HALAVEN PRODUCT INFORMATION

NAME OF THE MEDICINE

HALAVEN

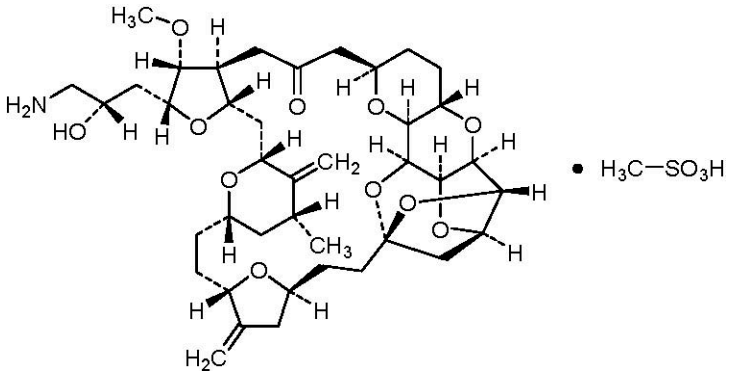
Eribulin mesilate

Chemical Structure

The chemical name for eribulin mesilate is 11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 for free base).

The empirical formula is $C_{40}H_{59}NO_{11}\bullet CH_4O_3S$.

Eribulin mesilate has the following structural formula:



CAS Number: 441045-17-6

DESCRIPTION

HALAVEN is a clear, colourless aqueous solution for injection. HALAVEN contains eribulin mesilate 1 mg in 2 mL (equivalent to eribulin free base 0.88 mg in 2 mL) as the active ingredient. It also contains ethanol absolute 0.1 mL, hydrochloric acid qs, sodium hydroxide qs and water for injection qs.

PHARMACOLOGY

Pharmacodynamic properties

HALAVEN (eribulin mesilate) is a non-taxane, 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 mitotic blockage.

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 mesilate doses of 0.25 to 4.0 mg/m^2.

Eribulin is eliminated primarily by biliary excretion. The transport protein involved in the excretion is presently unknown. Preclinical studies indicate that eribulin is transported by Pgp. However, it is unknown whether Pgp is contributing to the biliary excretion of eribulin**.**

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 PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment due to liver metastases. 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 1.1mg/m^2 to patients with mild hepatic impairment and 0.7mg/m^2 to patients with moderate hepatic impairment resulted in a somewhat higher exposure than after 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). There is no study in patients with hepatic impairment due to cirrhosis. See section Dosage and Administration for dosage recommendation.

Renal impairment

No formal PK trials were conducted with HALAVEN in patients with renal impairment. Available data suggests that no dose adjustment is necessary for patients with stage 2 chronic kidney disease (GFR 60 - 89 mL/min/1.73m^2). However, for patients with stage 3 chronic kidney disease (GFR 30 - 59 mL/min/1.73m^2), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function. HALAVEN was not studied in patients with stage 4-5 chronic kidney disease (GFR <30 mL/min/1.73m^2). See section Dosage and Administration for treatment recommendations.

CLINICAL TRIALS

The efficacy of HALAVEN in breast cancer is supported by a randomized Phase 3 comparative study.

The 762 patients in the pivotal Phase 3 EMBRACE 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). Patients must have progressed within 6 months of their last chemotherapeutic regimen. They were randomized 2:1 to receive either HALAVEN at a dose of 1.4 mg/m^2 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 TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), or 3% hormonal therapy. The median duration of treatment (range) for each treatment group was: vinorelbine 1.6 months (0-13.1 months); gemcitabine 2.3 months (0-14.5 months); capecitabine 3.9 months (0-21.2 months); taxane 2.9 months (0-14.5 months); anthracycline 1.9 months (0-6.5 months) and eribulin 3.9 months (0.7-16.3 months).

The primary endpoint, overall survival, was significantly better with eribulin than TPC (See Table 1).

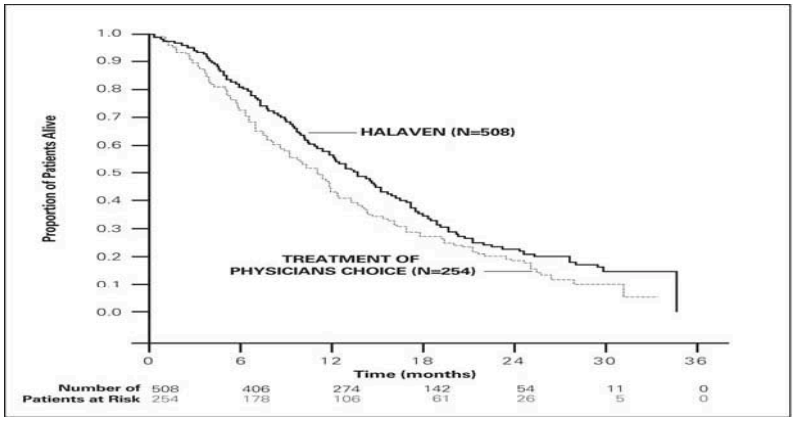
Table 1: Efficacy of HALAVEN versus Treatment of Physician's Choice – Primary and Updated Survival Analysis in the ITT Population

Efficacy Parameter	**HALAVEN (n = 508)**	**TPC (n = 254)**
Primary Overall Survival		
Number of Events (%)	274 (53.9%)	148 (58.3%)
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI)[a]	0.809 (0.660, 0.991)	
P-value (log-rank)[b]	0.041	
Updated Overall Survival		
Number of Events	386 (76.0%)	203 (79.9%)
Median, months (95% CI)	13.2 (12.1, 14.4)	10.6 (9.2, 12.0)
Hazard Ratio (95% CI)[a]	0.805 (0.677, 0.958)	
Nominal *P*-value (log-rank)[b]	0.014	

CI = confidence interval

[a] Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.

[b] Based on a log-rank test stratified by geographic region, HER2 status, and prior capecitabine therapy.



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

At the time of the original cut-off, analysis of progression free survival by independent and investigator review is shown in table 2 below.

Table 2: Efficacy of HALAVEN versus Treatment of Physician's Choice – Progression Free Survival

	HALAVEN (n=508)	**TPC (n=254)**
Independent		
Number of events	357 (70.3%)	164 (64.6%)
Median, months (95% CI)	3.7 (3.3, 3.9)	2.2 (2.1, 3.8)
Hazard Ratio[a] (95% CI)	0.865 (0.714 – 1.048)	
p-value[b] (Log rank)	0.137	
Investigator		
Number of events	429 (84.4%)	206 (81.1%)
Median, months (95%CI)	3.6 (3.3, 3.7)	2.2 (2.0, 2.6)
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/neu status, and prior capecitabine use.		

In response evaluable patients who received HALAVEN, the objective response rate by the RECIST criteria was 12.2% (95% CI: 9.4%, 15.5%) by independent review and 13.2% (95% CI: 10.3%, 16.7%) by investigator review. The median response duration in this population by independent review was 4.2 months (95% CI: 3.8, 5.0 months).

The positive effect on OS and PFS 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. In the Investigator assessment-based analysis of PFS (based on original data cut-off), the HR was 0.77 (95% CI 0.61, 0.97) for taxane-refractory patients and 0.76 (95% CI 0.58, 0.99) for patients not taxane-refractory.

The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The analysis of updated OS 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 11 capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI 0.606, 1.233). Investigator assessment-based analysis of PFS (based on original data cut-off), also showed a positive effect in the capecitabine pre-treated group with a HR of 0.68 (0.56, 0.83). For the capecitabine-naïve group the corresponding HR was 1.03 (0.73, 1.45).

Paediatric population

No studies have been undertaken in the paediatric population in the indication of breast cancer.

INDICATIONS

HALAVEN monotherapy 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 unless patients were not suitable for these treatments.

CONTRAINDICATIONS

Hypersensitivity to eribulin mesilate or to any of the other ingredients.

Breast feeding

PRECAUTIONS

Haematology

Myelosuppression is dose dependent and primarily manifested as neutropenia. In the EMBRACE study, neutropenia occurred in 82% of breast cancer patients treated with eribulin, with severe neutropenia (> Grade 3) in 57% of patients leading to discontinuation in <1% of patients (See Adverse Effects). 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 breast cancer patients treated with eribulin. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommended doses (See Dosage and Administration).

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.

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines.

Peripheral neuropathy

In the EMBRACE study, peripheral neuropathy occurred in 35% of breast cancer patients treated with eribulin. Severe peripheral neuropathy (> Grade 3) occurred in 8% of patients, leading to discontinuation in 5% of patients (See Adverse Effects).

Patients should be closely monitored prior to each dose for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose (see Dosage and Administration).

In clinical trials, patients with pre-existing neuropathy greater than Grade 2 were excluded.

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, 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 HALAVEN and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

Use in combination with anti-HER2 therapy

There is no experience of using eribulin in combination with anti-HER2 therapy in clinical trials.

Excipients

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

Effects on Fertility

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 (testicular hypocellularity and epididymal hypospermia/aspermia) at less than one third of the expected clinical exposure (based on AUC data), male fertility may be compromised by treatment with eribulin.

Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with HALAVEN.

Use in Pregnancy (Category D)

There is no information on the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats at less than the recommended human dose (based on body surface area, mg/m^2). HALAVEN should not be used during pregnancy.

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.

In a developmental and reproductive toxicity study, pregnant rats received IV bolus injection of eribulin mesilate during organogenesis on gestation days 8, 10 and 12. Severe external or soft tissue malformations in offspring (absence of lower jaw, tongue, stomach and spleen) were observed at 0.15 mg/kg (0.64 times the recommended human dose based on body surface area, mg/m^2) and increased embryofoetal death/early resorptions and decreased foetal weights were recorded at $\geq$ 0.1 mg/kg ($\geq$ 0.43 times the recommended human dose based on body surface area). Maternal toxicity was observed at $\geq$ 0.43 times the recommended human dose based on body surface area, and included enlarged spleen, reduced body weight gain and decreased food consumption.

Use in Lactation

There is no information on the excretion of eribulin or its metabolites in human or animal breast milk. A risk to newborns or infants cannot be excluded and therefore HALAVEN must not be used during breastfeeding (see Contraindications).

Carcinogenicity

No carcinogenicity studies have been conducted with eribulin.

Genotoxicity

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

INTERACTIONS WITH OTHER MEDICINES

Effects of other drugs on eribulin

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-glycoprotein (Pgp) inhibitors. Clinically meaningful differences in exposure (AUC) were not observed in patients with advanced solid tumors when HALAVEN was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a Pgp inhibitor) and when HALAVEN was administered with or without rifampicin (a CYP3A4 inducer).

Eribulin is mainly (up to 70%) eliminated through biliary excretion. The transport protein involved in this process is unknown (see Pharmacology, Elimination). Based on a study of coadministration of eribulin and ketoconazole (a Pgp inhibitor), eribulin exposure is unlikely to be increased with substances inhibiting Pgp. However, coadministration of eribulin with substances inhibiting other hepatic transport proteins (e.g. organic anion transporting proteins, multidrug resistance proteins) may increase eribulin exposure. Such coadministration is not recommended at the present time.

Effects of eribulin on other drugs

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

ADVERSE EFFECTS

Clinical Trials

In the Phase 3 clinical study, 750 patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 9%, capecitabine 18%, gemcitabine 18%, taxanes 16%, vinorelbine 26%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 3 below reports the most common adverse events occurring in at least 10% of patients in either group.

Table 3: Very Common (≥10%) Adverse Events in the EMBRACE Trial

	HALAVEN		**Control Group**	
MedDRA ver 10.0	**n=503**		**n=247**	
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0
Blood and Lymphatic System Disorders [a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%

Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhoea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
General disorders and administration site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Investigations				
Weight decreased	21%	1%	14%	<1%

[a.] based upon laboratory data.
[b] includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[c] not applicable; (grading system does not specify > Grade 2 for alopecia).

Table 4 provides a listing of Very Common (≥10%), common (≥ 1% to < 10%) and uncommon (≥ 0.1% to < 1%) adverse reactions observed in 827 breast cancer patients who received the recommended dose in two Phase II and one Phase III study.

Table 4: Very Common (≥10%), Common (≥ 1% to < 10%) and Uncommon (≥ 0.1 to < 1%) Adverse Reactions to HALAVEN in Pooled Data from the EMBRACE trial and two phase II trials (n=827)

System Organ Class	Adverse Reactions – all Grades		
	Very Common	**Common**	**Uncommon**
Infections and infestations		Urinary tract infection Oral candidiasis Upper respiratory tract infection Nasopharyngitis	Pneumonia Neutropenic sepsis Oral herpes Herpes zoster

		Rhinitis	
Blood and lymphatic disorders	Neutropenia Leukopenia Anaemia	Febrile neutropenia Thrombocytopenia Lymphopenia	
Metabolism and nutrition disorders	Decreased appetite	Hypokalaemia Hypomagnesaemia Dehydration Hyperglycaemia Hypophosphataemia	
Psychiatric disorders		Insomnia Depression	
Nervous system disorders	Peripheral neuropathy Headache	Dysgeusia Dizziness Hypoaesthesia Lethargy Neurotoxicity	
Eye disorders		Lacrimation increased Conjunctivitis	
Ear and Labyrinth Disorders		Vertigo	Tinnitus
Cardiac disorders		Tachycardia	
Vascular disorders		Hot flush	Deep vein thrombosis Pulmonary embolism
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough Oropharyngeal pain Epistaxis Rhinorrhoea	Interstitial lung disease
Gastrointestinal disorders	Nausea Constipation Diarrhoea Vomiting	Abdominal pain Stomatitis Dry mouth Dyspepsia Gastrooesophageal reflux disease Mouth ulceration Abdominal distension	
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Alopecia	Rash Pruritus Nail disorder Night sweats Palmar plantar erythrodysaesthesia Dry skin Erythema Hyperhidrosis	Angioedema
Musculoskeletal and connective tissue disorders	Arthralgia and Myalgia	Pain in extremity Muscle spasms Musculoskeletal pain and musculoskeletal	

		chest pain Muscular weakness Bone pain Back pain	
Renal and urinary disorders			Dysuria Haematuria Proteinuria Renal failure
General disorders **and administration site conditions**	Fatigue/Asthenia Pyrexia	Mucosal inflammation Peripheral oedema Pain Chills Influenza like illness Chest pain	
Investigations		Weight decreased	

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.

In the phase 3 clinical study, Grade 3 neutropenia occurred in 28% (143/503) of patients and Grade 4 neutropenia occurred in 29% (144/503) of patients who received HALAVEN. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients.

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% of breast cancer patients treated in a phase 3 study with eribulin received G-CSF (See Precautions, Haematology).

Peripheral neuropathy

In the pivotal clinical study, 17 % of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

From the pooled data on the 827 breast cancer patients in the Phase 2 and Phase 3 studies, the most common adverse reaction resulting in discontinuation of treatment with HALAVEN

was peripheral neuropathy (4%). The median time to Grade 2 peripheral neuropathy was 12 weeks (post 4 cycles), with the median time to Grade 2 or greater being 53 weeks. Development of Grade 3 or 4 peripheral neuropathy occurred in 7% of HALAVEN treated breast cancer 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 patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 10%. From the limited data available the median time to resolution of all peripheral neuropathy after the last dose was about 13 weeks (See Precautions, Peripheral Neuropathy).

Liver Function Test Abnormalities

Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Special populations

Elderly population

In studies of 1,222 patients treated with eribulin, 244 patients (20.0%) were > 65 - 75 years of age and 66 patients (5.4%) were > 75 years of age. Among the 827 of these patients who received the recommended dose of eribulin in the Phase 2/3 breast cancer studies, 121 patients (14.6%) were > 65- 75 years of age and 17 patients (2.1%) were > 75 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. 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 pharmacokinetic and Dosage and Administration sections).

DOSAGE AND ADMINISTRATION

HALAVEN should be administered in units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

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

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 a maximum of 1 week, for any of the following:

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

− Platelets < 75 x 10^9/L

− Grade 3 or 4 non-haematological toxicities.

If toxicities do not resolve or improve to ≤ grade 2 severity by Day 15, omit the dose.

If toxicities resolve or improve to ≤ grade 2 severity by Day 15, administer HALAVEN at a reduced dose (see dose reduction table below) and initiate the next cycle no sooner than 2 weeks later.

Dose reduction during therapy

Dose reduction recommendations for retreatment are shown in the table 5.

Table 5: Dose reduction recommendations

Adverse reaction after previous HALAVEN administration	**Recommended dose**
Haematological:	
ANC < 0.5 x 10^9/L lasting more than 7 days	1.1 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	0.7 mg/m^2
Despite reduction to 1.1 mg/m^2	
Despite reduction to 0.7 mg/m^2	Consider discontinuation

Do not re-escalate the eribulin 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/m2 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.

Patients with renal impairment

No dose adjustment is needed in patients with stage 2 chronic kidney disease (GFR 60 - 89 mL/min/1.73m^2).

Physicians should exercise caution in the use of HALAVEN in patients with stage 3-5 chronic kidney disease (GFR <60 mL/min/1.73m^2). Based on limited data, the recommended HALAVEN dose in patients with stage 3 chronic kidney disease (GRF 30-59 mL/min/1.73m^2) is 1.1 mg/m^2 administered over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. HALAVEN has not been studied in patients with stage 4-5 chronic kidney disease (GFR <30 mL/min/1.73m^2); therefore, it is not possible to provide dose recommendations for this group (See Pharmacology, Renal Impairment).

Elderly patients

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

Paediatric patient

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

Method of administration

HALAVEN is a ready to use solution and may be used undiluted, or 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. 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.

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. It must not be mixed with other medicinal products and should not be diluted in glucose 5% infusion solution.

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

OVERDOSAGE

In one case of overdose the patient inadvertently received 8.6 mg of eribulin mesilate (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.

In the event of overdosage, please contact the Poisons Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Presentations

HALAVEN is a clear, colourless aqueous solution for injection. HALAVEN contains eribulin mesilate 1 mg in 2 mL (equivalent to eribulin free base 0.88 mg in 2 mL) as the active ingredient in a type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal. The pack sizes are cartons of 1 or 6 vials. Not all pack sizes may be marketed. (AUST R 187136)

Storage

Store below 25ºC.

In use storage

From a microbiological point of view unless the method of opening precludes the risk of microbial contamination the product should be used immediately. 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 0.2mg/mL in sodium chloride 9 mg/mL (0.9%)) solution for injection should not be stored longer than 24 hours at 2°C - 8°C.

The product is for single use in one patient only. Discard any unused residue.

NAME AND ADDRESS OF THE SPONSOR

Eisai Australia Pty Ltd
288-292 Churchill Avenue
SUBIACO WA 6008

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

30 August 2012