, radiation therapy, surgery).

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage:

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
Single and repeat-dose toxicity	Nonclinical toxicology studies of eribulin in rats and dogs indicated that myelosuppression was the primary dose-limiting toxicity. Other toxicities included lymphoid, gastrointestinal and testicular toxicity typical of antiproliferative agents. Histopathologic changes in skeletal muscle and the sciatic nerve were observed in rats only. All toxicities were reversible upon discontinuation of eribulin, with the exception of changes in the testes and the rat sciatic nerve.	Myelosuppression and neurotoxicity principal anticipated toxicities based on animal data. See below.
	Single Dose Toxicity In range-finding studies, a single IV dose of 0.75 eribulin mesilate mg/kg/day (4.5 mg/m^2/day) was lethal to rats and two doses of 0.075 mg/kg/day (1.5 mg/m^2/day) were lethal to dogs. Bone marrow toxicity appeared to be dose-limiting in both rats and dogs. Intestinal toxicity was also present in dogs.	Bone marrow toxicity likely to be dose limiting based on animal data. Intestinal toxicity likely to be observed in clinical use.
	Repeated-Dose Toxicity In the repeated-dose toxicity studies of a Q4Dx3 dosing regimen in rats and dogs, the dose of 0.013 mg/kg/day (eribulin mesilate) in rats and 0.004 mg/kg/day in dogs (0.08 mg/m^2/day in rats and dogs) produced no toxicity, while doses of 0.6 or 0.8 mg/m^2/day produced reversible bone marrow toxicity in both species. Other toxicities that were considered to be drug-related occurred in the lymphoid tissue, testes, and skeletal muscle. All observed toxicities (except testicular toxicity) were reversible in both dogs and rats. In the repeated-dose toxicity studies of a Q7Dx3 dosing regimen of eribulin mesilate in rats, bone marrow testicular and thymic toxicities were found at 0.10 mg/kg/day (0.60 mg/m^2/day). The doses of 0.20 and 0.25 mg/kg/day (1.2 and 1.5 mg/m^2/day) were lethal. These doses produced testicular toxicity, thymic atrophy, and bone marrow toxicity. Fiber degeneration of sciatic nerve was also observed at both doses. Although the changes in testes and sciatic nerve were still	Repeated-dose toxicities anticipate bone marrow effects, testicular toxicity, and neurological toxicity in humans. See below.

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
	present after 14-day recovery period, other toxicities were reversible. In the repeated-dose toxicity study of a Q7Dx3 dosing regimen of eribulin mesilate in dogs at nominal doses of 0.02, 0.04, and 0.05 mg/kg/day, the doses of 0.04 and 0.05 mg/kg/day (0.8 and 1.0 mg/m^2/day) produced leukocytopenia, which was fully reversible in 14 days with compensatory extramedullary hematopoiesis. At 0.02 mg/kg/day (0.4 mg/m2/day), extramedullary hematopoiesis alone was observed. In this study, the concentrations of test article in dosing solutions for each dose level were approximately 30% lower than nominal. Therefore, actual dose levels administered were estimated to be 0.014, 0.028, and 0.034 mg/kg, respectively. In the chronic toxicity study in rats, the dosing regimen of Q7Dx3 eribulin mesilate followed by a 14-day recovery period was repeated for a total of six times (a total of 18 doses) in 6 months at doses of 0.015, 0.05, and 0.15 mg/kg/day. Bone marrow hypocellularity and testicular toxicity (consisting of a reduction in testes weight, hypocellularity of seminiferous epithelium, and hypospermia/aspermia of the epididymides) were found at 0.05 mg/kg/day (0.30 mg/m^2/day) and higher. Increases in alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), and cholesterol (CHOL) were also observed at 0.15 mg/kg/day (0.9 mg/m^2/day). In the chronic toxicity study in dogs, the dosing regimen of Q7Dx3 eribulin mesilate followed by a 14-day recovery period was repeated for a total of six times (a total of 18 doses) in 6 months at doses of 0.0045, 0.015 and 0.045 mg/kg/day. Bone marrow toxicity represented by decreases of white blood cell (WBC) and hematological parameters was observed at 0.045 mg/kg/day (0.9 mg/m^2/day). Test article-related pathological changes were limited to the high dose. They included decrease of testes weights with correlating microscopic changes in the testes and epididymides. Mild to moderate hypocellularity of testis was associated with hypospermia/aspermia of the epididymides. Hypercellularity of bone marrow, lymphoid	

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
	depletion in mesenteric lymph nodes and Peyer's patches, and thymic atrophy were noted at 0.045 mg/kg/day (0.9 mg m^2/day).	
Bone marrow toxicity	Drug-related reversible bone marrow toxicity represented by decreases of white blood cell (WBC) and hematological parameters observed in both rats and dogs.	In humans myelosuppression is dose dependent and primarily manifested as neutropenia. Treatment with eribulin should only be initiated in patients with ANC values ≥ 1.5 x 10^9/L and platelets > 100 x 10^9/L. Patients should be clinically evaluated during treatment with eribulin by physical examination and laboratory testing including complete blood counts. Development of febrile neutropenia is infrequent with eribulin. (Expressed in the SmPC, section 4.8, with a frequency of 4.6% i.e. under the common category (occurring in clinical trials at a frequency of between 1/100 to < 1/10). Frequent monitoring of complete blood counts should be performed on all patients receiving eribulin. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommendations in SmPC (section 4.2 "Dose adjustment during therapy"). Patients should be clinically evaluated during treatment with eribulin by physical examination and laboratory testing including complete blood counts. If Grade 3 and 4 hematological toxicities are present, then treatment should be delayed to allow recovery. Patients should only be retreated when absolute neutrophil count (ANC) is ≥1 x 10^9/L and platelets are ≥75 x 10^9/L and all other toxicity from a previous cycle has recovered to Grade 2 or less If toxicities reoccur, an additional dose reduction should be considered.
Reproductive and	Testicular toxicity: Drug-related testicular toxicity has been observed in rats and dogs.	Male patients should seek advice on conservation of sperm prior to

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
developmental toxicity	The testicular changes did not completely resolve during the postdosing recovery period in the repeated-dose toxicity studies. An embryo-foetal developmental toxicity study was conducted in rats. The data show that eribulin, like other microtubule inhibitors, adversely affects embryo-foetal growth and survival, and caused teratogenic effects.	treatment because of the possibility of irreversible infertility due to therapy with eribulin. Like other cytotoxic agents, eribulin affects embryo-foetal growth and survival, and is teratogenic. Given that this is related to the mode of action, eribulin is expected to be teratogenic in humans. Exposure to eribulin needs to be avoided during pregnancy. Eribulin should not be used in pregnant women unless their clinical condition requires treatment with eribulin.
Genotoxicity, Carcinogenicity	Eribulin was genotoxic in the in vitro mouse lymphoma assay and in vivo micronucleus assay in rats.	There is a theoretical risk of secondary cancers occurring after eribulin treatment.
General safety pharmacology	The effects of eribulin mesilate on the central nervous and respiratory systems in rats, and the cardiovascular system in dogs were evaluated in safety pharmacology studies. Two in vitro electrophysiological studies were also conducted to assess the effects on the human-ether-à-go-go related gene (hERG) potassium current and action potential parameters in isolated dog Purkinje fibers. No significant adverse effects were observed in any of these studies, except for transient decreases in blood pressure and heart rate in conscious dogs. The neurotoxic effects of eribulin mesilate on peripheral nerves were evaluated in BALB/c mice and were directly compared with the effects of paclitaxel and ixabepilone. Eribulin induced no significant reduction in nerve conduction velocity or peak nerve amplitude in caudal and digital nerves. This was in sharp contrast to the significant decreases induced by paclitaxel and ixabepilone dosed to similar levels of toxicity. The morphological changes in sciatic nerve and dorsal root ganglia were less severe for eribulin than those observed with paclitaxel and ixabepilone. The results indicated that eribulin induced markedly less neuropathy than paclitaxel and ixabepilone in BALB/c mice.	Cardiac electrophysiology studies were negative. Neurotoxicity likely to be less pronounced than with paclitaxel and ixabepilone. Peripheral neuropathy is removed as a safety concern based on CHMP/PRAC assessment.
Drug-Drug Interactions	Eribulin exposure (area under the curve [AUC] and maximum concentration [C_{max}]) was almost the same when administered alone or in combination with ketoconazole, a potent	No drug-drug interactions are expected with CYP3A4 inhibitors,

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
	CYP3A4 and P-gp inhibitor, and when administered alone, or in combination with rifampicin, a CYP3A4 inducer. Eribulin is mainly (up to 70%) eliminated through biliary excretion. The transport protein involved in this process is unknown. Complete inhibition of the transport could in theory give rise to a more than 3-fold increase in plasma concentrations.	CYP3A4 inducers or P-glycoprotein (P-gp) inhibitors. See also section SV11.4.1 as this draws together non clinical and clinical data: Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. It is not recommended to use substances which are inhibitors of hepatic transport proteins such as organic anion-transporting proteins (OATPs), P-glycoprotein (Pgp), or multidrug resistant proteins (MRPs) concomitantly with eribulin. Inhibitors of such transporters include, but are not limited to: cyclosporine, ritonavir, saquinavir, lopinavir and certain other protease inhibitors, efavirenz, emtricitabine, verapamil, clarithromycin, quinine, quinidine, disopyramide. It cannot be excluded that concomitant treatment with inducing substances, such as carbamazepine, phenytoin, St John´s wort (Hypericum perforatum), could give rise to reduced plasma concentrations of eribulin, and co-administration with inducers should be carried out with caution considering a potential risk for reduced drug efficacy. No marked effects on eribulin exposure (AUC and C_{max}) were observed during treatment with the CYP3A4 inducer rifampicin. However, rifampicin may, due to its transporter inhibitory property, counteract its possible inducing effect on eribulin elimination. Therefore, the effect of rifampicin may not presently be extrapolated to other inducers.

Nonclinical Studies	Key Safety Findings	Relevance to Human Usage
Other toxicity-related information or data	Not applicable.	Not applicable

CONCLUSIONS ON NON-CLINICAL DATA

Important identified risks and potential risks from the nonclinical safety findings are shown below.

Safety Concerns
Important potential risks (not refuted by clinical data or which are of unknown significance) • Testicular toxicity (male infertility) • Adverse pregnancy outcomes
Missing nonclinical safety information None.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

As of 14 May 2015, approximately 5932 subjects have been enrolled in the eribulin clinical trial program sponsored by Eisai, of which 4129 have been exposed to eribulin. Of the 5932 subjects enrolled in clinical studies 3947 had breast cancer and 1985 had other tumor types such as prostate cancer, non-small cell lung cancer, soft tissue sarcoma and metastatic urothelial tract cancer.

This RMP considers the data supporting a breast cancer indication and a liposarcoma indication.

The breast cancer indication refers to the relevant integrated data sets. i.e, Clinical trial exposure which underpins the data to support the safety of eribulin in the current indication comes from 1559 subjects enrolled in one of 8 completed trials in metastatic breast cancer as follows:

- 544 eribulin-treated subjects with locally advanced or metastatic breast cancer enrolled in the Phase 3 trial, E7389-G000-301, of eribulin vs. oral capecitabine
- 503 eribulin-treated subjects with locally advanced or metastatic breast cancer enrolled in the Phase 3 registration trial, E7389-G000-305, of eribulin vs. treatment of Physicians Choice
- 512 eribulin-treated subjects who enrolled in one of six completed Phase 2 trials in breast cancer (Studies 201 [n=33], 206 [n=56], 209 [n=51], 211 [n=291], 221 [n=81], and 224 [n=6]), all of whom received eribulin 1.23 mg/m^2 as a single agent on Day 1 and Day 8 of each 21-day cycle (these six subjects continued to receive eribulin in extension Study 224 after receiving eribulin in Study 221, and are included in the total of 81 treated subjects for Study 221). Subjects who received 28-day cycles of eribulin in Study 201 have been excluded from the analysis.

In these Phase 2/3 breast cancer trials conducted by Eisai, subjects received a mean (±SD) of 6.7 (±6.47) cycles of eribulin, with 20.4% of the 1559 subjects receiving 10 cycles or more (Table 1, ISS Table 4.1). The mean (±SD) duration of exposure was 21.2 (±20.44) weeks. The mean (±SD) cumulative dose of eribulin (mesilate) received was 17.00 (±16.709) mg/m^2 and the mean (±SD) relative dose intensity was 0.856 (±0.1621).

Table 1 Extent of Exposure to Eribulin – Phase 2/3 Breast Cancer Trials, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)
Number of cycles received	
N	1559
Mean (SD)	6.7 (6.47)
Median	5.0
Q1 – Q3	3.0, 8.0
Min, Max	1, 65
Duration of exposure (weeks)[a]	
N	1559
Mean (SD)	21.2 (20.44)
Median	15.9
Q1 – Q3	9.0, 27.0
Min, Max	3, 196
Dose Intensity ($mg/m^2/wk$)[b]	
N	1558
Mean (SD)	0.799 (0.1512)
Median	0.855
Q1 – Q3	0.702, 0.925
Min, Max	0.24, 1.04
Relative Dose Intensity[c]	
N	1558
Mean (SD)	0.856 (0.1621)
Median	0.916
Q1 – Q3	0.752, 0.991
Min, Max	0.25, 1.12
Cumulative Dose Received (mg/m^2)	
N	1559
Mean (SD)	17.00 (16.709)
Median	12.40
Q1 – Q3	6.40, 20.83
Min, Max	1.4, 182.3

Table 1 Extent of Exposure to Eribulin – Phase 2/3 Breast Cancer Trials, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)

Max = maximum, Min = minimum; Q = quartile; SD = standard deviation.
a: Duration of exposure = (Date of Day 1 dose of last cycle + 21 – date of first dose) ÷ 7.
b: Actual dose intensity = Total dose received ÷ duration of exposure.
c: Relative dose intensity = Actual dose intensity ÷ planned dose intensity, where planned dose intensity is 1.4 mg/m^2 for subjects receiving eribulin..
Source: Integrated Safety Data, Tables 4.1 and 4.2 (June 2015)

Table 2 Extent of Exposure to Eribulin by Race – Phase 2/3 Breast Cancer Studies, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)				
	White (N=1250)	Black or African American (N=77)	Asian/Pacific Islander (N=111)	Other (N=55)	Unknown (N=66)
Number of cycles received					
n	1250	77	111	55	66
Mean (SD)	6.9 (6.65)	5.7 (4.95)	6 0 (5.83)	6.5 (7.53)	5.6 (3.93)
Median	5.0	4.0	5.0	4.0	5.0
Q1 – Q3	3.0, 9.0	2.0, 7.0	2.0, 7.0	2.0, 7.0	2.0, 8.0
Min, Max	1, 65	1, 32	1, 40	1, 39	1, 23
Duration of exposure (weeks)[a]					
n	1250	77	111	55	66
Mean (SD)	21.8 (20.90)	18.0 (15.93)	19.2 (19.26)	20.7 (24.52)	17.4 (12.22)
Median	16.6	12.7	14.9	12.1	14.9
Q1 – Q3	9.0, 27.1	6.1, 23.0	7.6, 23.9	7.0, 21.4	7.0, 24.0
Min, Max	3, 196	3, 103	3, 130	3, 125	3, 70

Max = maximum, Min = minimum; Q = quartile; SD = standard deviation.
a: Duration of exposure = (Date of Day 1 dose of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.1 (June 2015)

Table 3 Extent of Exposure to Eribulin by Gender– Phase 2/3 Breast Cancer Trials, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)	
	Male	Female
Number of cycles received		
N	0	1559
Mean (SD)		6.7 (6.47)
Median		5.0
Q1 – Q3		3.0, 8.0
Min, Max		1, 65
Duration of exposure (weeks)[a]		
N	0	1559
Mean (SD)		21.2 (20.44)
Median		15.9
Q1 – Q3		9.0, 27.0
Min, Max		3, 196

Max = maximum, Min = minimum; Q = quartile; SD = standard deviation.
a: Duration of exposure = (Date of Day 1 dose of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.2 (June 2015)

Table 4 Extent of Exposure to Eribulin by Age Group– Phase 2/3 Breast Cancer Trials, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)	
	<65	≥65
Number of cycles received		
N	1276	283
Mean (SD)	6.7 (6.31)	6.9 (7.15)
Median	5.0	5.0
Q1 – Q3	3.0, 8.0	3.0, 8.0
Min, Max	1, 55	1, 65
Duration of exposure (weeks)[a]		
N	1276	283
Mean (SD)	21.1 (19.95)	21.7 (22.52)
Median	15.9	16.0
Q1 – Q3	9.0, 27.0	9.0, 25.1
Min, Max	3, 177	3, 196

Table 4 Extent of Exposure to Eribulin by Age Group– Phase 2/3 Breast Cancer Trials, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)	
	<65	≥65

Max = maximum, Min = minimum; Q = quartile; SD = standard deviation.
a: Duration of exposure = (Date of Day 1 dose of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.3 (June 2015)

Table 5 Extent of Exposure to Eribulin by Geographic Region – Phase 2/3 Breast Cancer Studies, Safety Population

Parameter	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Studies (N=1559)			
	Region 1 (N=405)	Region 2 (N=467)	Region 3 (N=606)	Region 4 (N=81)
Number of cycles received				
n	405	467	606	81
Mean (SD)	6.4 (6.21)	6.0 (5.36)	7.6 (7.29)	6.2 (6.45)
Median	4.0	5.0	6.0	5.0
Q1 – Q3	2.0, 8.0	3.0, 8.0	3.0, 9.0	2.0, 7.0
Min, Max	1, 43	1, 65	1, 55	1, 40
Duration of exposure (weeks)[a]				
n	405	467	606	81
Mean (SD)	20.2 (19.57)	19.0 (16.82)	23.9 (23.01)	19.7 (21.44)
Median	13.0	15.0	18.0	14.9
Q1 – Q3	6.6, 27.0	9.0, 24.0	9.3, 29.0	6.1, 24.0
Min, Max	3, 134	3, 196	3, 177	3, 130

Max = maximum, Min = minimum; Q = quartile; SD = standard deviation. Region 1 = USA and Canada; Region 2 = Western Europe, Australia, and Israel; Region 3 = Eastern Europe, Latin America, South Africa, and Asia (excluding Japan); Region 4 = Japan.
a: Duration of exposure = (Date of Day 1 dose of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.4 (June 2015)

Soft Tissue Sarcoma

For the approved indication in advanced/metastatic liposarcoma, safety data from 2 Phase 2 studies (E7389-E044-207 [Study 207] and E7389-J081-217 [Study 217]) and 1 Phase 3 study (E7389-G000-309 [Study 309]) are summarized in this RMP as follows:

- **The Study 309 Safety Population**. Data from all subjects who received at least 1 dose of eribulin in Study 309 (N = 226).
- **The Eribulin Sarcoma Safety Population** (STS population) (N = 404). Data from all subjects who received at least 1 dose of eribulin in sarcoma studies 207, 217 and 309.

The 3 sarcoma studies were conducted in compliance with Good Clinical Practices and International Conference on Harmonisation recommendations, as well as all applicable to local, state, and federal regulations and guidelines regarding the conduct of clinical trials.

In these Phase 2/3 STS studies conducted by Eisai, subjects received a mean (±SD) of 5.7 (±6.47) cycles of eribulin, with 16.6% of the 404 subjects receiving 10 cycles or more (ISS Table 4.1). The mean (±SD) duration of exposure was 18 (±20.58) weeks. The mean (±SD) cumulative dose of eribulin (mesilate) received was 14.09 (±15.635) mg/m^2 and the mean (±SD) relative dose intensity was 0.870 (±0.1585).

Table 6 Extent of Exposure to Eribulin – Phase 2/3 Soft Tissue Sarcoma Studies, Safety Population

Parameter	Eribulin Study 309 (N=226)	All Eribulin treated subjects in Phase 2/3 Sarcoma Studies (N=404)
Number of cycles received		
N	226	404
Mean (SD)	5.5 (5.75)	5.7 (6.47)
Median	3.0	4.0
Q1 – Q3	2.0, 7.0	2.0, 7.0
Min, Max	1, 34	1, 58
Duration of Exposure (weeks)[a]		
N	226	404
Mean (SD)	17.4 (18.65)	18 (20.58)
Median	10.0	12.0
Q1 – Q3	6.0, 21.0	6.0, 21.2
Min, Max	3, 112	3, 178
Actual Dose Intensity (mg/m^2/wk)[b]		
N	226	404
Mean (SD)	0.803 (0.1591)	0.812 (0.1478)
Median	0.873	0.872
Q1 – Q3	0.709, 0.932	0.717, 0.930
Min, Max	0.32, 0.97	0.32, 0.97
Relative Dose Intensity[c]		
N	226	404
Mean (SD)	0.861 (0.1705)	0.870 (0.1585)

Table 6 Extent of Exposure to Eribulin – Phase 2/3 Soft Tissue Sarcoma Studies, Safety Population

Parameter	Eribulin Study 309 (N=226)	All Eribulin treated subjects in Phase 2/3 Sarcoma Studies (N=404)
Median	0.935	0.934
Q1 – Q3	0.759, 0.998	0.768, 0.998
Min, Max	0.35, 1.04	0.35, 1.04
Cumulative Dose Received (mg/m^2)		
N	226	404
Mean (SD)	13.44 (13.719)	14.09 (15.635)
Median	8.03	8.41
Q1 – Q3	5.56, 16.73	5.58, 16.80
Min, Max	1.4, 84.7	1.3, 164.8

a: Duration of exposure = (Date of Day 1 of last cycle + 21 – date of first dose) ÷ 7.

b: Actual dose intensity (mg/m^2/week) = cumulative dose (mg/m^2/week) / duration of exposure (weeks).

c: Relative dose intensity = actual dose intensity (mg/m^2/week) / planned dose intensity (mg/m^2/week), where planned dose intensity is 1.4 $mg/m^2 \times 2/3$ for subjects receiving eribulin.

Source: Integrated Safety Data, Tables 4.1 and 4.2 (June 2015).

Table 7 Extent of Exposure to Eribulin by Race– Phase 2/3 Soft Tissue Sarcoma Studies, Safety Population

Parameter	Eribulin Study 309 (N=226)					All Eribulin treated subjects in Phase 2/3 Sarcoma Studies (N=404)				
	White N=161	Black or African American	Asian / Pacific Islander	Other	Unknown	White (N=161)	Black or African American	Asian / Pacific Islander	Other	Unknown
Number of cycles received										
n	161	6	19	6	34	161	6	70	6	161
Mean (SD)	5.6 (5.87)	3.3 (2.88)	5.7 (7.52)	5.7 (6.09)	5.2 (4.46)	5.6 (5.87)	3.3 (2.88)	7.1, (8.49)	5.7 (6.09)	5.3 (6.10)
Median	4.0	2.0	2.0	3.0	3.5	4.0	2.0	4.0	3.0	4.0
Q1 – Q3	2.0, 7.0	1.0, 7.0	2.0, 7.0	1.0, 10.0	2.0, 7.0	2.0, 7.0	1.0, 7.0	2.0, 8.0	1.0, 10.0	2.0, 6.0
Min, Max	1, 34	1, 7	1, 31	1, 16	2, 18	1, 34	1, 7	1, 49	1, 16	1, 58
Duration of Exposure (weeks)[a]										
n	161	6	19	6	34	161	6	70	6	161
Mean (SD)	17.8 (19.0)	10.2 (8.85)	18.2 (25.04)	18.1 (19.62)	16.3 (14.03)	17.8 (19.0)	10.2 (8.85)	22.7 (27.57)	18.1 (19.62)	16.4 (18.68)
Median	12.0	6.1	6.0	9.1	10.5	12.0	6.1	12.1	9.1	11.9
Q1 – Q3	6.0, 21.0	3.0, 20.9	6.0, 21.9	3.0, 34.7	6.0, 21.0	6.0, 21.0	3.0, 20.9	6.0, 25.0	3.0, 34.7	6.0, 19.6
Min, Max	3, 112	3, 22	3, 105	3, 50	6, 56	3, 112	3, 22	3, 158	3, 50	3, 178

a: Duration of exposure = (Date of Day 1 of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.1 (June 2015).

Table 8 Extent of Exposure to Eribulin by Geographic Region– Phase 2/3 Soft Tissue Sarcoma Studies, Safety Population

	Eribulin Study 309 (N=226)				All Eribulin treated subjects in Phase 2/3 Sarcoma Studies (N=404)			
Parameter	**Region 1**	**Region 2**	**Region 3**	**Region 4**	**Region 1**	**Region 2**	**Region 3**	**Region 4**
Number of cycles received								
n	86	105	35	0	86	228	39	51
Mean (SD)	6.0 (6.21)	4.9 (4.93)	6.0 (6.82)	N/A	6.0 (6.21)	5.2 (5.86)	5.6 (6.53)	7.6 (8.84)
Median	3.0	3.0	4.0	N/A	3.0	3.0	4.0	4.0
Q1 – Q3	2.0, 7.0	2.0, 6.0	2.0, 7.0	N/A	2.0, 7.0	2.0, 6.0	2.0, 7.0	2.0, 9.0
Min, Max	1, 28	1, 34	1, 31	N/A	1, 28	1, 58	1, 31	1, 49
Duration of Exposure (weeks)[a]								
n	86	105	35	0	86	228	39	51
Mean (SD)	19.3 (20.32)	15.4 (15.77)	18.8 (22.05)	NA	19.3 (20.32)	16.1 (18.17)	17.7 (21.12)	24.4 (28.50)
Median	9.6	10.0	12.0	NA	9.6	10.0	12.0	13.4
Q1 – Q3	6.0, 22.9	6.0, 18.0	6.0, 22.0	NA	6.0, 22.9	6.0, 19.0	6.0, 21.3	6.6, 30.6
Min, Max	3, 86	3, 112	3, 105	NA	3, 86	3, 178	3, 105	3, 158

NA = not applicable. Region 1 = USA and Canada; Region 2 = Western Europe, Australia, and Israel; Region 3 = Eastern Europe, Latin America, South Africa, and Asia (excluding Japan); Region 4 = Japan.
a: Duration of exposure = (Date of Day 1 of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.4 (June 2015).

Table 9 Extent of Exposure to Eribulin by Gender– Phase 2/3 Soft Tissue Sarcoma Studies, Safety Population

	Eribulin Study 309 (N=226)		All Eribulin treated subjects in Phase 2/3 Sarcoma Studies (N=404)	
Parameter	**Male**	**Female**	**Male**	**Female**
Number of cycles received				
n	67	159	151	253
Mean (SD)	6.4 (6.25)	5.1 (5.51)	6.3 (7.01)	5.4 (6.11)
Median	4.0	3.0	4.0	3.0
Q1 – Q3	2.0, 10.0	2.0, 6.0	2.0, 8.0	2.0, 6.0
Min, Max	1, 34	1, 31	1, 58	1, 49
Duration of Exposure (weeks)[a]				
n	67	159	151	253
Mean (SD)	20.7 (20.82)	16.0 (17.54)	19.8 (22.22)	16.9 (19.50)
Median	12.0	10.0	12.0	10.0
Q1 – Q3	6.0, 30.1	6.0, 20.9	6.0, 24.0	6.0, 20.9
Min, Max	3, 112	3, 105	3, 178	3, 158

a: Duration of exposure = (Date of Day 1 of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.2 (June 2015).

Table 10 Extent of Exposure to Eribulin by Age Group– Phase 2/3 Soft Tissue Sarcoma Studies, Safety Population

	Eribulin Study 309 (N=226)		All Eribulin treated subjects in Phase 2/3 Sarcoma Studies (N=404)	
Parameter	**<65**	**≥65**	**<65**	**≥65**
Number of cycles received				
n	176	50	314	90
Mean (SD)	5.4 (5.59)	6.0 (6.34)	5.6 (5.99)	6.1 (7.95)
Median	3.0	4.0	3.0	4.0
Q1 – Q3	2.0, 7.0	2.0, 7.0	2.0, 7.0	2.0, 7.0
Min, Max	1, 31	1, 34	1, 49	1, 58
Duration of Exposure (weeks)[a]				
n	176	50	314	90
Mean (SD)	16.8 (17.73)	19.5 (21.64)	17.6 (18.92)	19.4 (25.62)
Median	9.7	12.0	11.4	12.0
Q1 – Q3	6.0, 21.0	6.0, 21.0	6.0, 21.9	6.0, 21.0
Min, Max	3, 105	3, 112	3, 158	3, 178

a: Duration of exposure = (Date of Day 1 of last cycle + 21 – date of first dose) ÷ 7.
Source: Integrated Safety Data, Table 4.1.3 (June 2015).

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Table 11 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Pre-existing neuropathy > Grade 2	Known risk based on existing clinical data and data from similar agents.	No	The risk is known and warning statements are included in the label to manage this condition.
Hypersensitivity to any of the ingredients	Standard warning.	No	
Prior treatment with eribulin	Prior treatment with the study drugs is usually an exclusion criterion to avoid bias in efficacy outcomes.	No	If clinical benefit was observed with eribulin, there is no biological reason to exclude it as an option for future lines of chemotherapy.
Radiation therapy encompassing > 30% of marrow	Patients are at risk of medullary aplasia and may bias the general outcome of the trial.	No	There is no evidence that these patients should be contraindicated provided there is careful monitoring of blood counts as specified in the SmPC.
Patients with meningeal carcinomatosis	These patients have a poor prognosis and may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition
Patients with brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (e.g. radiologic) and/or symptoms of brain metastases must be stable for at least 4 weeks.	Patients whose condition is unstable may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition.

Table 11 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen	These patients have a poor prognosis and may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition
Patients who have received chemotherapy, radiation or trastuzumab within two weeks before study treatment, or hormonal therapy within one week before study treatment.	A wash-out period is necessary to enable assessment of efficacy and safety.	No	Managed in routine clinical practice.
Prior treatment with mitomycin C or nitrosourea	Patients who have received these drugs may bias the general outcome of the trial.	No	Managed in routine clinical practice.
Severe/uncontrolled intercurrent illness/infection	Patients with this condition may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition. Adequate warnings are included in the label.
Patients with organ allografts requiring immunosuppression	Patients with this condition may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition. Adequate warnings are included in the label.
Patients with known positive HIV status	Patients with this condition may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition. Adequate warnings are included in the label.
Patients who have had a prior malignancy, other than carcinoma in situ of the cervix, or non-melanoma skin cancer, unless the prior malignancy was diagnosed and definitively treated $\geq$ 5 years previously with no subsequent evidence of recurrence	There is a need to differentiate whether the tumour relapse is due to the tumor under treatment or to prior malignancy. This may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition.

Table 11 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Patients who are receiving anti-coagulant therapy with warfarin or related compounds, other than for line patency, and cannot be changed to heparin-based therapy, are not eligible. If a patient is to continue on mini-dose warfarin, then the prothrombin time (PT) or international normalized ratio (INR) must be closely monitored.	At the time of the studies the extent of interaction of eribulin with anti-coagulants was unknown	No	No interaction is observed between eribulin and warfarin.
Significant cardiovascular impairment and patients with history of congestive heart failure > NYHA Grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia.	Patients with this condition may bias the general outcome of the trial.	Yes until RMP V4.2	There is no specific safety concern to indicate that eribulin cannot be used in patients with these conditions.
Subjects that have previously been treated with dacarbazine, or its analogue temozolomide.	Patients who have received these drugs may bias the general outcome of the trial.	No	Managed in routine clinical practice.
Any malignancy that required treatment, or has shown evidence of recurrence (except for soft tissue sarcoma, non-melanoma skin cancer, or histologically confirmed complete excision of carcinoma in situ) during the 5 years prior to randomization.	There is a need to differentiate whether the tumour relapse is due to the tumor under treatment or to prior malignancy. This may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition.
Major surgery within 21 days prior to randomization.	Patients who had major surgery within 21 days prior to randomization may bias the general outcome of the trial.	No	There is no specific safety concern to indicate that eribulin cannot be used in patients with this condition.

Table 11 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing Information	Rationale (if not included as missing information)
Pregnancy	Standard practice to exclude pregnant women from clinical trials. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats	Yes	There are no data from the use of eribulin in pregnant women. HALAVEN should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.
Breast feeding	Alternative means of infant nutrition are available.	No	There are no data from the use of eribulin in breast feeding women. It is unknown whether eribulin/metabolites are excreted in human or animal breast milk. A risk to newborns/infants cannot be excluded and therefore eribulin must not be used during breastfeeding

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

The clinical development programme is unlikely to detect rare adverse drug reactions (ADRs).

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare (it may be appropriate to choose other ADR frequencies)	1963 breast cancer and STS patients were available for inclusion in the integrated safety analysis	For the total of 1963 breast cancer and STS patients, there is at least a 95% probability of observing one or more subjects experiencing an adverse event if the true event rate is at least 1/655 (or 1 in 655).
Due to prolonged exposure	Mean exposure was 6 cycles over approximately 20 weeks. This limits the ability to detect any adverse drug reactions which develop over a longer period. However the nature of the underlying condition is such that this is unlikely to be a long term concern.	Data on long term effects are unlikely to become available or to be relevant given the condition under treatment.
Due to cumulative effects	Not applicable – see comments above	Not applicable – see comments above

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which have a long latency	See comment above	See comment above.

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

Table 12 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	There are no data from the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats. Eribulin should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus. Women of childbearing potential must be advised to avoid becoming pregnant whilst they or their male partner are receiving eribulin and have to use effective contraception during and up to 3 months after treatment.
Breastfeeding women	It is unknown whether eribulin/metabolites are excreted in human or animal breast milk. A risk to newborns/infants cannot be excluded and therefore eribulin must not be used during breastfeeding (see section 4.3 of the Summary of Product Characteristics).
Patients with hepatic impairment	The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Compared to patients with normal hepatic function, exposure to eribulin increased 1.75-fold and 2.79-fold in patients with mild and moderate hepatic impairment, respectively. Administration of eribulin mesilate at a dose of 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as that following a 1.4 mg/m^2 dose to patients with normal hepatic function. In conclusion, hepatic impairment increases exposure to eribulin. This effect is more pronounced for moderate hepatic impairment. Eribulin has not been studied in patients with severe hepatic impairment, therefore, its use is not recommended in these patients. Patients with ALT or AST > 3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia

Patients with renal impairment	Eribulin is minimally excreted via the kidney. Eribulin disposition in patients with mild (creatinine clearance [CrCl] ≥50 ml/min) or moderate (50 ml/min>CrCl≥30 ml/min) renal impairment did not differ from that in patients with normal renal function (CrCl ≥80 ml/min). To provide data on the effect of renal impairment on eribulin exposure, a study in patients with renal impairment was conducted since the first RMP was approved at the request of the FDA: E7389-A001-106: An Open-label Phase I study to assess the Pharmacokinetics and Safety of HALAVEN in Subjects With Cancer Who Also Have Impaired Renal Function. Data in patients with different degrees of impaired renal function showed that the exposure of eribulin in patients with mild to moderate renal impairment (creatinine clearance ≥ 40 to 80 ml/min) was increased in some patients, as compared to patients with normal renal function. The mean exposure in patients with severe impairment was increased by 75% (creatinine clearance < 40 ml/min, n=4). Based on these results, dose reduction is recommended for patients with moderate to severe renal impairment.
Patients with CV impairment	Cardiovascular safety of eribulin was investigated in an Open-Label, Multicenter, Single Arm Study of Eribulin Mesylate (E7389-E044-110) in Patients with Advanced Solid Tumors to evaluate the effect of eribulin on cardiac repolarization. This study evaluated cardiovascular safety in 26 patients with advanced solid tumours and an extensive ECG schedule was applied in another 103 patients with advanced non-small cell lung cancer (Study E7389-A001-202). In study E7389-E044-110, a PK/PD analysis found no relationship between observed eribulin concentration and baseline-adjusted QTc intervals on Days 1 and 8. QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalemia or hypomagnesemia should be corrected prior to initiating eribulinand these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome. However, eribulin has not been studied in population with significant cardiovascular impairment and

	patients with history of congestive heart failure > NYHA Grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia were excluded from the studies.
Immunocompromised patients	The safety and effectiveness of eribulin in immune-compromised and transplant patients in clinical trials have not been established
Patients with a disease severity different from inclusion criteria in clinical trials	The safety and effectiveness of eribulin in patients with disease severity different than studied in clinical trials have not been established.
Population with relevant different racial and/or ethnic origin	In the studied breast cancer and STS populations the majority of subjects (72%) were White and 9% Asian/Pacific Islander; more than one third of the patients (35%) were from Western Europe/Australia/Israel. Thirty three percent of patients were from Eastern Europe/Latin America/South Africa/Asia (excluding Japan), and 25% of patients were from the USA/Canada. There were no notable differences in extent of exposure by race subgroup. The safety and effectiveness of eribulin in patients of Hispanic origin have not been established.
Elderly patients	Of the 1963 breast cancer and STS patients treated with the recommended dose of eribulin, 373 patients (19.0 %) were ≥ 65 years of age. The safety profile of eribulin in elderly patients (≥ 65 years of age) was similar to that of patients < 65 years of age except for asthenia/fatigue which showed an increasing trend with age. No dose adjustments are recommended for the elderly population.
Children	Eribulin is currently not licensed for use in children. A paediatric investigational plan (PIP) is in place for the treatment of soft tissue sarcoma in patients from 6 months to less than 18 years of age (with a waiver from birth to less than 6 months), EMEA-001261-PIP01-11-M057. The results for the 3 clinical trials (E7389-A001-113, E7389-G000-223, and E7389-G000-213) conducted under the PIP do not show adequate efficacy in the paediatric population studied and, therefore, do not support further continued clinical development of eribulin as monotherapy or in combination with irinotecan as a potential antitumor treatment strategy in paediatric patients with refractory or recurrent solid tumors. The observed safety profile of eribulin as a single therapy or in combination with irinotecan in paediatric subjects was acceptable with no new safety signals and was consistent with the known eribulin mesilate and irinotecan hydrochloride safety profiles in adults and in children. Based on the results of these studies, no firm conclusions can be drawn from a safety perspective, regarding the use of eribulin in a paediatric population.

Sub-populations Carrying Known and Relevant Polymorphisms:	The safety and effectiveness of eribulin in patients with genetic polymorphism have not been established.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The available worldwide data (where information is available) provided is based on ex-production sales data and the number of vials sold. A lag-time between shipment and actual patient exposure should be considered; however one set of data is provided for eribulin (Halaven) globally and cumulative data is provided from the international birth date (IBD).

One vial contains 1 mg/2 ml (0.5 mg/mL) of eribulin mesilate (Halaven), which is equivalent to 0.88 mg/2 mL eribulin (0.44 mg/mL) free base. The following assumptions were undertaken to calculate the number of patients exposed to eribulin during the reporting period:

- Total average number of vials/units required by a single patient for one cycle (2 infusions in a 21 day cycle) is 6 vials/units. The estimate of 3 vials per infusion is based on the clinical trial data.
- Estimated number of cycles during the reporting period is the total amount of vials sold during the reporting period divided by average number of vials per cycle.

SV.1.2 Exposure

Estimated cumulative exposure to eribulin since IBD is 313,000 cycles. The post-marketing exposure data are not currently broken down by sex, age, or indication, however the available post-marketing exposure data are estimated to be in females over 18 years of age, based on the approved indication.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes:

There have been no psychoactive effects reported with the use of eribulin. Therefore, there is no perceived potential for eribulin to be used for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

The summary of safety concerns in the approved initial RMP for eribulin is presented in Table 13.

Table 13 Summary of Safety Concerns After Approval of Initial RMP (Version 1.2)

Summary of safety concerns	
Important identified risks	• Myelosuppression and associated infections • Peripheral neuropathy • Nausea/Vomiting • Depression & Insomnia • Tachycardia • Disseminated intravascular coagulation
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal perforation
Missing information	• Use in severe hepatic impairment • Use in cardiovascular impairment • Use in pregnant women • Use in the paediatric and adolescent population

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

Not applicable as this is not the initial RMP for the product.

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

Not applicable as this is not the initial RMP for the product.

For completeness, the summary of safety concerns in the current approved RMP (Version 6.0) is presented in Table 14.

Table 14 Summary of Safety Concerns in Current Approved RMP (Version 7.0)

Summary of safety concerns	
Important identified risks	• Peripheral neuropathy • Tachycardia • Disseminated intravascular coagulation
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal perforation
Missing information	None.

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

None.

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

Identified Risk: Tachycardia	
Potential mechanisms:	The exact mechanism is not known.
Evidence source(s) and strength of evidence:	Integrated Safety Analysis completed breast cancer and STS studies 201, 206, 207, 209, 211, 217, 221, 224, 301, 305, 309 (June 2015)
Characterisation of the risk:	• Frequency Cardiac SOC disorders occurred in 2.4% of the breast cancer treated population. Cardiac treatment emergent related adverse events reported with the highest incidence were: - Tachycardia 1.0% all Grade 1 or 2 - Palpitations 0.7%. (12/13 subjects = Grade 1 or 2; 1 subject Grade 3) Other cardiac treatment emergent related adverse events occurred with the incidence less than 1% in the population. • Seriousness/outcomes Among the 1963 eribulin-treated subjects in the Phase 2/3 breast cancer and STS trials, 48 subjects (2.4%) had cardiac TEAEs reported as treatment related, with the majority of the related events being tachycardia (n=20, 1.0%), all of which were Grade 1 or 2. Thirteen subjects (0.7%) had palpitations reported as treatment related, 12 of which were Grade 1 or 2 and one of which was reported to be Grade 3. • Severity and nature of risk Please see above.

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.
Preventability	Patients with cardiovascular impairment are carefully monitored as part of standard medical care.
Impact on the risk-benefit balance of the product:	Routine risk minimization is in place.
Public health impact:	None identified.

Identified Risk: Disseminated intravascular coagulation	
Potential mechanisms:	Patients with cancer are in a hypercoagulable state. The pathophysiology of DIC is complex including a combination of impaired coagulation inhibitor systems, defective fibrinolysis and inflammatory activation, Sepsis is a trigger. Expression of tissue factor by cancer cells is thought to play an important role in the pathogenesis of DIC in patients with malignancy (Kusuma et al, 2009). A specific and direct mechanism by which eribulin would cause DIC is not known. Eribulin causes neutropenia which may predispose to sepsis and hence DIC.
Evidence source(s) and strength of evidence:	Post-marketing data
Characterisation of the risk:	• Frequency The frequency calculation for inclusion in the SmPC defined the event as 'rare' based on post-marketing data. The true frequency is unknown. Using the required frequency calculation method prescribed by the EMA , the frequency calculation is based on the total of five events reported (3 reports from the HAL01S post-marketing observation study and two spontaneous reports). The event has not been reported from controlled clinical trials. The frequency is therefore 'rare' derived using the standard calculation whereby the upper limit of the 95% confidence interval is not higher 3/X with X representing the total sample size across all relevant clinical trials and studies i.e. from the number exposed at the datalock point for PSUR 4 (14 November 2012) 4091]. Therefore 3/4091 = 0.001 = "rare" (rare >1/10,000 to < 1/1,000). • Seriousness/outcomes Important identified risk added at the request of medical assessor (PAR3), post datalock for this RMP. Identification based on 3 reports from the HAL01S post-marketing observational study run routinely as part of standard post-marketing activity in Japan, and two spontaneous events. Of note two events were mentioned in the reporter's narrative but not submitted as adverse events; multiple contributing factors including underlying malignancy, infection, blood transfusion etc. • Severity and nature of risk No clinical trial reports have been received at the time of writing. One spontaneous event of DIC was reported in association with sepsis, tumour lysis syndrome, neutropenia and leucopenia; the patient died. The second reported event was reported in association with febrile neutropenia, leucopenia and stomatitis.

Risk factors and risk groups:	Malignancy and sepsis are key risk factors for DIC.
Preventability	Appropriate clinical management of the underlying cancer including attention to coagulation status and of drug-induced neutropenia and any consequent sepsis as routine standard of care. Advice on dose reduction if neutropenia occurs is already included in the labeling.
Impact on the risk-benefit balance of the product:	Routine risk minimization is in place. DIC is considered unlikely to have significant impact on the risk-benefit profile of the product.
Public health impact:	None identified

Important Potential Risk: Adverse pregnancy outcomes	
Potential mechanisms:	Drug-related testicular toxicity that did not completely resolve during the postdosing recovery period has been observed in rats and dogs All anti-proliferative agents have the potential for teratogenicity, due to the nature of the mechanism of action.
Evidence source(s) and strength of evidence:	Pre-clinical data
Characterisation of the risk:	• Frequency No pregnancies have occurred during the use of eribulin. • Seriousness/outcomes No pregnancies have occurred during the use of eribulin. • Severity and nature of risk No pregnancies have occurred during the use of eribulin.
Risk factors and risk groups:	Fertile men and women of child bearing potential are advised to take adequate precautions.
Preventability	Foetal toxicity is likely to be linked with the anti-proliferative effect of the drug, therefore, women of childbearing age must be advised to avoid becoming pregnant whilst they or their male partner are receiving eribulin and should use effective contraception.
Impact on the risk-benefit balance of the product:	Routine risk minimization is in place. Further characterization is unlikely to have a significant impact on the risk-benefit balance of the product.
Public health impact:	None identified.

Important Potential Risk: Male infertility	
Potential mechanisms:	All cytotoxic agents have the potential for infertility, due to the nature of the mechanism of action.
Evidence source(s) and strength of evidence:	Pre-clinical data

Characterisation of the risk:	• Frequency No information available • Seriousness/outcomes • No information available Severity and nature of risk No information available
Risk factors and risk groups:	Men considering therapy with eribulin are advised to take adequate precautions.
Preventability	Due to teratogenic potential of eribulin male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with eribulin.
Impact on the risk-benefit balance of the product:	Routine risk minimization is in place. Male infertility is considered unlikely to have significant impact to the risk-benefit profile of the product.
Public health impact:	None identified

Important Potential Risk: Gastrointestinal perforation	
Potential mechanisms:	The clinical trial cases described were not considered to be drug-related by the MAH.
Evidence source(s) and strength of evidence:	Clinical trials in advanced bladder cancer (n=2 exposed to drug) and breast cancer (n=1 exposed to drug)
Characterisation of the risk:	• Frequency Frequency in approved breast cancer population unknown at this time. At the time of addition as an important potential risk, three events of GI perforation occurred in patients who had received Halaven in clinical trials. Two male patients were enrolled in an advanced bladder cancer study receiving concurrent chemotherapy with gemcitabine and cisplatin; the perforations were attributed to complications of their underlying disease (perforation into a malignancy/ prior abdominal surgery with clip placement). The third patient was a female subject with advanced breast cancer in whom the perforation was attributed to prior (non-cancer-related) abdominal surgery. • Seriousness/outcomes Potential risk added at the request of medical assessor (PAR3, post datalock). Gastrointestinal perforation may be fatal. • Severity and nature of risk Two events identified in individuals receiving treatment for advanced bladder cancer with underlying risk factors. One additional report in the safety database for a patient with breast cancer and prior abdominal surgery. Risk unquantifiable in the approved breast cancer population at this time.
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.
Preventability	To maintain a high index of suspicion for early signs and symptoms of mechanical intestinal obstruction following surgery, radiotherapy or adjacent tumour invasion in such a population.

Impact on the risk-benefit balance of the product:	No information is available
Public health impact:	None identified

SVII.3.2. Presentation of the missing information

Not applicable.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 15 Summary of Safety Concerns	
Important identified risks	• Tachycardia • Disseminated intravascular coagulation
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal perforation

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

For all safety concerns routine pharmacovigilance is conducted. There are no modifications or additional routine pharmacovigilance activities for eribulin.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are ongoing or planned.

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

V.1. Routine Risk Minimisation Measures

Table 16 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Identified Risk:	
Tachycardia	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Information on incidence of tachycardia Other routine risk minimisation measures beyond the Product Information: • None • Characterisation and confirmation of consistency with current safety profile
Disseminated intravascular coagulation	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities to address risk: • Information on occurrence of DIC Other routine risk minimisation measures beyond the Product Information: • None.
Potential risks	
Adverse pregnancy outcomes	Routine risk communication: • SmPC section 4.6 • PL section 4 Routine risk minimisation activities to address risk: • Warning to avoid eribulin in pregnancy unless benefit outweighs the risks Other routine risk minimisation measures beyond the Product Information: • None
Male infertility	Routine risk communication:

	• SmPC section 4.6 • PL section 2 Routine risk minimisation activities to address risk: • Information on testicular toxicity and advice to male patients to conserve sperm prior to treatment Other routine risk minimisation measures beyond the Product Information: • None
Gastrointestinal perforation	• None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Identified Risks		
Tachycardia	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4	Additional pharmacovigilance activities: None
Disseminated intravascular coagulation	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4	Additional pharmacovigilance activities: None
Potential Risks		
Adverse pregnancy outcomes	Routine risk minimisation measures: • SmPC section 4.6 • Warning to avoid eribulin in pregnancy unless benefit outweighs the risks	Additional pharmacovigilance activities: None.
Male infertility	Routine risk minimisation measures: • SmPC Sections 4.6 provides information on testicular toxicity and advice to male patients to conserve sperm prior to treatment • PL section 4	Additional pharmacovigilance activities: None.

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Gastrointestinal perforation	• None	Additional pharmacovigilance activities: None.

PART VI: 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	• 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: 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
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

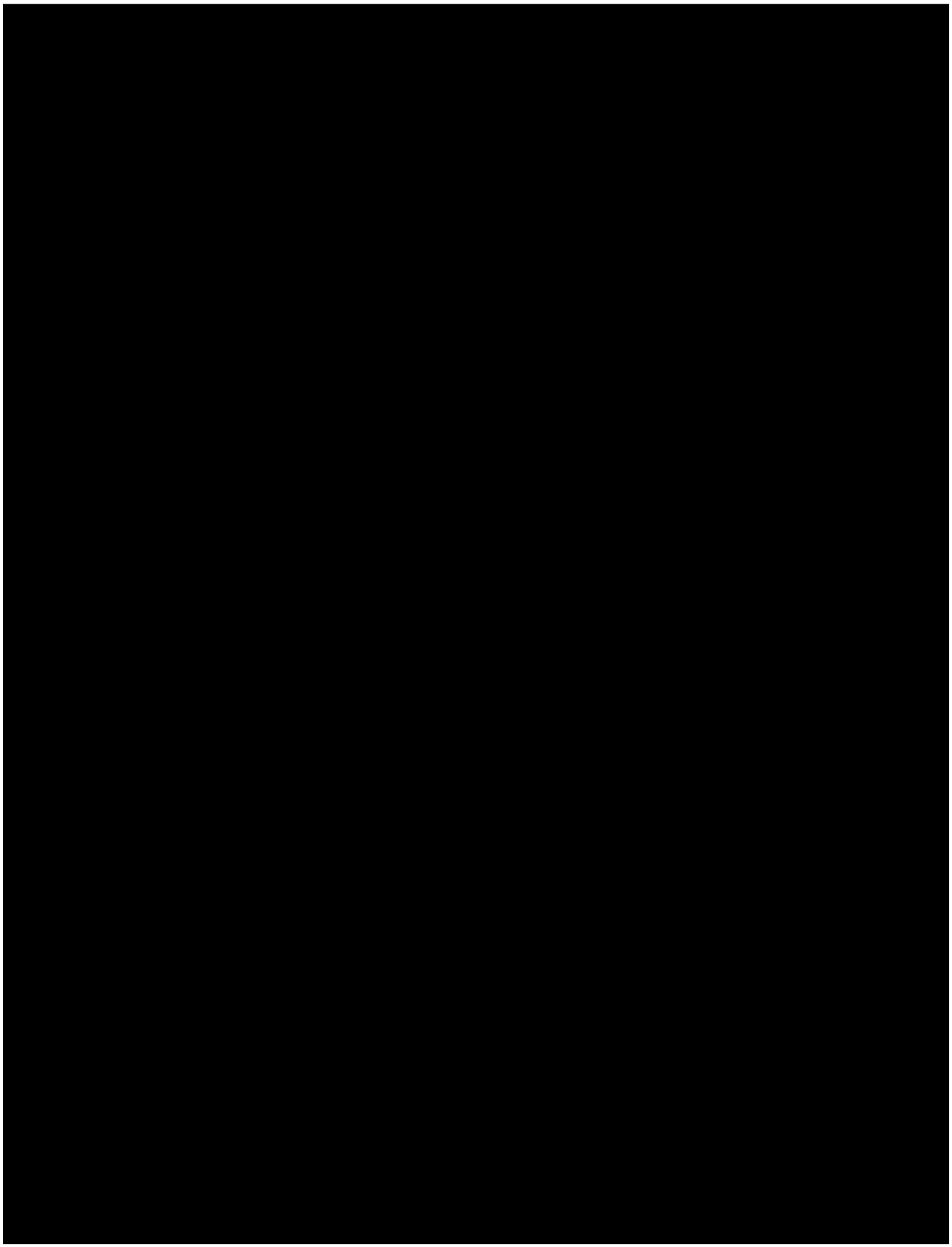
II.C.1 Studies which are conditions of the marketing authorisation

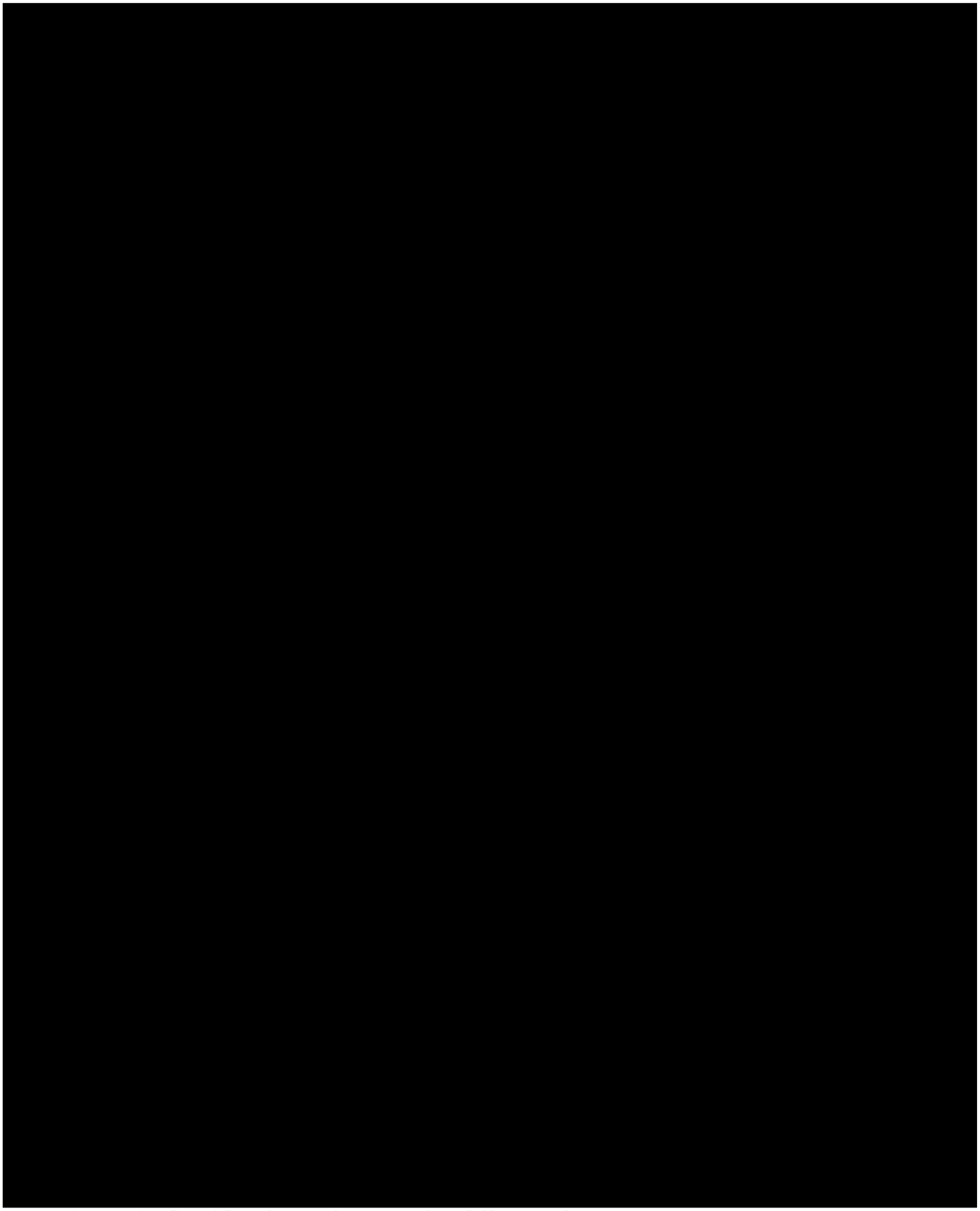
There are no studies which are conditions of the marketing authorisation or specific obligation of Halaven.

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

There are no other studies that are conditions of the marketing authorisation or specific obligation of Halaven.

PART VII: ANNEXES





Annex 4 – Specific adverse drug reaction follow-up forms

Not Applicable

[redacted]

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

Not Applicable

[redacted]