1. NAME OF THE MEDICINAL PRODUCT

HALAVEN® 0.5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1.0 mg of eribulin mesylate equivalent to 0.88mg eribulin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless aqueous solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HALAVEN® is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

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 be administered only under the supervision of a qualified physician experienced in the appropriate use of cytotoxic drugs.

The recommended dose of HALAVEN® as the ready to use solution is 1.4 mg/m^2 which should be administered intravenously over 2-5 minutes on Days 1 and 8 of every 21-day cycle

Dose delays during therapy
Delay the administration of HALAVEN® 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
Patients should be clinically evaluated during treatment by physical examination and laboratory testing including complete blood counts (see section 4.4). If Grade 3 or 4 toxicities are present, then treatment should be delayed to allow recovery. Patients should only be retreated when the 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.

Dose reduction recommendations for retreatment are shown in the following table. If toxicities reoccur, an additional dose reduction should be made as shown.

Dose reduction recommendations

Adverse Reaction	Recommended Dose
Haematological:	
Grade 4 neutropenia lasting more than 7 days	1.1 mg/m^2
Grade 3 or 4 neutropenia complicated by fever or infection	
Grade 4 thrombocytopenia	
Grade 3 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 1.1 mg/m^2	0.7 mg/m^2
Despite reduction to 0.7 mg/m^2	Consider Discontinuation

Do not re-escalate the HALAVEN® dose after it has been reduced.

Patients with hepatic impairment
Impaired liver function due to metastases
The recommended dose of HALAVEN® in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of HALAVEN® in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 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 HALAVEN® 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.

Paediatric patients
HALAVEN® is not recommended for use in patients below age 18 years due to insufficient data on safety and efficacy.

Elderly patients
Clinical studies did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. There was no evidence to suggest that the safety profile of HALAVEN® is different in elderly patients. No specific dose adjustments are recommended based on the age of the patient (see section 4.8).

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)

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
- 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 HALAVEN®. Treatment with HALAVEN® should only be initiated in patients with ANC values ≥ 1.5 x 10^9/l and platelets > 100 x 10^9/l.

Febrile neutropenia occurred in < 5% of patients treated with HALAVEN®. 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
Peripheral neuropathy commonly occurs and is usually of mild to moderate severity. Monitor patients closely for signs of peripheral motor and sensory neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort or neuropathic pain. Peripheral neuropathy should be treated according to the recommendations in 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, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalaemia, hypocalcaemia or hypomagnesaemia prior to initiating HALAVEN® and monitor these electrolytes periodically during therapy. Avoid HALAVEN® in patients with congenital long QT syndrome.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-gp inhibitors. The effect of ketoconazole, a strong inhibitor of CYP3A4 and a P-gp inhibitor, on the pharmacokinetics of eribulin was studied in an open-label, two-treatment, two-sequence, two-way crossover trial in 12 patients with advanced solid tumours. The mean dose-normalized AUC values were similar when eribulin was administered with or without ketoconazole (ratio of the mean AUC: 0.97; 90% CI: 0.83, 1.12). Eribulin exposure (AUC and Cmax) was also unaffected by rifampicin, a CYP3A4 inducer.

Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant concentrations. Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes.

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

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

Pregnancy
There is no information on the use of HALAVEN® in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats, and testicular toxicity has been revealed in rats and dogs (section 5.3). 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.

Breastfeeding
There is insufficient information on the excretion of eribulin or its metabolites in human or animal breast milk. A risk to newborn or infants cannot be excluded and therefore HALAVEN® should not be used during breast feeding (section 4.3).

Fertility
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

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The most commonly reported adverse reactions to HALAVEN® are shown in the table below.

The following 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.

Frequencies 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), very rare (< 1/10,000) and not known (cannot be estimated from the available data). 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]
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%)[a] 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%)	
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[b] 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

In the same breast cancer population in clinical trials the following medically significant adverse reactions were reported as uncommon (≥ 1/1,000 to < 1/100)

Infection and Infestations: Pneumonia, Neutropenic sepsis
Vascular Disorders: Thrombosis (including DVT and Pulmonary embolism)
Hepatobiliary Disorders: Hepatic disorder

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.
Haematologic toxicities resulted in discontinuation in <1% of patients receiving HALAVEN®.
Neuropathy: In the 1559 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with HALAVEN® 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%.

Special populations

Elderly Population
In studies of 1559 patients treated with HALAVEN®, 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 HALAVEN® in elderly patients (≥65 years of age) was similar to that of patients ≤65 years of age except for astenia/fatigue which showed an increasing trend with age. No dose adjustments are recommended based on the age of the patient.

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 section 4.4 and 5.2.

4.9 Overdose

In one case of overdose the patient inadvertently received 8.6 mg of eribulin mesylate (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 HALAVEN® 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.

HALAVEN® (Eribulin mesylate) is a tubulin-targeted, non-taxane microtubule dynamics inhibitor that is a structurally simplified, synthetic analogue of the marine natural product halichondrin B.

Mechanism of action
Eribulin mesylate is a tubulin-targeted antimitotic agent that exerts its antiproliferative effects on cancer cells via a mechanistically novel mode of inhibition of microtubule dynamics. Such inhibition leads to G_2/M (Gap 2/mitosis stages of cell cycle) cell cycle blocks, disruption of mitotic spindles, and ultimately apoptotic cell death after prolonged mitotic blockage.

In addition, eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness in vitro. In mouse xenograft models of human breast cancer, eribulin treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype.

Clinical experience

Breast cancer
The efficacy of HALAVEN® in breast cancer is supported by two single-arm Phase 2 studies in 403 patients and the randomized Phase 3 comparative study in 762 patients. The patients in the pivotal study 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).

In the pivotal Phase 3 EMBRACE study, patients must have progressed within 6 months of their last therapeutic regimen. They were randomized 2:1 to receive either HALAVEN® (1.4 mg/m2 on Days 1 and 8 in a 21-day cycle administered intravenously over 2 to 5 minutes), or treatment of physician's choice (TPC), defined as any single-agent chemotherapy, hormonal treatment, or biologic therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, reflecting local practice.

The study met its primary endpoint with an overall survival result that was statistically significantly better in the eribulin group compared to TPC at 55% of events. The median survival of the HALAVEN® group (median: 399 days/13.1 months) compared with the TPC group (median: 324 days/10.6 months) improved by 75 days/2.5 months (HR 0.809, 95% CI: 0.660, 0.991, p=0.041).

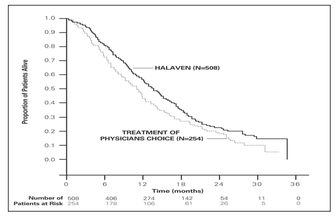
This result was confirmed with an updated overall survival analysis carried out at 77% of events with the median survival of the HALAVEN® group (median: 403 days/13.2 months) compared with the TPC group (median: 321 days/10.5 months) improved by 82 days/2.7 months (HR 0.805, 95% CI: 0.677, 0.958, nominal p=0.014).

Efficacy of HALAVEN® vs Treatment of Physician's Choice – Updated Survival Analysis in the ITT Population

Efficacy Parameter	HALAVEN® (n = 508)	TPC (n = 254)
Overall Survival		
Number of Events	386	203
Median	403 days	321 days
(95% CI)	(367 - 438)	(281 - 365)
Hazard Ratio (95% CI)[a]	0.805 (0.677 - 0.958)	
Nominal P-value (log-rank)[a]	0.014	

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

Kaplan-Meier Analysis of OS-Update Data (ITT Population)



At the time of the original data cut-off, the PFS and ORR results according to independent and investigator's assessment are described in the following tables:

Efficacy of HALAVEN® versus Treatment of Physician's Choice – Progression Free Survival at initial primary response analysis (ITT Population)

	HALAVEN® n=508	TPC n=254
Independent		
Number of events	357	164
Median	113 days	68 days
(95% CI)	(101 - 118)	(63 – 103)
Hazard Ratio[a] (95% CI)	0.865 (0.714 – 1.048)	
p-valueb (Log rank)	0.137	
Investigator		
Number of events	429	206
Median	110 days	66 days
(95% CI)	(100 - 114)	(60 – 79)
Hazard Ratio[a] (95% CI)	0.757 (0.638 – 0.900)	
p-value[b] (Log rank)	0.002	

[a] For the hazard ratio, a value less than 1.00 favours eribulin
[b] Stratified by geographic region, HER2 status, and prior capecitabine use.

Efficacy of HALAVEN® versus Treatment of Physician's Choice – Objective Tumor Response Rate at initial primary response analysis (Response Evaluable Population)

	HALAVEN® n=468	TPC n=214
Independent		
Rate (95% CI)	12.2% (9.4 – 15.5)	4.7% (2.3 – 8.4)
p-value[a] (CMH)[b]	0.002	
Investigator		
Rate (95% CI)	13.2% (10.3 – 16.7)	7.5% (4.3 – 11.9)
p-value[a] (CMH)[b]	0.028	

[a] Stratified by geographic region, HER2 status, and prior capecitabine use.
[b] Cochran-Mantel-Haenszel test

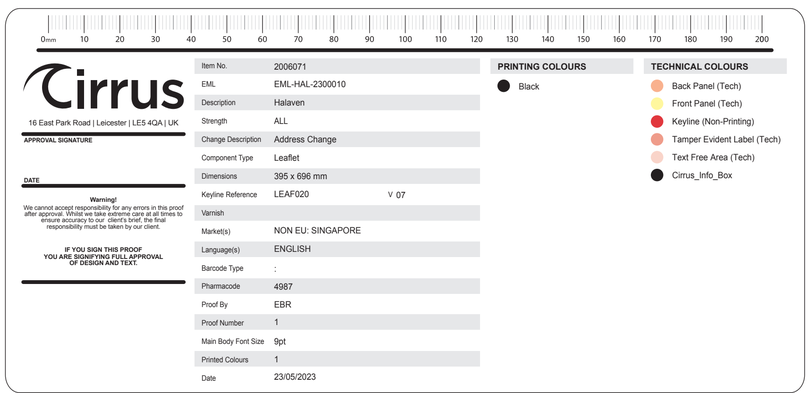
Liposarcoma
In liposarcoma the efficacy of eribulin is supported by the pivotal Phase 3 sarcoma study (Study 309). The patients in this study (n=452) had locally recurrent, inoperable and/or metastatic soft tissue sarcoma of one of two subtypes – leiomyosarcoma or liposarcoma. Patients had received at 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.

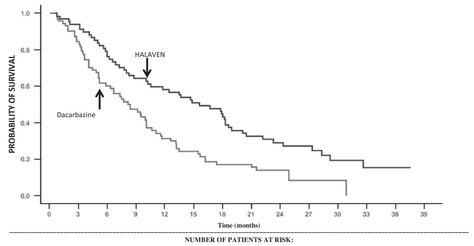
In Study 309, a statistically significant improvement in OS was observed in patients randomized to the eribulin arm compared to the control arm. This translated into a 2 month improvement in median OS (13.5 months for eribulin treated patients vs. 11.5 months for dacarbazine treated patients). There 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	



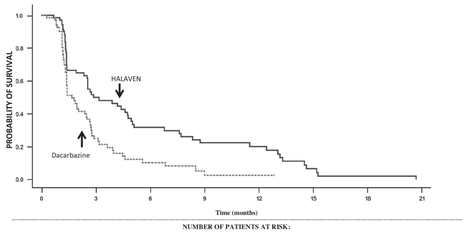
Study 309 - Overall Survival in the Liposarcoma Subgroup



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

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 hr. It has a large volume of distribution (range of means 43 to 114 L/m^2) and low clearance (range of means 1.16 to 2.42 L/hr/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
Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for the human hepatic metabolism of eribulin. Eribulin (0.05 to 5μM) did not show induction potential for CYP1A and CYP3A in human primary hepatocytes. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected with eribulin at concentrations up to 5 μM in pooled human liver microsomes. Therefore, at the current recommended human dose eribulin is unlikely to affect plasma levels of drugs that are substrates of CYP enzymes.

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

Elimination
Eribulin is eliminated primarily in faeces. 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. Based on the population PK analysis, renal impairment is not expected to significantly influence eribulin exposure.

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

Hepatic impairment
A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=4) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN® at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. HALAVEN® was not studied in patients with severe hepatic impairment (Child-Pugh C).

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 I 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.

5.3 Preclinical safety data

The nonclinical safety of eribulin mesylate has been evaluated in the following studies: safety pharmacology, repeated toxicity including chronic toxicity, genotoxicity, and reproductive toxicity studies. No significant adverse effects were observed in any safety pharmacology studies except for transient decreases in blood pressure and heart rate in conscious dogs. Results from the toxicology studies showed that the target organ of toxicity is limited to the bone marrow, skeletal muscle, peripheral nerves, gastrointestinal system, and testes. Most of these observed toxic effects were partially or completely reversible by 2 to 4 weeks of recovery. In addition, eribulin mesylate, like other cytotoxic agents, is genotoxic and teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

HALAVEN® solution for injection should not be diluted in glucose 5% infusion solution.

6.3 Shelf life

The drug should not be used after the expiry date "EXP" printed on the pack.

From a microbiological point of view HALAVEN® should be used immediately. The product is not intended to be stored after opening or after dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

If not used immediately HALAVEN® as the undiluted solution in a syringe should not normally be stored longer than 4 hours at 25°C and ambient lighting, or 24 hours at 2°C - 8°C. Diluted solutions of HALAVEN® (0.02 mg/ml to 0.2 mg/ml in sterile sodium chloride 9 mg/ml (0.9%) solution for injection should not be stored longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

To be stored at room temperature (15°C - 25°C).

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 butyl rubber stopper and flip-off aluminium over seal, containing 2 ml of solution (0.5 mg/ml).

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

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

HALAVEN® is a cytotoxic anticancer medicinal product and, as with other toxic compounds, caution should be exercised in handling HALAVEN®. The use of gloves, goggles, and protective clothing is recommended. If the solution contacts the skin, the skin 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.

7. PRODUCT REGISTRANT

Eisai (Singapore) Pte Ltd
152 Beach Road
#15-07/08 Gateway East
Singapore 189721

8. DATE OF REVISION OF PACKAGE INSERT

2nd May 2023

HALAVEN® 0.5 mg/ml solution for injection

2006071

PHARMA CODE
READ DIRECTION

0mm 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200

Cirrus
16 East Park Road | Leicester | LE5 4QA | UK

APPROVAL SIGNATURE

DATE

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Item No.	2006071
EML	EML-HAL-2300010
Description	Halaven
Strength	ALL
Change Description	Address Change
Component Type	Leaflet
Dimensions	395 x 696 mm
Keyline Reference	LEAF020 V 07
Varnish	
Market(s)	NON EU: SINGAPORE
Language(s)	ENGLISH
Barcode Type	:
Pharmacode	4987
Proof By	EBR
Proof Number	1
Main Body Font Size	9pt
Printed Colours	1
Date	23/05/2023

PRINTING COLOURS
- Black

TECHNICAL COLOURS
- Back Panel (Tech)
- Front Panel (Tech)
- Keyline (Non-Printing)
- Tamper Evident Label (Tech)
- Text Free Area (Tech)
- Cirrus_Info_Box