ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains eribulin mesilate equivalent to 0.44 mg eribulin.
Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HALAVEN is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). 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.

HALAVEN 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 (see section 5.1).

4.2 Posology and method of administration

HALAVEN should only be prescribed by a qualified physician experienced in the appropriate use of anti-cancer therapy. It should be administered by an appropriately qualified healthcare professional only.

Posology

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

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

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

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

Dose delays during therapy

The administration of HALAVEN should be delayed on Day 1 or Day 8 for any of the following:
- Absolute neutrophil count (ANC) < 1 x 10^9/l
- Platelets < 75 x 10^9/l
- Grade 3 or 4 non-hematological toxicities.

Dose reduction during therapy

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

Dose reduction recommendations

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

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

Patients with hepatic impairment

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

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

Patients with renal impairment

Some patients with moderately or severely impaired renal function (creatinine clearance <50 ml/min) may have increased eribulin exposure and may need a reduction of the dose. For all patients with renal impairment, caution and close safety monitoring is advised. (See section 5.2)

Elderly patients

No specific dose adjustments are recommended based on the age of the patient (see section 4.8).

Paediatric population

There is no relevant use of HALAVEN in children and adolescents for the indication of breast cancer.

There is no relevant use of HALAVEN in the paediatric population for the indication of soft tissue sarcoma (see section 5.1).

Method of administration

HALAVEN is for intravenous use. The dose may be diluted in up to 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. It should not be diluted in glucose 5% infusion solution. For instructions on the dilution of the medicinal product before administration, see section 6.6. Good peripheral venous access, or a patent central line, should be ensured prior to administration. There is no evidence that eribulin mesilate is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic. For information relevant to the handling of cytotoxic medicinal products see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Breast-feeding

4.4 Special warnings and precautions for use

Haematology

Myelosuppression is dose dependent and primarily manifested as neutropenia (section 4.8). Monitoring of complete blood counts should be performed on all patients prior to each dose of eribulin. Treatment with eribulin should only be initiated in patients with ANC values $\geq 1.5 \times 10^9$/l and platelets $> 100 \times 10^9$/l.

Febrile neutropenia occurred in < 5% of patients treated with eribulin. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommendations in section 4.2.

Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (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.

Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported.

Severe neutropenia may be managed by the use of granulocyte colony-stimulating factor (G-CSF) or equivalent at the physician's discretion in accordance with relevant guidelines (see section 5.1).

Peripheral neuropathy

Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose (see section 4.2)

In clinical trials, patients with pre-existing neuropathy greater than Grade 2 were excluded. However, patients with pre-existing neuropathy Grade 1 or 2 were no more likely to develop new or worsening symptoms than those who entered the study without the condition.

QT prolongation

In an uncontrolled open-label ECG study in 26 patients, 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 or concomitant treatment with medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalaemia, hypocalcaemia or hypomagnesaemia should be corrected prior to initiating HALAVEN and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

Excipients

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction

Eribulin is mainly (up to 70%) eliminated through biliary excretion. The transport protein involved in this process is unknown. Eribulin is not a substrate of breast cancer resistance protein (BCRP), organic anion (OAT1, OAT3, OATP1B1, OATP1B3), multi-drug resistance-associated protein (MRP2, MRP4) and bile salt export pump (BSEP) transporters.

No drug-drug interactions are expected with CYP3A4 inhibitors and inducers. Eribulin exposure (AUC and C_{max}) was unaffected by ketoconazole, a CYP3A4 and P glycoprotein (Pgp) inhibitor, and rifampicin, a CYP3A4 inducer.

Effects of eribulin on the pharmacokinetics of other medicines

In vitro data indicate that eribulin is a mild inhibitor of the important drug metabolising enzyme CYP3A4. No *in vivo* data are available. Caution and monitoring for adverse events is recommended with concomitant use of substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-mediated metabolism (e.g. alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

Eribulin does not inhibit the CYP enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 at relevant clinical concentrations.

At relevant clinical concentrations, eribulin did not inhibit BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3 transporter-mediated activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats. 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.

Women of childbearing potential must be advised to avoid becoming pregnant whilst they or their male partner are receiving HALAVEN and have to use effective contraception during and up to 3 months after treatment.

Breast-feeding

It is unknown whether eribulin/metabolites are excreted in human or animal breast milk. A risk to newborns/infants cannot be excluded and therefore HALAVEN must not be used during breast-feeding (see section 4.3).

Fertility

Testicular toxicity has been observed in rats and dogs (see section 5.3). Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with HALAVEN.

4.7 Effects on ability to drive and use machines

HALAVEN may cause adverse reactions such as tiredness and dizziness which may lead to minor or moderate influence on the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions related to HALAVEN, are bone marrow suppression manifested as neutropenia, leucopenia, anaemia, thrombocytopenia with associated infections. New onset or worsening of pre-existing peripheral neuropathy has also been reported. Gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, and stomatitis are among reported undesirable effects. Other undesirable effects include fatigue, alopecia, increased liver enzymes, sepsis and musculoskeletal pain syndrome.

Tabulated list of adverse reactions

Unless otherwise noted, the table shows the incidence rates of adverse reactions observed in breast cancer and soft tissue sarcoma patients who received the recommended dose in Phase 2 and Phase 3 studies.

Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).
Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Where Grade 3 or 4 reactions occurred, the actual total frequency and the frequency of Grade 3 or 4 reactions are given.

System Organ Class	**Adverse Reactions – all Grades**			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare or not known**
Infections and infestations		Urinary tract infection (8.5%) (G3/4: 0.7%) Pneumonia (1.6%) (G3/4: 1.0%) Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis Herpes zoster	Sepsis (0.5%) (G3/4: 0.5%)[a] Neutropenic sepsis (0.2%) (G3/4: 0.2%)[a] Septic Shock (0.2%) (G3/4:0.2%)[a]	
Blood and lymphatic system disorders	Neutropenia (53.6%) (G3/4: 46.0%) Leukopenia (27.9%) (G3/4: 17.0%) Anaemia (21.8%) (G3/4: 3.0%)	Lymphopenia (5.7%) (G3/4: 2.1%) Febrile neutropenia (4.5%) (G3/4: 4.4%)[a] Thrombocytopenia (4.2%) (G3/4: 0.7%)		[*]Disseminated intravascular coagulation[b]

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare or not known**
Metabolism and nutrition disorders	Decreased appetite (22.5%) (G3/4: 0.7%)[d]	Hypokalaemia (6.8%) (G3/4: 2.0%) Hypomagnesaemia (2.8%) (G3/4: 0.3%) Dehydration (2.8 %) (G3/4: 0.5%)[d] Hyperglycaemia Hypophosphataemia Hypocalcaemia		
Psychiatric disorders		Insomnia Depression		
Nervous system disorders	Peripheral neuropathy[c] (35.9%) (G3/4: 7.3%) Headache (17.5%) (G3/4: 0.7%)	Dysgeusia Dizziness (9.0%) (G3/4: 0.4%)[d] Hypoaesthesia Lethargy Neurotoxicity		
Eye disorders		Lacrimation increased (5.8%) (G3/4: 0.1%)[d] Conjunctivitis		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders		Tachycardia		
Vascular disorders		Hot flush Pulmonary embolism (1.3%) (G3/4: 1.1%)[a]	Deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (15.2%)[a] (G3/4: 3.5%)[a] Cough (15.0%) (G3/4: 0.5%)[d]	Oropharyngeal pain Epistaxis Rhinorrhoea	Interstitial lung disease (0.2%) (G3/4: 0.1%)	
Gastrointestinal disorders	Nausea (35.7%) (G3/4: 1.1%)[d] Constipation (22.3%) (G3/4: 0.7%)[d] Diarrhoea (18.7%) (G3/4: 0.8%) Vomiting (18.1%) (G3/4: 1.0%)	Abdominal pain Stomatitis (11.1%) (G3/4: 1.0%)[d] Dry mouth Dyspepsia (6.5%) (G3/4: 0.3%)[d] Gastrooesophageal reflux disease Abdominal distension	Mouth ulceration Pancreatitis	
Hepatobiliary disorders		Aspartate aminotransferase increased (7.7%) (G3/4: 1.4%)[d] Alanine aminotransferase increased (7.6%) (G3/4: 1.9%)[d] Gamma glutamyl transferase increased (1.7%) (G3/4: 0.9%)[d] Hyperbilirubinaemia (1.4%) (G3/4: 0.4%)	Hepatotoxicity (0.8%) (G3/4: 0.6%)	

System Organ Class	Adverse Reactions – all Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare or not known**
Skin and subcutaneous tissue disorders	Alopecia	Rash (4.9%) (G3/4: 0.1%) Pruritus (3.9%) (G3/4: 0.1%)[d] Nail disorder Night sweats Dry skin Erythema Hyperhidrosis Palmar plantar erythrodysaesthesia (1.0%) (G3/4: 0.1%)[d]	Angioedema	[**]Stevens-Johnson syndrome/ Toxic epidermal necrolysis[b]
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia (20.4%) (G3/4: 1.0%) Back pain (12.8%) (G3/4: 1.5%) Pain in extremity (10.0%) (G3/4: 0.7%)[d]	Bone pain (6.7%) (G3/4: 1.2%) Muscle spasms (5.3%) (G3/4: 0.1%)[d] Musculoskeletal pain Musculoskeletal chest pain Muscular weakness		
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure	
General disorders and administration site conditions	Fatigue/Asthenia (53.2%) (G3/4 : 7.7%) Pyrexia (21.8%) (G3/4: 0.7%)	Mucosal Inflammation (6.4%) (G3/4: 0.9%)[d] Peripheral oedema Pain Chills Chest pain Influenza like illness		
Investigations	Weight decreased (11.4%) (G3/4: 0.4%)[d]			

[a] Includes Grade 5 events.
[b] From spontaneous reporting
[c] Includes preferred terms of peripheral neuropathy, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy, peripheral sensorimotor neuropathy and demyelinating polyneuropathy
[d] No Grade 4 events
[*] Rare
[**] Frequency not known

Overall, the safety profiles in the breast cancer and soft tissue sarcoma patient populations were similar.

Description of selected adverse reactions

Neutropenia
The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 x 10^9/l) was 8 days.
Neutrophil counts of < 0.5 x 10^9/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin in the EMBRACE study.
Neutropenia was reported as a Treatment Emergent Adverse Event (TEAE) in 151/404 (37.4% for all grades) in the sarcoma population, compared with 902/1559 (57.9% for all grades) in the breast cancer population. The combined grouped TEAE and neutrophil laboratory abnormality frequencies were

307/404 (76.0%) and 1314/1559 (84.3%), respectively. The median duration of treatment was 12.0 weeks for sarcoma patients and 15.9 weeks for breast cancer patients.
Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported. Out of 1963 breast cancer and soft tissue sarcoma patients who received eribulin at the recommended dose in clinical trials there was one fatal event each of neutropenic sepsis (0.1%) and febrile neutropenia (0.1%). In addition there were 3 fatal events of sepsis (0.2%) and one of septic shock (0.1%).
Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% and 13% of eribulin treated patients received G-CSF in the two phase 3 breast cancer studies (Studies 305 and 301, respectively). In the phase 3 sarcoma study (Study 309), 26% of the eribulin treated patients received G-CSF.
Neutropenia resulted in discontinuation in < 1% of patients receiving eribulin.

Disseminated intravascular coagulation
Cases of disseminated intravascular coagulation have been reported, typically in association with neutropenia and/or sepsis.

Peripheral neuropathy
In the 1559 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with eribulin was peripheral neuropathy (3.4%). The median time to Grade 2 peripheral neuropathy was 12.6 weeks (post 4 cycles). Out of the 404 sarcoma patients, 2 patients discontinued treatment with eribulin due to peripheral neuropathy. The median time to Grade 2 peripheral neuropathy was 18.4 weeks.
Development of Grade 3 or 4 peripheral neuropathy occurred in 7.4% of breast cancer patients and 3.5% of sarcoma patients. In clinical trials, patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition.
In breast cancer patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 14%.

Hepatotoxicity
In some patients with normal/abnormal liver enzymes prior treatment with eribulin, increased levels of liver enzymes have been reported with initiation of eribulin treatment. Such elevations appeared to have occurred early with eribulin treatment in cycle 1 – 2 for the majority of these patients and whilst thought likely to be a phenomenon of adaptation to eribulin treatment by the liver and not a sign of significant liver toxicity in most patients, hepatotoxicity has also been reported.

Special populations

Elderly population
Of the 1559 breast cancer patients treated with the recommended dose of eribulin, 283 patients (18.2%) were ≥ 65 years of age. In the 404 sarcoma patient population, 90 patients (22.3%) treated with eribulin 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.

Patients with hepatic impairment
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 (see also sections 4.2 and 5.2).

Paediatric population

Three open-label studies, Studies 113, 213 and 223, were conducted in paediatric patients with refractory or recurrent solid tumours and lymphomas, but excluding central nervous system (CNS) tumours (see section 5.1).

The safety of eribulin monotherapy was evaluated in 43 paediatric patients who received up to 1.58 mg/m^2 on Days 1 and 8 of a 21-day cycle (Studies 113 and 223). The safety of eribulin in

combination with irinotecan was also evaluated in 40 paediatric patients who received eribulin 1.23 mg/m^2 on Days 1 and 8 and irinotecan 20 or 40 mg/m^2 on Days 1 to 5 of a 21-day cycle, or 100 or 125 mg/m^2 on Days 1 and 8 of a 21-day cycle (Study 213).

In Study 113 (Phase 1), the most frequently reported adverse drug reactions were white blood cell count decreased, lymphocyte count decreased, anaemia and neutrophil count decreased.

In Study 213 (Phase 1/2), the most frequently reported adverse drug reactions were neutropenia (Phase 1) and diarrhoea and neutrophil count decreased (Phase 2).

In Study 223 (Phase 2), the most frequently reported adverse drug reactions were neutrophil count decreased, anaemia, and white blood cell count decreased.

The safety profile of eribulin as monotherapy or in combination with irinotecan hydrochloride in this paediatric population was consistent with the known safety profile of either study drug in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In one case of overdose the patient inadvertently received 7.6 mg of eribulin (approximately 4 times the planned dose) and subsequently developed a hypersensitivity reaction (Grade 3) on Day 3 and neutropenia (Grade 3) on Day 7. Both adverse reactions resolved with supportive care.

There is no known antidote for eribulin overdose. In the event of an overdose, the patient should be closely monitored. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX41

Eribulin mesilate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage.

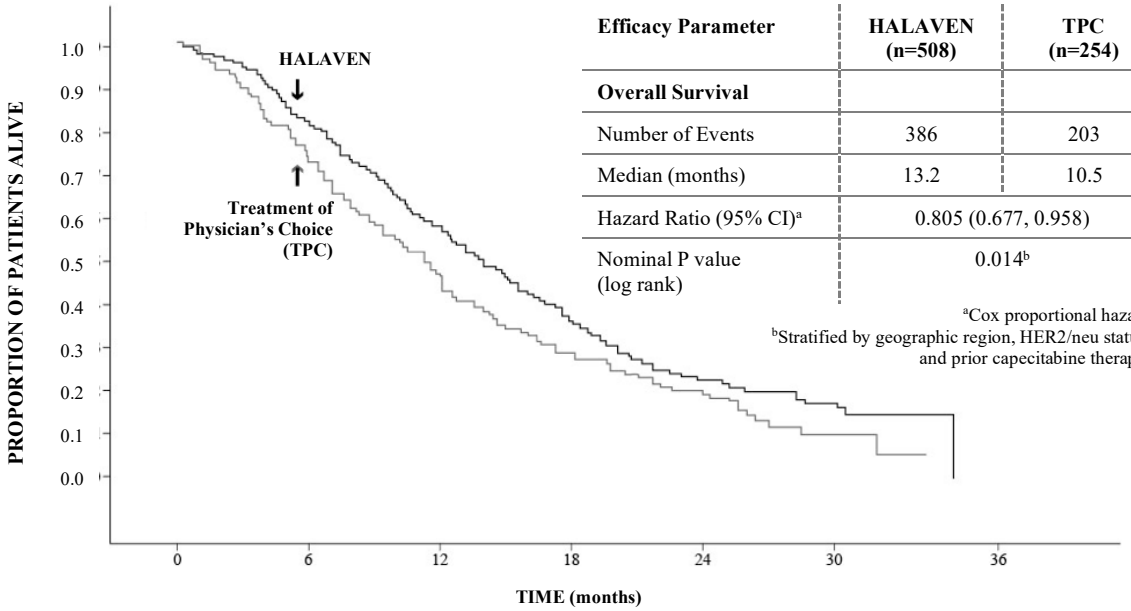
Clinical efficacy

Breast cancer

The efficacy of HALAVEN in breast cancer is primarily supported by two randomized Phase 3 comparative studies.

The 762 patients in the pivotal Phase 3 EMBRACE study (Study 305) had locally recurrent or metastatic breast cancer, and had previously received at least two and a maximum of five chemotherapy regimens, including an anthracycline and a taxane (unless contraindicated). Patients must have progressed within 6 months of their last chemotherapeutic regimen. The HER2 status of the patients was: 16.1% positive, 74.2% negative and 9.7% unknown, whilst 18.9% of patients were triple negative. They were randomized 2:1 to receive either HALAVEN, or treatment of physician's choice (TPC), which consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), or 3% hormonal therapy.
The study met its primary endpoint with an overall survival (OS) result that was statistically significantly better in the eribulin group compared to TPC at 55% of events.
This result was confirmed with an updated overall survival analysis carried out at 77% of events.

Study 305 - Updated Overall Survival (ITT Population)



Efficacy Parameter	HALAVEN (n=508)	TPC (n=254)
Overall Survival		
Number of Events	386	203
Median (months)	13.2	10.5
Hazard Ratio (95% CI)[a]	0.805 (0.677, 0.958)	
Nominal P value (log rank)	0.014[b]	

[a]Cox proportional hazard
[b]Stratified by geographic region, HER2/neu status, and prior capecitabine therapy.

NUMBER OF PATIENTS AT RISK

HALAVEN	508	406	274	142	54	11	0
TPC	254	178	106	61	26	5	0

By independent review, the median progression free survival (PFS) was 3.7 months for eribulin compared to 2.2 months for the TPC arm (HR 0.865, 95% CI: 0.714, 1.048, p=0.137). In response evaluable patients, the objective response rate by the RECIST criteria was 12.2% (95% CI: 9.4%, 15.5%) by independent review for the eribulin arm compared to 4.7% (95% CI: 2.3%, 8.4%) for the TPC arm.

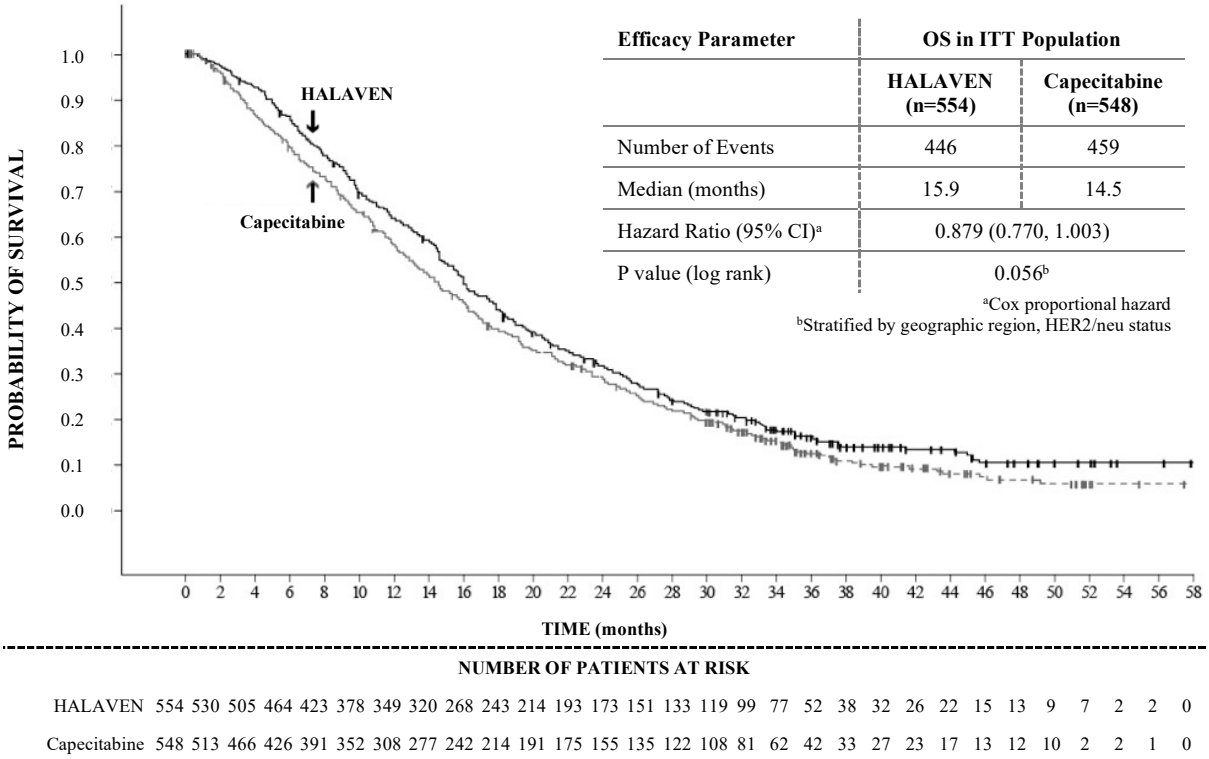
The positive effect on OS was seen in both taxane-refractory and non-refractory groups of patients . In the OS update, the HR for eribulin versus TPC was 0.90 (95% CI: 0.71, 1.14) in favour of eribulin for taxane-refractory patients and 0.73 (95% CI: 0.56, 0.96) for patients not taxane-refractory.

The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The updated OS analysis showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI: 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI: 0.606, 1.233).

The second Phase 3 study in earlier line metastatic breast cancer, Study 301, was an open-label, randomized, study in patients (n=1102) with locally advanced or metastatic breast cancer to investigate the efficacy of HALAVEN monotherapy compared to capecitabine monotherapy in terms of OS and PFS as co-primary endpoint. Patients had previously received up to three prior chemotherapy regimens, including both an anthracycline and a taxane and a maximum of two for

advanced disease, with the percentage who had received 0, 1 or 2 prior chemotherapy treatments for metastatic breast cancer being 20.0%, 52.0% or 27.2% respectively. The HER2 status of the patients was: 15.3% positive, 68.5% negative and 16.2% unknown, whilst 25.8% of patients were triple negative.

Study 301 - Overall Survival (ITT Population)



Efficacy Parameter	OS in ITT Population	
	HALAVEN (n=554)	Capecitabine (n=548)
Number of Events	446	459
Median (months)	15.9	14.5
Hazard Ratio (95% CI)[a]	0.879 (0.770, 1.003)	
P value (log rank)	0.056[b]	

[a]Cox proportional hazard
[b]Stratified by geographic region, HER2/neu status

NUMBER OF PATIENTS AT RISK

HALAVEN	554	530	505	464	423	378	349	320	268	243	214	193	173	151	133	119	99	77	52	38	32	26	22	15	13	9	7	2	2	0
Capecitabine	548	513	466	426	391	352	308	277	242	214	191	175	155	135	122	108	81	62	42	33	27	23	17	13	12	10	2	2	1	0

Progression free survival assessed by independent review was similar between eribulin and capecitabine with medians of 4.1 months vs 4.2 months (HR 1.08; [95% CI: 0.932, 1.250]) respectively. Objective response rate as assessed by independent review was also similar between eribulin and capecitabine; 11.0% (95% CI: 8.5, 13.9) in the eribulin group and 11.5% (95% CI: 8.9, 14.5) in the capecitabine group.

The overall survival in patients in HER2 negative and HER2 positive patients in the eribulin and control groups in Study 305 and Study 301 is shown below:

Efficacy Parameter	Study 305 Updated Overall Survival ITT Population			
	HER2 Negative		HER2 Positive	
	HALAVEN (n = 373)	TPC (n = 192)	HALAVEN (n = 83)	TPC (n = 40)
Number of Events	285	151	66	37
Median months	13.4	10.5	11.8	8.9
Hazard Ratio (95% CI)	0.849 (0.695, 1.036)		0.594 (0.389, 0.907)	
p-value (log rank)	0.106		0.015	

Efficacy Parameter	Study 301 Overall Survival ITT Population			
	HER2 Negative		HER2 Positive	
	HALAVEN (n = 375)	Capecitabine (n = 380)	HALAVEN (n = 86)	Capecitabine (n = 83)
Number of Events	296	316	73	73
Median months	15.9	13.5	14.3	17.1
Hazard Ratio (95% CI)	0.838 (0.715, 0.983)		0.965 (0.688, 1.355)	
p-value (log rank)	0.030		0.837	

Note: Concomitant anti-HER2 therapy was not included in Study 305 and Study 301.

Liposarcoma

In liposarcoma the efficacy of eribulin is supported by the pivotal Phase 3 sarcoma study (Study 309). The patients in this study (n=452) had locally recurrent, inoperable and/or metastatic soft tissue sarcoma of one of two subtypes – leiomyosarcoma or liposarcoma. Patients had received at least two prior chemotherapy regimens, one of which must have been an anthracycline (unless contraindicated).

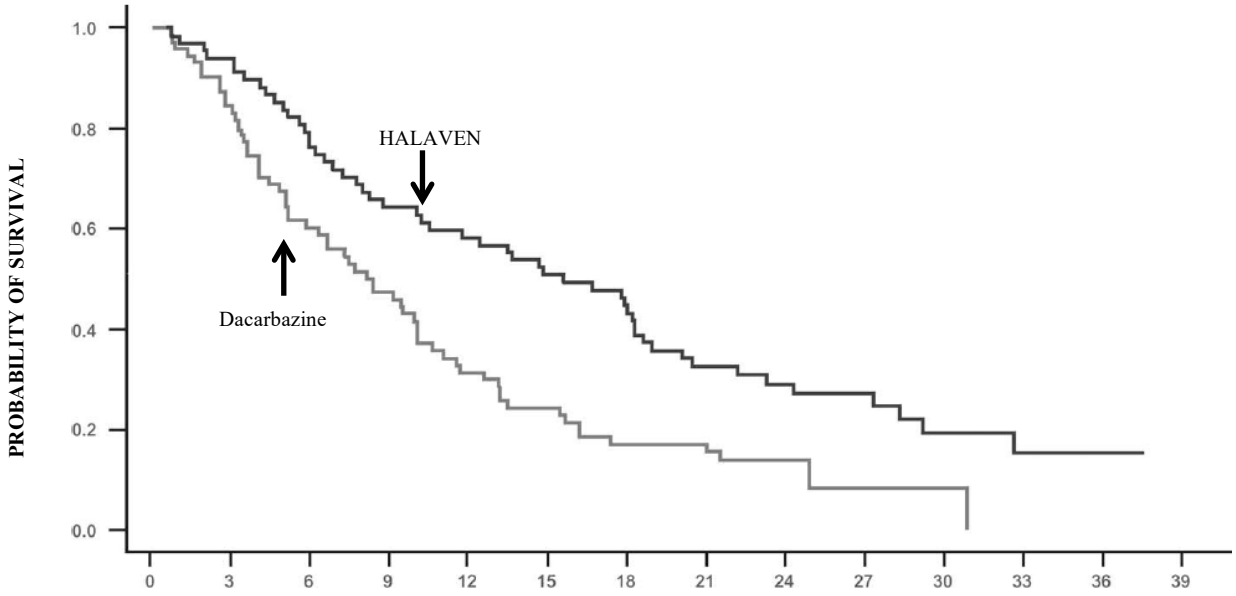
Patients must have progressed within 6 months of their last chemotherapeutic regimen. They were randomized 1:1 to receive either eribulin 1.23 mg/m^2 on days 1 and 8 of a 21 day cycle or dacarbazine 850 mg/m^2, 1000 mg/m^2 or 1200 mg/m^2 (dose determined by the investigator prior to randomization), every 21 days.

In Study 309, a statistically significant improvement in OS was observed in patients randomized to the eribulin arm compared to the control arm. This translated into a 2 month improvement in median OS (13.5 months for eribulin treated patients vs. 11.5 months for dacarbazine treated patients). There was no significant difference in progression-free survival or overall response rate between the treatment arms in the overall population.

Treatment effects of eribulin were limited to patients with liposarcoma (45% dedifferentiated, 37% myxoid/round cell and 18% pleomorphic in Study 309) based on pre-planned subgroup analyses of OS and PFS. There was no difference in efficacy between eribulin and dacarbazine in patients with advanced or metastatic leiomyosarcoma.

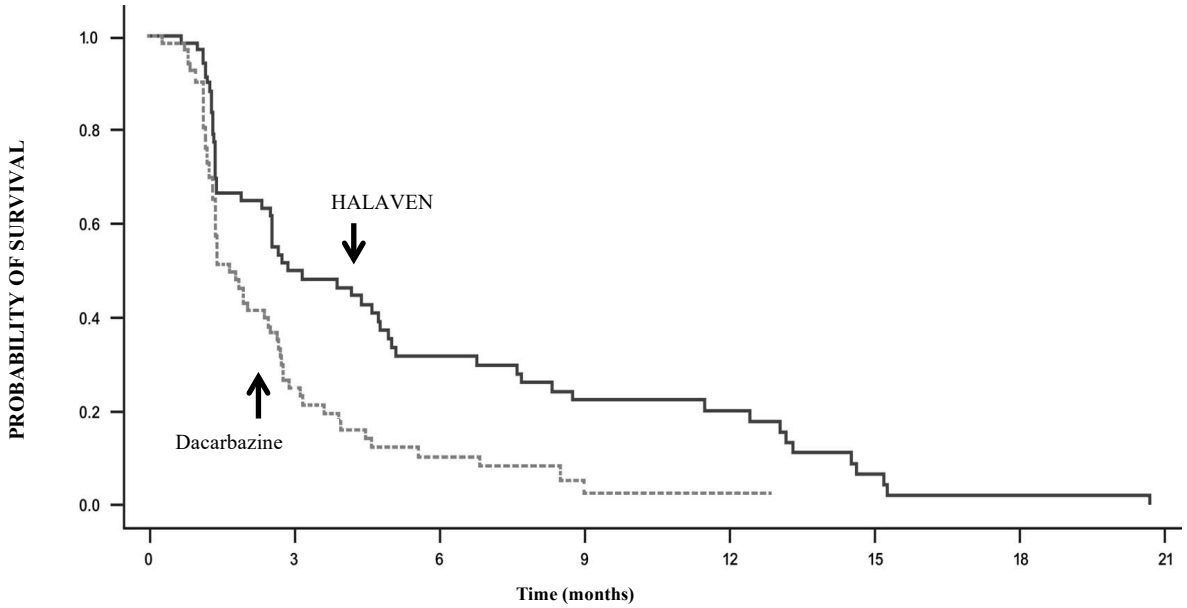
	Study 309 Liposarcoma Subgroup		Study 309 Leiomyosarcoma Subgroup		Study 309 ITT Population	
	HALAVEN (n=71)	Dacarbazine (n=72)	HALAVEN (n=157)	Dacarbazine (n=152)	HALAVEN (n=228)	Dacarbazine (n=224)
Overall survival						
Number of Events	52	63	124	118	176	181
Median months	15.6	8.4	12.7	13.0	13.5	11.5
Hazard Ratio (95% CI)	0.511 (0.346, 0.753)		0.927 (0.714, 1.203)		0.768 (0.618, 0.954)	
Nominal p-value	0.0006		0.5730		0.0169	
Progression-free survival						
Number of Events	57	59	140	129	197	188
Median months	2.9	1.7	2.2	2.6	2.6	2.6
Hazard Ratio (95% CI)	0.521 (0.346, 0.784)		1.072 (0.835, 1.375)		0.877 (0.710, 1.085)	
Nominal p-value	0.0015		0.5848		0.2287	

Study 309 - Overall Survival in the Liposarcoma Subgroup



NUMBER OF PATIENTS AT RISK:														
HALAVEN	71	63	51	43	39	34	30	20	15	12	7	4	2	0
Dacarbazine	72	59	42	33	22	17	12	11	6	3	2	0	0	0

Study 309 – Progression Free Survival in the Liposarcoma Subgroup



NUMBER OF PATIENTS AT RISK:								
HALAVEN	71	28	17	12	9	3	1	0
Dacarbazine	72	15	5	2	1	0	0	0

Paediatric population

Breast Cancer
The European Medicines Agency has waived the obligation to submit the results of studies with eribulin in all subsets of the paediatric population in the indication of breast cancer (see section 4.2 for information on paediatric use).

Soft Tissue Sarcoma

Efficacy of eribulin was assessed but not established in three open-label studies:

Study 113 was a Phase 1, open-label, multicentre, dose-finding study that assessed eribulin in paediatric patients with refractory or recurrent solid tumours and lymphomas but excluding CNS tumours. A total of 22 paediatric patients (age range: 3 to 17 years) were enrolled and treated. The patients were administered eribulin intravenously on Days 1 and 8 of a 21-day cycle at three dose levels (0.97, 1.23 and 1.58 mg/m^2). The maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of eribulin was determined as 1.23 mg/m^2 on Days 1 and 8 of a 21-day cycle.

Study 223 was a Phase 2, open-label, multicentre study that assessed the safety and preliminary activity of eribulin in paediatric patients with refractory or recurrent rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) or Ewing sarcoma (EWS). Twenty-one paediatric patients (age range: 2 to 17 years) were enrolled and treated with eribulin at a dose of 1.23 mg/m^2 intravenously on Days 1 and 8 of a 21-day cycle (the RP2D from Study 113). No patient achieved confirmed partial response (PR) or complete response (CR).

Study 213 was a Phase 1/2, open-label, multicentre study to evaluate the safety and efficacy of eribulin in combination with irinotecan hydrochloride in paediatric patients with relapsed/refractory solid tumours and lymphomas but excluding CNS tumours (Phase 1), and to assess the efficacy of the combination treatment in paediatric patients with relapsed/refractory RMS, NRSTS and EWS (Phase 2). A total of 40 paediatric patients were enrolled and treated in this study. In Phase 1, 13 paediatric patients (age range: 4 to 17 years) were enrolled and treated; the RP2D was determined as eribulin 1.23 mg/m^2 on Days 1 and 8 with irinotecan hydrochloride 40 mg/m^2 on Days 1 to 5 of a 21-day cycle. In Phase 2, 27 paediatric patients (age range: 4 to 17 years) were enrolled and treated at the RP2D. Three patients had confirmed PR (1 patient in each of the RMS, NRSTS, and EWS histology cohorts). The objective response rate (ORR) was 11.1%.

No new safety signals were observed in the three paediatric studies (see section 4.8); however, due to the small patient populations no firm conclusions can be made.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of eribulin are characterized by a rapid distribution phase followed by a prolonged elimination phase, with a mean terminal half-life of approximately 40 h. It has a large volume of distribution (range of means 43 to 114 l/m^2).

Eribulin is weakly bound to plasma proteins. The plasma protein binding of eribulin (100-1000 ng/ml) ranged from 49% to 65% in human plasma.

Biotransformation

Unchanged eribulin was the major circulating species in plasma following administration of ^{14}C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin.

Elimination

Eribulin has a low clearance (range of means 1.16 to 2.42 l/h/m^2). No significant accumulation of eribulin is observed on weekly administration. The pharmacokinetic properties are not dose or time dependent in the range of eribulin doses of 0.22 to 3.53 mg/m^2.

Eribulin is eliminated primarily by biliary excretion. The transport protein involved in the excretion is presently unknown. Preclinical in vitro studies indicate that eribulin is transported by Pgp. However it has been shown that at clinically relevant concentrations eribulin is not a Pgp inhibitor in vitro. Additionally, in vivo, concomitant administration of ketoconazole, a Pgp inhibitor, has no effect on eribulin exposure (AUC and C_{max}). In vitro studies have also indicated that eribulin is not a substrate for OCT1.

After administration of ^{14}C-eribulin to patients, approximately 82% of the dose was eliminated in faeces and 9% in urine indicating that renal clearance is not a significant route of eribulin elimination.

Unchanged eribulin represented most of the total radioactivity in faeces and urine.

Hepatic impairment

A study evaluated the pharmacokinetics of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=4) hepatic impairment due to liver metastases. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 3-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 0.97 mg/m^2 to patients with mild hepatic impairment and 0.62 mg/m^2 to patients with moderate hepatic impairment resulted in a somewhat higher exposure than after a dose of 1.23 mg/m^2 to patients with normal hepatic function. HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C). There is no study in patients with hepatic impairment due to cirrhosis. See section 4.2 for dosage recommendation.

Renal impairment

Increased eribulin exposure was seen in some patients with moderately or severely impaired renal function, with high between-subject variability. The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with normal renal function (Creatinine clearance: ≥ 80 ml/min; n=6), moderate (30-50 ml/min; n=7) or severe (15-<30 ml/min; n=6) renal impairment. Creatinine clearance was estimated with the Cockcroft-Gault formula. A 1.5-fold (90% CI: 0.9-2.5) higher dose-normalised $AUC_{(0\text{-inf})}$ was observed in patients with moderate and severe renal impairment. See section 4.2 for treatment recommendations.

Paediatric population

Eribulin plasma concentrations were collected from 83 paediatric patients (age range: 2 to 17 years), with refractory/relapsed and recurrent solid tumours and lymphomas, who received eribulin in Studies 113, 213 and 223. Eribulin PK in paediatric patients was comparable to adult patients with STS and patients with other types of tumour. Eribulin exposure in paediatric patients was similar to exposure in adult patients. Concomitant irinotecan did not have an effect on eribulin PK in paediatric patients with refractory/relapsed and recurrent solid tumours.

5.3 Preclinical safety data

Eribulin was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test). Eribulin was positive in the mouse lymphoma mutagenesis assay and was clastogenic in the *in vivo* rat micronucleus assay.

No carcinogenicity studies have been conducted with eribulin.

A fertility study was not conducted with eribulin, but based on non-clinical findings in repeated-dose studies where testicular toxicity was observed in both rats (hypocellularity of seminiferous epithelium with hypospermia/aspermia) and dogs, male fertility may be compromised by treatment with eribulin. An embryofoetal development study in rat confirmed the developmental toxicity and teratogenic potential of eribulin. Pregnant rats were treated with eribulin mesilate equivalent to 0.009, 0.027, 0.088 and 0.133 mg/kg eribulin at gestation days 8, 10 and 12. Dose related increased number of resorptions and decreased foetal weight were observed at doses ≥ 0.088 mg/kg and increased incidence of malformations (absence of lower jaw, tongue, stomach and spleen) was recorded at 0.133 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol anhydrous
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

5 years.

In-use shelf life
From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability of HALAVEN as an undiluted solution in a syringe has been demonstrated for up to 4 hours at 15-25°C and ambient lighting or up to 24 hours at 2°C - 8°C.

Chemical and physical in-use stability of HALAVEN as a diluted solution (0.018 mg/mL to 0.18 mg/mL eribulin in sodium chloride 9 mg/mL (0.9%) has been demonstrated for up to 72 hours at 2°C - 8°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 2 ml of solution.

The pack sizes are cartons of 1 or 6 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

HALAVEN is a cytotoxic anticancer medicinal product and, as with other toxic compounds, caution should be exercised in its handling. The use of gloves, goggles, and protective clothing is recommended. If the skin comes into contact with the solution it should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. HALAVEN should only be prepared and administered by personnel appropriately trained in handling of cytotoxic agents. Pregnant staff should not handle HALAVEN.

Using aseptic technique HALAVEN can be diluted up to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose. It must not be mixed with other medicinal products and should not be diluted in glucose 5% infusion solution.

If using a spike to administer the product refer to the instructions provided from the device manufacturer. HALAVEN vials have a 13mm stopper. The device selected should be compatible with small vial stoppers.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/678/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 March 2011
Date of latest renewal: 19 November 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton 2ml vial

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/ml solution for injection
Eribulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin

3. LIST OF EXCIPIENTS

Ethanol anhydrous, Water for injections,Hydrochloric acid, Sodium hydroxide
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial of 2 ml
6 vials of 2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/678/001 1 vial
EU/1/11/678/002 6 vials

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 2 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HALAVEN 0.44 mg/ml injection
Eribulin
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 0.88 mg eribulin in 2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

HALAVEN 0.44 mg/ml solution for injection
eribulin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What HALAVEN is and what it is used for

HALAVEN contains the active substance eribulin and is an anti-cancer medicine which works by stopping the growth and spread of cancer cells.

It is used in adults for locally advanced or metastatic breast cancer (breast cancer that has spread beyond the original tumour) when at least one other therapy has been tried but has lost its effect.

It is also used in adults for advanced or metastatic liposarcoma (a type of cancer that arises from fat tissue) when previous therapy has been tried but has lost its effect.

2. What you need to know before you use HALAVEN

Do not use HALAVEN:
- if you are allergic to eribulin mesilate or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding

Warnings and precautions
Talk to your doctor or nurse before using HALAVEN:
- if you have liver problems
- if you have a fever or an infection
- if you experience numbness, tingling, prickling sensations, sensitivity to touch or muscle weakness
- if you have heart problems

If any of these affects you, tell your doctor who may wish to stop treatment or reduce the dose.

Children and adolescents

Do not give this medicine to children between the ages of 0 to 18 years because it does not work.

Other medicines and HALAVEN

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility
HALAVEN may cause serious birth defects and should not be used if you are pregnant unless it is thought clearly necessary after carefully considering all the risk to you and the baby. It may also cause future permanent fertility problems in men if they take it and they should discuss this with their doctor before starting treatment. Women of childbearing age should use effective contraception during and up to 3 months after treatment with HALAVEN.

HALAVEN must not be used during breast-feeding because of the possibility of risk to the child.

Driving and using machines
HALAVEN may cause side effects such as tiredness (very common) and dizziness (common). Do not drive or use machines if you feel tired or dizzy.

HALAVEN contains ethanol (alcohol)
This medicine contains small amounts of ethanol (alcohol), less than 100 mg in a vial.

3. How to use HALAVEN

HALAVEN will be given to you by a qualified healthcare professional as an injection into a vein, over a period of 2 to 5 minutes. The dose you will receive is based on your body surface area (expressed in squared metres, or m^2) which is calculated from your weight and height. The usual dose of HALAVEN is 1.23 mg/m^2, but this may be adjusted by your doctor based on your blood test results or other factors. To ensure that the whole dose of HALAVEN is given it is recommended that a saline solution is flushed into the vein after HALAVEN is given.

How often will you be given HALAVEN?
HALAVEN is usually given on Days 1 and 8 of every 21-day cycle. Your doctor will determine how many cycles of treatment you should receive. Depending on the results of your blood tests, the doctor may need to delay administration of the medicine until the blood tests return to normal. The doctor may also then decide to reduce the dose you are given.

If you have any further questions about the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following serious symptoms, stop taking HALAVEN and seek medical attention straightaway:

- Fever, with a racing heart beat, rapid shallow breathing, cold, pale, clammy or mottled skin and/or confusion. These may be signs of a condition called sepsis – a severe and serious reaction to an infection. Sepsis is uncommon (may affect up to 1 in 100 people) and can be life-threatening and may result in death.
- Any difficulty breathing, or swelling of your face, mouth, tongue or throat. These could be signs of an uncommon allergic reaction (may affect up to 1 in 100 people).
- Serious skin rashes with blistering of the skin, mouth, eyes and genitals. These may be signs of a condition called Stevens-Johnson syndrome/toxic epidermal necrolysis. The frequency of this condition is not known but it can be life-threatening.

Other side effects:

Very common side effects (may affect more than 1 in 10 people) are:

- Decrease in the number of white blood cells or red blood cells
- Tiredness or weakness
- Nausea, vomiting, constipation, diarrhoea
- Numbness, tingling or prickling sensations
- Fever
- Loss of appetite, weight loss
- Difficulty breathing, cough
- Pain in the joints, muscles and back
- Headache
- Hair loss

Common side effects (may affect up to 1 in 10 people) are:

- Decrease in the number of platelets (which may result in bruising or taking longer to stop bleeding)
- Infection with fever, pneumonia, chills
- Fast heart rate, flushing
- Vertigo, dizziness
- Increased production of tears, conjunctivitis (redness and soreness of the surface of the eye), nosebleed
- Dehydration, dry mouth, cold sores, oral thrush, indigestion, heartburn, abdominal pain or swelling
- Swelling of soft tissues, pains (in particular chest, back and bone pain), muscle spasm or weakness
- Mouth, respiratory and urinary tract infections, painful urination
- Sore throat, sore or runny nose, flu-like symptoms, throat pain
- Liver function test abnormalities, altered level of sugar, bilirubin, phosphates, potassium, magnesium or calcium in the blood
- Inability to sleep, depression, changed sense of taste
- Rash, itching, nail problems, dry or red skin
- Excessive sweating (including night sweats)
- Ringing in the ears
- Blood clots in the lungs
- Shingles
- Swelling of the skin and numbness of the hands and feet

Uncommon side effects (may affect up to 1 in 100 people) are:

- Blood clots
- Abnormal liver function tests (hepatoxicity)
- Kidney failure, blood or protein in the urine
- Widespread inflammation of the lungs which may lead to scarring
- Inflammation of the pancreas
- Mouth ulcers

Rare side effects (may affect up to 1 in 1000 people) are:

- A serious disorder of blood clotting resulting in the widespread formation of blood clots and internal bleeding.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store HALAVEN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

If HALAVEN is diluted for infusion, the diluted solution should be used immediately. If not used immediately the diluted solution should be stored at 2- 8°C for no longer than 72 hours.

If HALAVEN as an undiluted solution has been transferred into a syringe, it should be stored at 15-25°C and ambient lighting for no longer than 4 hours, or at 2- 8°C for no longer than 24 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What HALAVEN contains

- The active substance is eribulin. Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin.
- The other ingredients are ethanol and water for injections, with hydrochloric acid and sodium hydroxide possibly present in very small amounts.

What HALAVEN looks like and contents of the pack

HALAVEN is a clear, colourless aqueous solution for injection provided in glass vials containing 2 ml of solution. Each carton contains either 1 or 6 vials.

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