Attachment 1: Product information for AusPAR Halaven-Eisai Australia Pty Ltd PM-2015-04001-1-4 Final 12 October 2017. This Product Information was approved at the time this AusPAR was published.

HALAVEN PRODUCT INFORMATION

NAME OF THE MEDICINE

HALAVEN

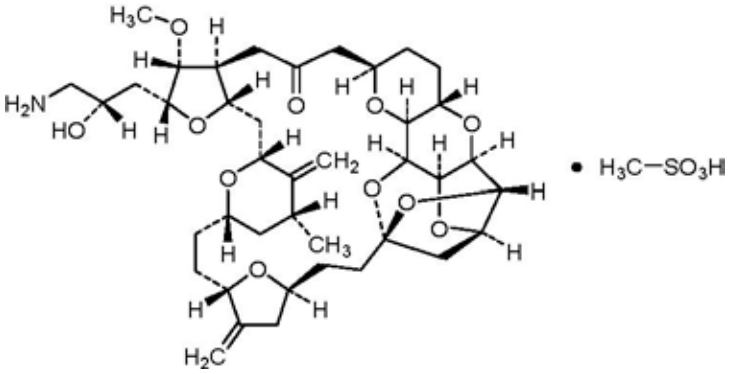
Eribulin mesilate

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.

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PHARMACOLOGY

Pharmacodynamic properties

HALAVEN (eribulin mesilate) is a first-in-class halichondrin B-based, microtubule dynamics inhibitor. 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 G2/M cell-cycle block, disruption of mitotic spindles and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage.

Eribulin also affects the tumour microenvironment and tumour phenotype by mechanisms that are not linked to its antimitotic effects. These additional effects of eribulin include: (i) tumour vasculature remodelling whereby inner tumour cores become better perfused and less hypoxic, and (ii) phenotypic shifts from more aggressive mesenchymal phenotypes to less aggressive epithelial phenotypes via reversal of the epithelial-mesenchymal transition (EMT).

Pharmacokinetic properties

Distribution

The pharmacokinetics of eribulin are characterised 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 (5-1000 ng/mL) ranged from 49% to 67% 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

The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with stage 2 chronic kidney disease (GFR 60 - 89 mL/min/1.73m^2), stage 3 chronic kidney disease (GFR 30 - 59 mL/min/1.73m^2), or stage 4-5 chronic kidney disease (GFR <30 mL/min/1.73m^2). Increase in dose-normalised C_{max} was 1.31-fold (90% CI 0.84-2.05) for stage 3 chronic kidney disease and 2.02-fold (90% CI 1.27-3.21) for stage 4-5 chronic kidney disease compared to normal renal function. Stage 3 chronic kidney disease and stage 4-5 chronic kidney disease increased mean dose-normalised AUC $_{(0\text{-inf})}$ 1.49-fold (90% CI 0.9-2.45) compared to normal renal function. Renal impairment therefore has an up to three fold effect on eribulin exposure and dosing modifications and extra haematology monitoring should be undertaken.

Refer to Dosage and Administration section for treatment recommendations in renal impairment.

CLINICAL TRIALS

Breast Cancer

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

The 762 patients in the pivotal Phase 3 EMBRACE (Study 305) 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 randomised 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 HALAVEN 3.9 months (0.7-16.3 months).

The primary endpoint, overall survival, was significantly better with HALAVEN 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

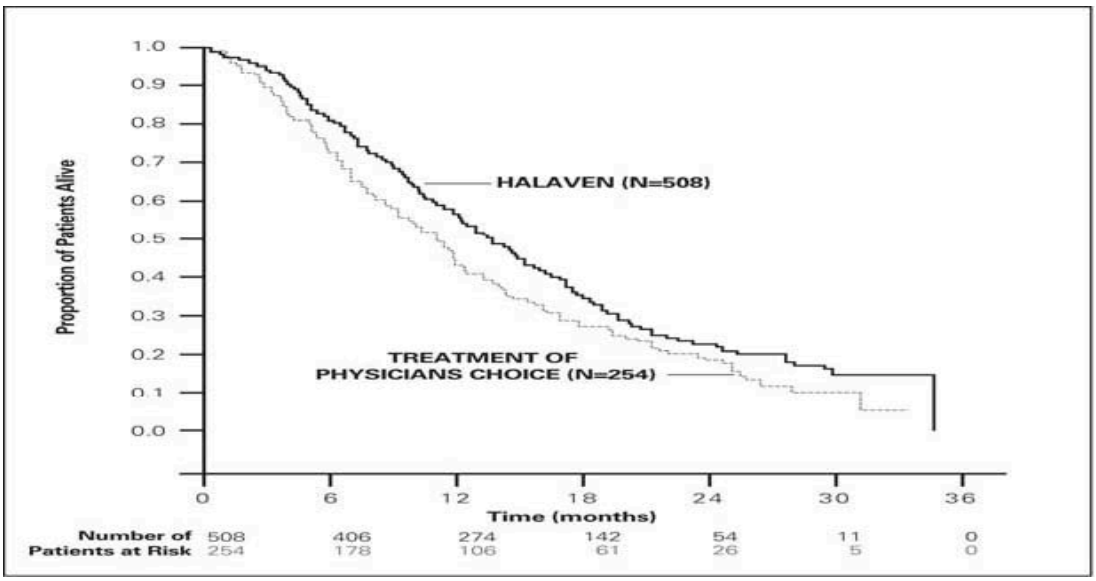
Efficacy Parameter	**HALAVEN (n = 508)**	**TPC (n = 254)**
Primary Overall Survival		
Number of Events (%)	274 (53.9%)	148 (58.3%)
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI)[a]	0.809 (0.660, 0.991)	
P-value (log-rank)[b]	0.041	
Updated Overall Survival		
Number of 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.

Figure 1: 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 2below.

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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 HALAVEN
[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 HALAVEN versus TPC was 0.90 (95% CI 0.71, 1.14) in favour of HALAVEN 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 HALAVEN 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).

The second Phase 3 study (study 301) in earlier line metastatic breast cancer, was an open-label, randomised, 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.

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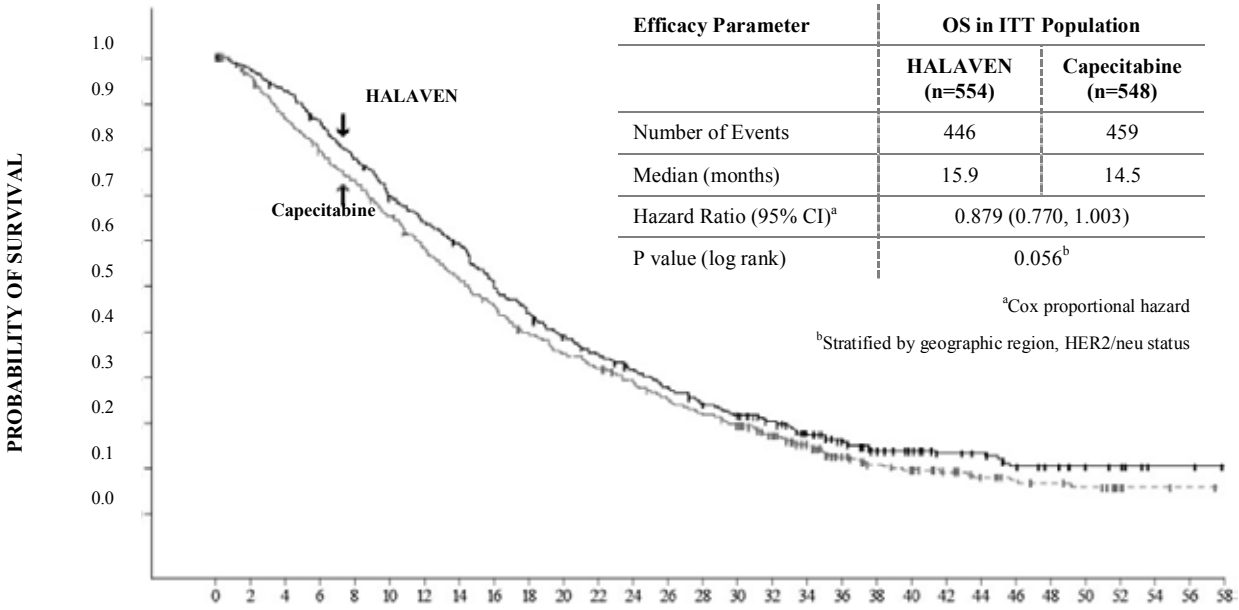
Figure 2: Study 301 - Overall Survival (ITT Population)



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 HALAVEN 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 HALAVEN and capecitabine; 11.0% (95% CI: 8.5, 13.9) in the HALAVEN group and 11.5% (95% CI: 8.9, 14.5) in the capecitabine group.

Liposarcoma

In liposarcoma the efficacy of HALAVEN is supported by the pivotal Phase 3 sarcoma study (Study 309). The patients (n=452) in this study 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). Enrolment was stratified by histology, number of prior therapies and geographic region.

Patients must have progressed within 6 months of their last chemotherapeutic regimen. They were randomised 1:1 to receive either HALAVEN 1.4 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 randomisation), every 21 days. Treatment continued until disease progression or unacceptable toxicity.

In Study 309, a statistically significant improvement in OS was observed in patients randomised to the HALAVEN arm compared to the control arm. This translated into a 2 month improvement in median OS (13.5 months for HALAVEN 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 HALAVEN 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 HALAVEN and dacarbazine in patients with advanced or metastatic leiomyosarcoma.

Table 3: Efficacy of HALAVEN versus dacarbazine in liposarcoma

	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	

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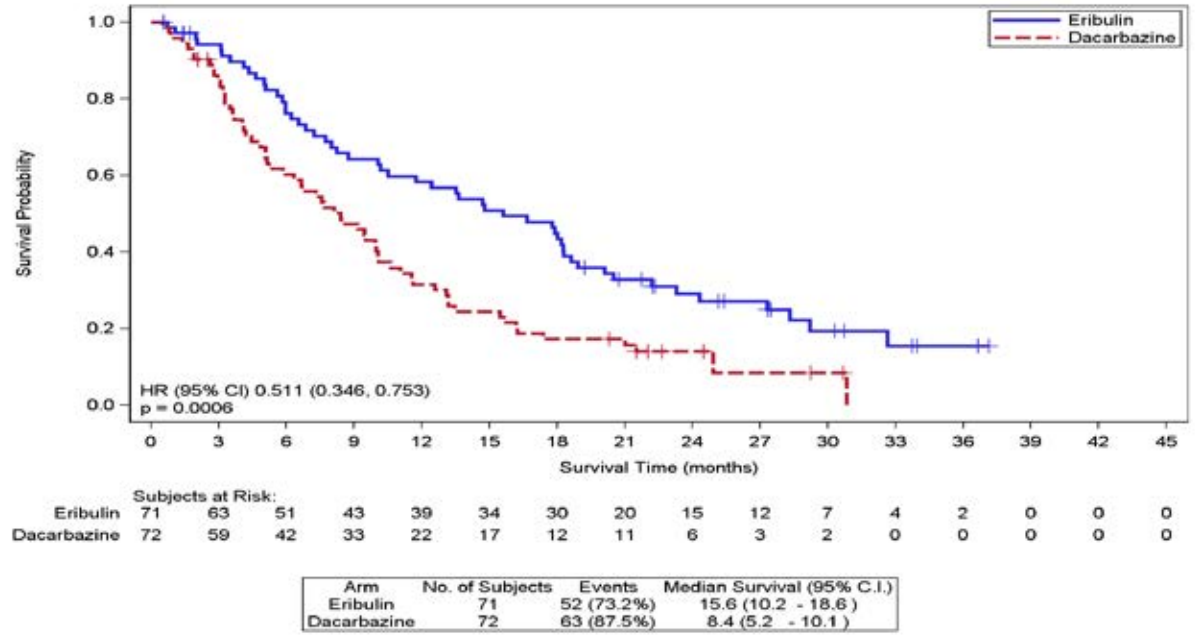
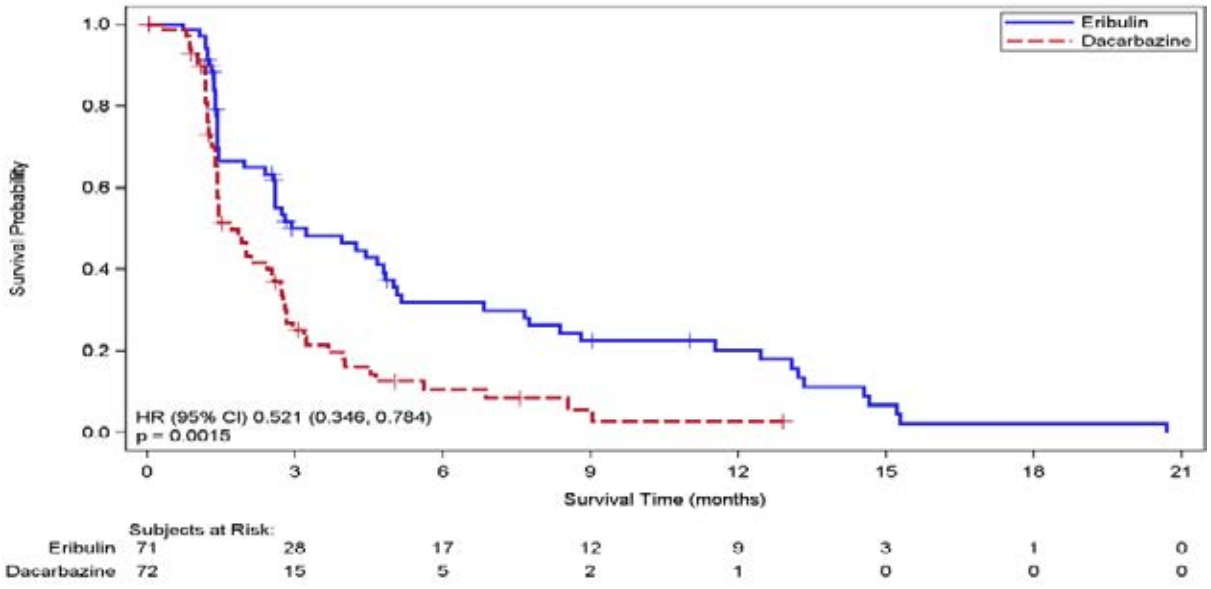
Figure 3: Study 309 - Overall Survival in the Liposarcoma Subgroup



Arm	No. of Subjects	Events	Median Survival (95% C.I.)
Eribulin	71	52 (73.2%)	15.6 (10.2 - 18.6)
Dacarbazine	72	63 (87.5%)	8.4 (5.2 - 10.1)

Figure 4: Study 309 – Progression Free Survival in the Liposarcoma Subgroup



Arm	No. of Subjects	Events	Median Survival (95% C.I.)
Eribulin	71	57 (80.3%)	2.9 (2.6 - 4.8)
Dacarbazine	72	59 (81.9%)	1.7 (1.4 - 2.6)

Paediatric population

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

No studies have been undertaken in the paediatric population in the indication of soft tissue sarcoma.

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INDICATIONS

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

HALAVEN is indicated for the treatment of patients with unresectable liposarcoma who have received prior chemotherapy for advanced or metastatic disease.

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 HALAVEN, with severe neutropenia (>Grade 3) in 57% of patients leading to discontinuation in <1% of patients (See Adverse Effects). In the patients treated with eribulin in soft tissue sarcoma studies (STS population), neutropenia (adverse events and laboratory abnormalities) occurred in 76.0%, with severe neutropenia (≥Grade 3) in 53% of patients.

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 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.

During clinical studies, a higher proportion of Asian and Pacific Islander subjects reported events of neutropenia and/or shifts in laboratory values for neutrophil count decreased compared with White subjects (See ADVERSE EFFECTS).

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 HALAVEN. 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 HALAVEN 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 or hypomagnesemia should be corrected prior to initiating HALAVEN and these electrolytes should be monitored periodically during therapy. HALAVEN should be avoided in patients with congenital long QT syndrome.

Use in combination with anti-HER2 therapy

The efficacy and safety of using HALAVEN in combination with anti-HER2 therapy have not been established.

Excipients

This medicinal product contains small amounts of ethanol (alcohol), 0.1 mL per vial.

Effects on Fertility

A fertility study was not conducted with HALAVEN, 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 HALAVEN.

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 HALAVEN 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 ≥0.1 mg/kg (≥0.43 times the recommended human dose based on body surface area). Maternal toxicity was observed at ≥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 tumours 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 a substrate of Pgp but not a substrate of BCRP, BSEP, MRP2 or MATE1 *in vitro*. 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 HALAVEN and ketoconazole (a Pgp inhibitor), eribulin exposure is unlikely to be increased with substances inhibiting Pgp. However, coadministration of HALAVEN 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 is a CYP3A4 inhibitor *in vitro*, with IC_{50}/Ki values ranging from 2 to 50 μM depending on the substrate. No *in vivo* data are available. Caution and monitoring for adverse events is recommended when HALAVEN is used with substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-mediated metabolism.

Eribulin does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes or induce CYP1A2, CYP2B6, 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. Eribulin down-regulated CYP2B6 and CYP1A2 expression in human hepatocytes *in vitro*, and the clinical relevance of this effect is unclear.

ADVERSE EFFECTS

Summary of safety profile

The most commonly reported undesirable effects related to HALAVEN, are bone marrow suppression manifested as neutropenia, leukopenia, 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.

Clinical Trials

Breast Cancer

In the EMBRACE study (Study 305), 750 patients were randomised (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 4below reports the most common adverse events occurring in at least 10% of patients in either group.

Table 4: 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%
Anaemia	58%	2%	55%	4%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%

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	HALAVEN		Control Group	
MedDRA ver 10.0	**n=503**		**n=247**	
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
Dyspnoea	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).

In Study 301, 1102 patients were randomised (1:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or capecitabine (1.25 g/m^2 twice daily from days 1-14 of a 21 day cycle). 12 patients in the study did not receive study treatment, so a total of 544 patients received HALAVEN, and 546 patients received capecitabine. The median duration of exposure was 125 days for patients receiving HALAVEN and 119 days for patients receiving capecitabine. Table 5below reports the most common adverse events occurring in at least 10% of patients in either group.

Table 5: Very Common (≥10%) Adverse Events in Study 301

	HALAVEN		**Capecitabine**	
	n=544		**n=546**	
	All Grades	**≥Grade 3**	**All Grades**	**≥Grade 3**
Blood and Lymphatic System Disorders				
Neutropenia	54.2%	45.8%	15.9%	4.9%
Leukopenia	31.4%	15.1%	10.4%	2.0%
Anaemia	19.1%	2.0%	17.6%	1.1%
General Disorders and Administration Site Conditions				
Fatigue	16.7%	2.0%	15.4%	2.4%
Asthenia	15.3%	4.2%	14.5%	3.7%
Pyrexia	12.9%	0.4%	5.7%	0.5%
Gastrointestinal Disorders				
Nausea	22.2%	0.2%	24.4%	1.6%
Diarrhoea	14.3%	1.1%	28.8%	5.3%
Vomiting	11.9%	0.4%	16.8%	2.2%
Skin and Subcutaneous Tissue Disorders				
Alopecia	34.6%	NA[a]	4.0%	NA[a]
Palmar-plantar erythrodysaesthesia	0.2%	0	45.1%	14.5%
Nervous System Disorders				

	HALAVEN		Capecitabine	
	n=544		n=546	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Peripheral neuropathy[b]	21.3%	6.1%	10.8%	0.7%
Headache	12.7%	0.7%	10.4%	0.5%
Musculoskeletal and Connective Tissue Disorders				
Back pain	10.3%	1.5%	7.9%	0.5%
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnoea	10.3%	2.9%	10.8%	4.4%
Metabolism and Nutrition Disorders				
Decreased appetite	12.5%	0.6%	14.8%	1.6%

a: Not applicable; (grading system does not specify >Grade 2 for alopecia).

b: Peripheral neuropathy includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, polyneuropathy and paraesthesia.

Soft Tissue Sarcoma

In Study 309, patients with soft tissue sarcoma were randomised (1:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or dacarbazine (850 mg/m2, 1000 mg/m^2, or 1,200 mg/m^2 as selected by the investigator prior to randomization according to the subject's clinical status). A total of 226 patients received HALAVEN, and 224 patients received dacarbazine. The median duration of exposure was 10.0 weeks for patients receiving HALAVEN and 9.0 weeks for patients receiving dacarbazine. Table 6below reports the most common adverse events occurring in at least 10% of patients in either group.

Table 6: Very Common (≥10%) Adverse Events in Study 309

	HALAVEN		Dacarbazine	
	n=226		n=224	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Blood and Lymphatic System Disorders				
Neutropenia	43.8%	35.4%	23.7%	15.6%
Anaemia	29.6%	6.9%	30.8%	12.1%
Leukopenia	15.9%	10.2%	10.3%	4.5%
Thrombocytopenia	5.8%	0.4%	27.7%	15.2%

Attachment 1: Product information for AusPAR Halaven-Eisai Australia Pty Ltd PM-2015-04001-1-4 Final 12 October 2017. This Product Information was approved at the time this AusPAR was published.

	HALAVEN		Dacarbazine	
	n=226		n=224	
	All Grades	≥Grade 3	All Grades	≥Grade 3
General Disorders and Administration Site Conditions				
Asthenia/Fatigue	64.6%	4.8%	61.2%	4.4%
Pyrexia	27.9%	0.9%	13.8%	0.4%
Peripheral oedema	11.9%	0	7.6%	0
Gastrointestinal Disorders				
Nausea	40.3%	0.9%	47.3%	0.4%
Constipation	31.4%	0.9%	25.9%	0.4%
Abdominal pain[a]	28.3%	1.7%	21.8%	3.6%
Vomiting	19.0%	0.9%	22.3%	0.4%
Diarrhoea	16.8%	0.4%	16.1%	0
Stomatitis	13.7%	0.9%	4.9%	0.4%
Skin and Subcutaneous Tissue Disorders				
Alopecia	35.0%	NA[b]	2.7%	NA[b]
Nervous System Disorders				
Peripheral neuropathy[c]	33.1%	0	7.5%	0
Headache	18.1%	0	9.4%	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia	18.6%	0	13.4%	1.3%
Back pain	15.5%	1.8%	13.8%	1.3%
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	18.6%	0	13.4%	0
Dyspnoea	16.8%	2.2%	18.3%	2.2%
Metabolism and Nutrition Disorders				
Decreased appetite	19.0%	0.4%	19.2%	0

Attachment 1: Product information for AusPAR Halaven-Eisai Australia Pty Ltd PM-2015-04001-1-4 Final 12 October 2017. This Product Information was approved at the time this AusPAR was published.

	HALAVEN		Dacarbazine	
	n=226		n=224	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Hypokalaemia	10.2%	2.7%	4.0%	1.8%
Infections				
Urinary Tract Infections	11.5%	2.2%	5.3%	0.4%

a: includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort.

b: Not applicable; (grading system does not specify >Grade 2 for alopecia).

c: Peripheral neuropathy includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, peripheral sensormotor neuropathy, polyneuropathy and paraesthesia.

Table 7 provides a listing of Very Common (≥10%), common (≥1% to <10%) and uncommon (≥0.1% to <1%) adverse reactions observed in breast cancer and soft tissue sarcoma patients who received the recommended dose in Phase 2 and Phase 3studies.

Table 7: Very Common (≥10%), Common (≥1% to <10%) and Uncommon (≥0.1 to <1%) Adverse Reactions to HALAVEN in Pooled Data from Phase 3 trials and phase 2 trials

System Organ Class	Adverse Reactions – all Grades		
	Very Common	Common	Uncommon
Infections and infestations		Urinary tract infection Pneumonia Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis Herpes zoster	Sepsis Neutropenic sepsis Septic Shock
Blood and lymphatic disorders	Neutropenia Leukopenia Anaemia	Febrile neutropenia Thrombocytopenia Lymphopenia	
Metabolism and nutrition disorders	Decreased appetite	Hypokalaemia Hypomagnesaemia Dehydration Hyperglycaemia Hypophosphataemia Hypocalcaemia	
Psychiatric disorders		Insomnia Depression	
Nervous system disorders	Peripheral neuropathy Headache	Dysgeusia Dizziness Hypoaesthesia Lethargy Neurotoxicity	
Eye disorders		Lacrimation	

Attachment 1: Product information for AusPAR Halaven-Eisai Australia Pty Ltd PM-2015-04001-1-4 Final 12 October 2017. This Product Information was approved at the time this AusPAR was published.

System Organ Class	Adverse Reactions – all Grades		
	Very Common	**Common**	**Uncommon**
		increased Conjunctivitis	
Ear and Labyrinth Disorders		Vertigo Tinnitus	
Cardiac disorders		Tachycardia	
Vascular disorders		Hot flush Pulmonary embolism	Deep vein thrombosis
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 Abdominal distension	Mouth ulceration
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased Hyperbilirubinaemia Gamma glutamyl transferase increased	Hepatotoxicity
Skin and subcutaneous tissue disorders	Alopecia	Rash Pruritus Nail disorder Night sweats Dry skin Erythema Hyperhidrosis Palmar plantar erythrodysaesthesia	Angioedema
Musculoskeletal and connective tissue disorders	Arthralgia and Myalgia Back pain Pain in extremity	Bone pain Muscle spasms Musculoskeletal pain Musculoskeletal chest pain Muscular weakness	
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure
General disorders and administration site conditions	Fatigue/Asthenia Pyrexia	Mucosal inflammation Peripheral oedema Pain	

System Organ Class	**Adverse Reactions – all Grades**		
	Very Common	**Common**	**Uncommon**
		Chills Chest pain Influenza like illness	
Investigations	Weight decreased		

Post Marketing Experience

Spontaneously reported adverse effects, presented in the table below, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 8: Adverse drug reactions derived from spontaneous reports

Blood and lymphatic disorders	Disseminated intravascular coagulation
Gastrointestinal disorders	Pancreatitis
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome, Toxic epidermal necrolysis

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

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 109/L) was 8 days.

Neutrophil counts of $< 0.5 \times 10^9$/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 STS 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. The incidence of Grade 3 or higher neutropenia was more common in Asian/Pacific Islander subjects (81.4%, n = 70) than in white subjects (41.0%, n = 161).

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 HALAVEN 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%).

In the phase 3 EMBRACE clinical study for breast cancer, Grade 3 neutropenia occurred in 28% (143/503) of patients and Grade 4 neutropenia occurred in 29% (144/503) of patients who received HALAVEN. Dose reduction due to neutropenia was required in 12% (62/503) of patients. In patients with breast cancer treated with HALAVEN, TEAEs of Grade 3 neutropenia occurred in 23% (358/1559) of patients and Grade 4 neutropenia occurred in 27% (419/1559) of patients who received HALAVEN. In patients with Soft Tissue Sarcoma treated with HALAVEN, TEAEs of Grade 3 neutropenia occurred in 13% (51/404) of patients and Grade 4 neutropenia occurred in 19% (75/404) of patients who received HALAVEN.

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

In a phase 3 study of breast cancer patients treated with HALAVEN, 18% received G-CSF, compared to 26% of the HALAVEN treated sarcoma patients in Study 309 (See Precautions, Haematology).

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 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 1559 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 (3.4%). The median time to Grade 2 peripheral neuropathy was 12.6 weeks (post 4 cycles), with the median time to Grade 2 or greater being 53 weeks. Out of the 404 sarcoma patients, 2 patients discontinued treatment with HALAVEN 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 HALAVEN treated breast cancer patients and 3.5% of HALAVEN treated 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%. 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

Of the 1559 breast cancer patients treated with the recommended dose of HALAVEN, 283 patients (18.2%) were ≥65 years of age. In the 404 sarcoma patient population, 90 patients (22.3%) treated with HALAVEN 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 asthenia/fatigue which showed an increasing trend with age. No dose adjustments are recommended for the elderly population.

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 only be administered 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 table 9.

Table 9: 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	
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.

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.

Renal impairment

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

In patients with moderate or severe renal impairment, reduction of the starting dose should be considered.

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). The recommended HALAVEN dose in patients with stage 3 chronic kidney disease (GFR 30-59 mL/min/1.73m^2) or stage 4-5 chronic kidney disease (GFR <30 mL/min/1.73m2) is 0.7 mg/m^2 administered over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle (See Pharmacology, Renal Impairment).

Elderly patients

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

Paediatric patients

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

The safety and efficacy of HALAVEN in children from birth to 18 years of age have not yet been established in soft tissue sarcoma. No data are available.

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 HALAVEN is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic.

During HALAVEN administration via infusion, a substantial part of the solution may be lost as a result of gravity flow therefore flush the intravenous line to ensure administration of the complete dose.

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 HALAVEN (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.

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

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VICTORIA 3004

POISON SCHEDULE OF THE MEDICINE

S4

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

30 August 2012

DATE OF MOST RECENT AMENDMENT

17 November 2016