Halaven® 0.44 mg/mL Eribulin

Solution for injection (Anticancer drug)

1. NAME OF THE MEDICINAL PRODUCT

HALAVEN 0.44 mg/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL contains eribulin mesylate equivalent to 0.44 mg eribulin.
Each 2 mL vial contains eribulin mesylate equivalent to 0.88 mg eribulin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

HALAVEN monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (see section 5.1【Clinical efficacy】). Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

HALAVEN is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1).

4.2. Posology and method of administration

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

Posology

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle., If desired, the dose may be diluted in up to 100 mL of normal saline for injection (an aqueous solution of 0.9% w/v of sodium chloride [NaCl]).

Good peripheral venous access, or a patent central line, should be ensured prior to administration. There is no evidence that eribulin mesylate is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic.

Please note:
In the EU the recommended dose refers to the base of the active substance (eribulin). Calculation of the individual dose to be administered to a patient must be based on the strength

of the ready to use solution that contains 0.44 mg/mL eribulin and the dose recommendation of 1.23 mg/m^2. The dose reduction recommendations shown below are also shown as the dose of eribulin to be administered based on the strength of the ready to use solution.

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

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

Dose delays during therapy

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

Dose reduction during therapy

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

Dose Reduction Recommendations

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

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

Patients with hepatic impairment

Impaired liver function due to metastases
The recommended dose of eribulin in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of eribulin in patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

Severe hepatic impairment (Child-Pugh C) has not been studied but it is expected that a more marked dose reduction is needed if eribulin is used in these patients.

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

Patients with renal impairment

Patients with severely impaired renal function (creatinine clearance <40 mL/min) may need a reduction of the dose (see section 5.2). The optimal dose for this patient groups remains to be established. Caution and close safety monitoring as advised. No specific dose adjustments are recommended for patients with mild to moderate renal impairment.

Elderly patients

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

Paediatric population

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

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 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 mesylate is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic. For information relevant to the handling of cytotoxic medicinal products see section 6.6.

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Haematology

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

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

Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.

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

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

Peripheral neuropathy

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

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

QT prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, 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.

Excipients

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

4.5. Interaction with other medicinal products and other forms of interaction

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

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

Effects of eribulin on the pharmacokinetics of other medicines

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

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

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

4.6. Fertility, pregnancy, and lactation

Pregnancy

There are no data from the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats. HALAVEN should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

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

Breast-feeding

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

Fertility

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of safety profile

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

Tabulated list of adverse reactions

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

Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Where Grade 3 or 4 reactions occurred, the actual total frequency and the frequency of Grade 3 or 4 reactions are given.

System Organ Class	Adverse Reactions – All Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare or Not Known**
Infections and infestations		Urinary tract infection (8.5%) (G3/4: 0.7%) Pneumonia (1.6%) (G3/4: 1.0%) Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis Herpes zoster	Sepsis (0.5%) (G3/4: 0.5%)[a] Neutropenic sepsis (0.2%) (G3/4: 0.2%)[a] Septic shock (0.2%) (G3/4: 0.2%)[a]	
Blood and lymphatic system disorders	Neutropenia (53.6%) (G3/4: 46.0%) Leukopenia (27.9%) (G3/4: 17.0%) Anaemia (21.8%) (G3/4: 3.0%)	Lymphopenia (5.7%) (G3/4: 2.1%) Febrile neutropenia (4.5%) (G3/4: 4.4%)[a] Thrombocytopenia (4.2%) (G3/4: 0.7%)		[*]Disseminated intravascular coagulation[b]
Metabolism and nutrition disorders	Decreased appetite (22.5%) (G3/4: 0.7%)[d]	Hypokalaemia (6.8%) (G3/4: 2.0%) Hypomagnesaemia (2.8%) (G3/4: 0.3%) Dehydration (2.8%) (G3/4: 0.5%)[d] Hyperglycaemia Hypophosphataemia Hypocalcaemia		
Psychiatric disorders		Insomnia Depression		
Nervous system disorders	Peripheral neuropathy[c] (35.9%) (G3/4: 7.3%) Headache (17.5%) (G3/4: 0.7%)	Dysgeusia Dizziness (9.0%) (G3/4: 0.4%)[d] Hypoaesthesia Lethargy Neurotoxicity		
Eye disorders		Lacrimation increased (5.8%) (G3/4: 0.1%)[d] Conjunctivitis		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders		Tachycardia		
Vascular disorders		Hot flush Pulmonary embolism (1.3%) (G3/4: 1.1%)[a]	Deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (15.2%)[a] (G3/4: 3.5%)[a] Cough (15.0%) (G3/4: 0.5%)[d]	Oropharyngeal pain Epistaxis Rhinorrhoea	Interstitial lung disease (0.2%) (G3/4: 0.1%)	

System Organ Class	Adverse Reactions – All Grades			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare or Not Known**
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] Gastroesophageal 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/Toxic epidermal necrolysis[b]
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia (20.4%) (G3/4: 1.0%) Back pain (12.8%) (G3/4: 1.5%) Pain in extremity (10.0%) (G3/4: 0.7%)[d]	Bone pain (6.7%) (G3/4: 1.2%) Muscle spasms (5.3%) (G3/4: 0.1%)[d] Musculoskeletal pain Musculoskeletal chest pain Muscular weakness		
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure	
General disorders and administration site conditions	Fatigue/Asthenia (53.2%) (G3/4: 7.7%) Pyrexia (21.8%) (G3/4: 0.7%)	Mucosal inflammation (6.4%) (G3/4: 0.9%)[d] Peripheral oedema Pain Chills Chest pain Influenza like illness		
Investigations	Weight decreased (11.4%) (G3/4: 0.4%)[d]			

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

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

Description of selected adverse reactions

Neutropenia
The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<0.5 x 10^9/L) was 8 days.

Neutrophil counts of <0.5 x 10^9/L that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin in the EMBRACE study.

Neutropenia was reported as a treatment emergent adverse event (TEAE) in 151/404 (37.4% for all grades) in the sarcoma population, compared with 902/1,559 (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 1,314/1,559 (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 1,963 breast cancer and soft tissue sarcoma patients who received eribulin at the recommended dose in clinical trials there was one fatal event each of neutropenic sepsis (0.1%) and febrile neutropenia (0.1%). In addition there were 3 fatal events of sepsis (0.2%) and one of septic shock (0.1%).

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% and 13% of eribulin treated patients received G-CSF in the two Phase 3 breast cancer studies (Studies 305 and 301, respectively). In the Phase 3 sarcoma study (Study 309), 26% of the eribulin treated patients received G-CSF.

Neutropenia resulted in discontinuation in <1% of patients receiving eribulin.

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

Peripheral neuropathy
In the 1,559 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with eribulin was peripheral neuropathy (3.4%). The median time to Grade 2 peripheral neuropathy was 12.6 weeks (post 4 cycles). Out of the 404 sarcoma patients, 2 patients discontinued treatment with eribulin due to peripheral neuropathy. The median time to Grade 2 peripheral neuropathy was 18.4 weeks.

Development of Grade 3 or 4 peripheral neuropathy occurred in 7.4% of breast cancer patients and 3.5% of sarcoma patients. In clinical trials, patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition.

In breast cancer patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 14%.

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

Special populations

Elderly population
Of the 1,559 breast cancer patients treated with the recommended dose of eribulin, 283 patients (18.2%) were ≥65 years of age. In the 404 sarcoma patient population, 90 patients (22.3%) treated with eribulin were ≥65 years of age. The safety profile of eribulin in elderly patients (≥65 years of age) was similar to that of patients <65 years of age except for asthenia/fatigue which showed an increasing trend with age. No dose adjustments are recommended for the elderly population.

Patients with hepatic impairment
Patients with ALT or AST >3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia (see also sections 4.2 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system to
Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560.
Email: pv-center@pom.go.id ; Website: https://e-meso.pom.go.id

4.9. Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX41.

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

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

Clinical efficacy

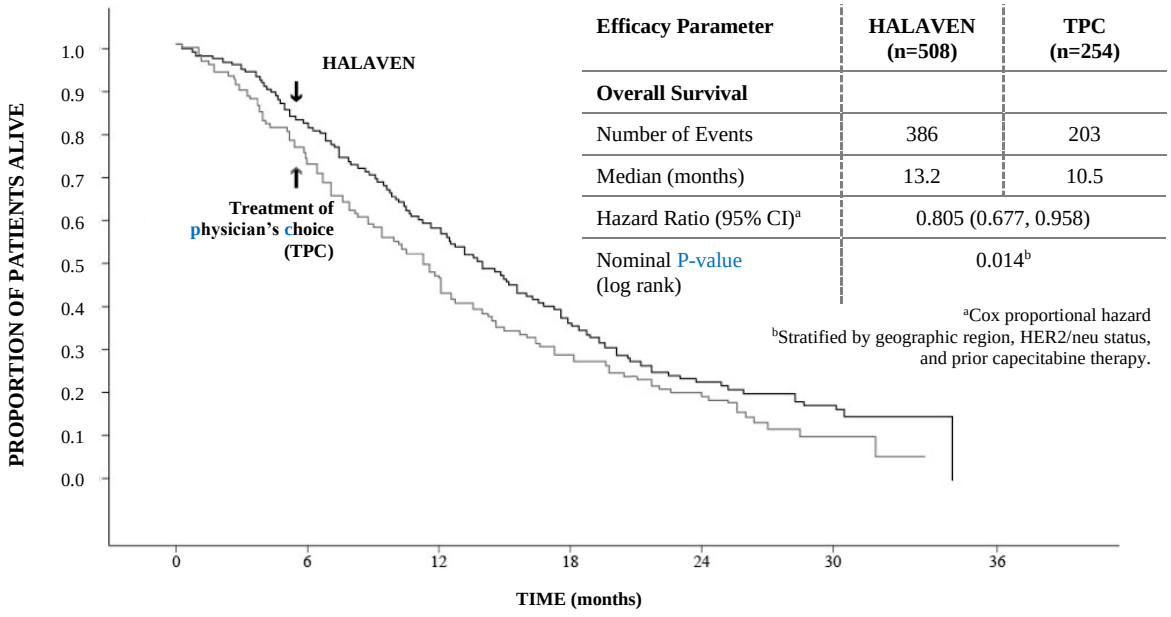
The efficacy of HALAVEN in breast cancer is supported by two single-arm Phase 2 studies and a randomized Phase 3 comparative study.

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 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate) 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 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).

Study 305 – Updated Overall Survival (ITT Population)



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

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

NUMBER OF PATIENTS AT RISK

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

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

	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-value[b] (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/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 128 days (95% CI: 116, 152 days) (4.2 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 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).

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.

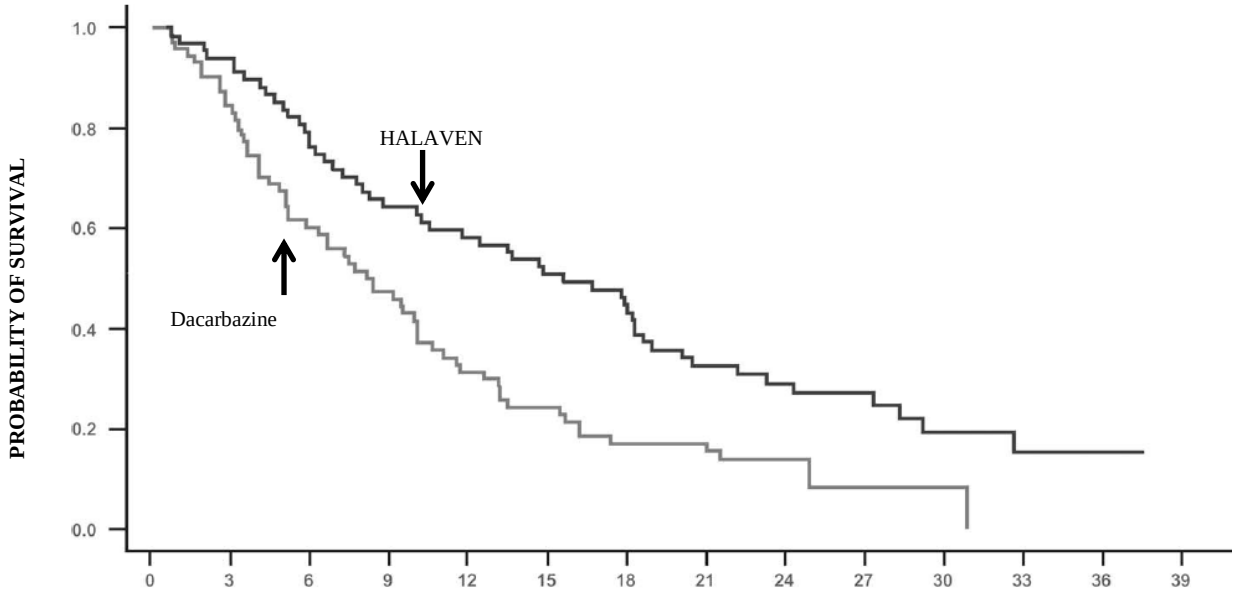
In Study 309, a statistically significant improvement in OS was observed in patients randomized to the eribulin arm compared to the control arm. This translated into a 2-month improvement in median OS (13.5 months for eribulin treated patients vs. 11.5 months for

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.

	Study 309 Liposarcoma Subgroup	
	HALAVEN (n=71)	**Dacarbazine (n=72)**
Overall survival		
Number of events	52	63
Median months	15.6	8.4
Hazard ratio (95% CI)	0.511 (0.346, 0.753)	
Nominal P-value	0.0006	
Progression-free survival		
Number of events	57	59
Median months	2.9	1.7
Hazard ratio (95% CI)	0.521 (0.346, 0.784)	
Nominal P-value	0.0015	

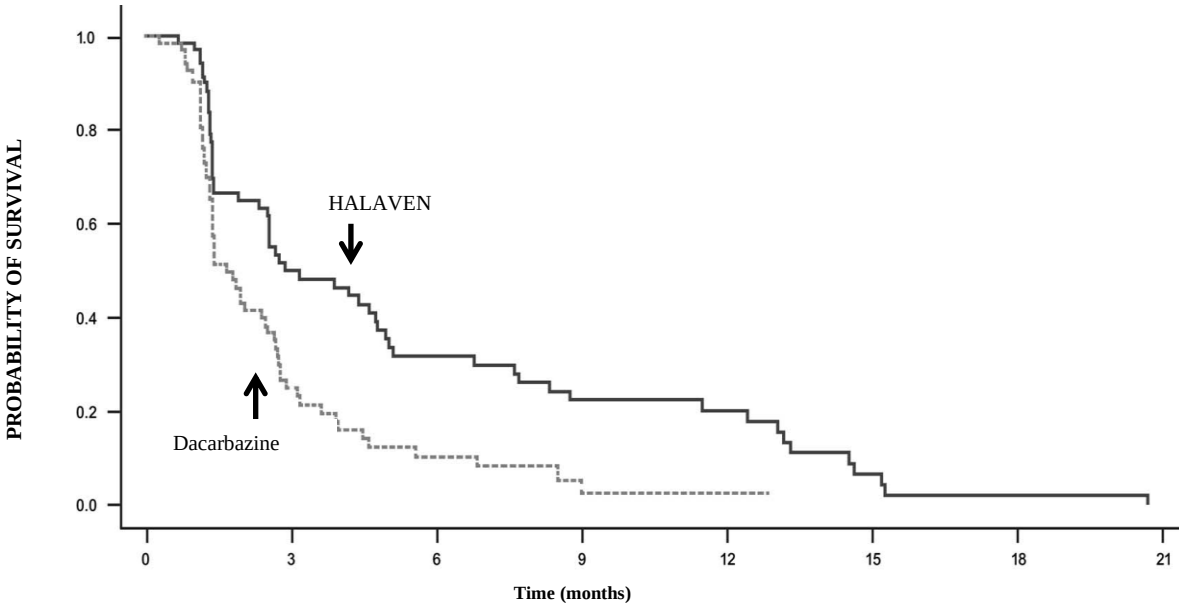
Study 309 – Overall Survival in The Liposarcoma Subgroup



NUMBER OF PATIENTS AT RISK

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

Study 309 – Progression Free Survival in The Liposarcoma Subgroup



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

Paediatric population

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

The European Medicines Agency has deferred the obligation to submit the results of studies with HALAVEN in one or more subsets of the paediatric population for the treatment of rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma. See section 4.2 for information on paediatric use.

5.2. Pharmacokinetic properties

Distribution

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

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

Biotransformation

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

Elimination

Eribulin has a low clearance (range of means 1.16 to 2.42 L/h/m^2). No significant accumulation of eribulin is observed on weekly administration. The pharmacokinetic

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

Renal impairment

A study in patients with different degrees of impaired renal function showed that the exposure of eribulin in patients with moderate renal function (creatinine clearance ≥40 to 59 mL/min, n=6) was similar to patients with normal renal function while the exposure in patients with severe impairment was increased by 75% (creatinine clearance <40 mL/min, n=4). See section 4.2 for treatment recommendations.

5.3. Preclinical safety data

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

No carcinogenicity studies have been conducted with eribulin.

A fertility study was not conducted with eribulin, but based on non-clinical findings in repeated-dose studies where testicular toxicity was observed in both rats (hypocellularity of seminiferous epithelium with hypospermia/aspermia) and dogs, male fertility may be compromised by treatment with eribulin. An embryofoetal development study in rat confirmed the developmental toxicity and teratogenic potential of eribulin mesylate. Pregnant rats were treated with 0.01, 0.03, 0.1 and 0.15 mg/kg at gestation Days 8, 10, and 12. Dose related increased number of resorptions and decreased foetal weight were observed at doses ≥0.1 mg/kg and increased incidence of malformations (absence of lower jaw, tongue, stomach and spleen) was recorded at 0.15 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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

6.2. Incompatibilities

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

6.3. Shelf life

Unopened vials

4 (four) years.

In-use shelf life

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 (0.018 mg/mL to 0.18 mg/mL eribulin in sodium chloride 9 mg/mL (0.9%)) solution for injection should not be stored longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store below 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 teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 2 mL of solution.

6.6. Special precautions for disposal and other handling

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

Using aseptic technique HALAVEN can be diluted up to 100 mL with sodium chloride 9 mg/mL (0.9%) solution for injection. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to

ensure administration of the complete dose. It must not be mixed with other medicinal products and should not be diluted in glucose 5% infusion solution.

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

HARUS DENGAN RESEP DOKTER

Reg. No.: XXXXXXXXXXXXXXX

Manufactured by: **BSP Pharmaceuticals S.p.A., Latina (LT), Italy**

Packaged by:
Eisai Manufacturing Limited
UNITED KINGDOM

Eisai

Imported by:
PT Eisai Indonesia
BOGOR, INDONESIA

Informasi Produk untuk Pasien

HALAVEN® 0.44 mg/mL Larutan Injeksi

Eribulin

Bacalah keseluruhan lembar informasi ini dengan teliti sebelum Anda mulai menggunakan obat ini karena informasi di dalamnya penting untuk Anda ketahui.

- Simpanlah lembar informasi ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakanlah pada dokter atau perawat Anda.
- Jika Anda mengalami efek samping, bicarakanlah dengan dokter atau perawat Anda. Termasuk dugaan efek samping yang tidak tercantum dalam lembar informasi ini. Lihat bagian 4.

Apa isi lembar informasi ini

1. Apa itu HALAVEN dan digunakan untuk apa

HALAVEN mengandung zat aktif eribulin dan adalah merupakan obat anti kanker yang bekerja dengan cara menghambat pertumbuhan dan penyebaran sel-sel kanker.

HALAVEN digunakan pada orang dewasa dengan kanker payudara yang sudah mengalami tahap lanjut lokal atau metastatik (kanker payudara yang sudah menyebar di luar lokasi tumor asal) bila sudah diberikan sedikitnya dua jenis terapi lain tetapi tidak lagi memberikan manfaat.

HALAVEN juga digunakan pada orang dewasa dengan liposarkoma (jenis kanker yang muncul dari jaringan lemak) tahap lanjut lokal atau metastatik bila sudah diberikan terapi lain tetapi tidak lagi memberikan manfaat.

2. Apa yang perlu Anda ketahui sebelum menggunakan HALAVEN

Jangan menggunakan HALAVEN:

- Jika Anda alergi terhadap eribulin mesilate atau salah satu senyawa dalam obat ini (tercantum di bagian 6).
- Jika Anda sedang menyusui.

Perhatian dan peringatan

Bicarakan dengan dokter atau perawat Anda sebelum menggunakan HALAVEN:

- Jika Anda mengalami gangguan/penyakit hati.
- Jika Anda sedang demam atau infeksi.
- Jika Anda mengalami kebas, kesemutan, rasa seperti tertusuk-tusuk, sensitif terhadap sentuhan atau kelemahan otot.
- Jika Anda mengalami gangguan jantung.

Jika Anda mengalami salah satu hal di atas, beritahukan dokter Anda sebagai pertimbangan apakah terapi perlu dihentikan atau dosis obat diturunkan.

DISETUJUI OLEH BPOM : 24/07/2025 ID : EREG17180812500002

Anak dan remaja
HALAVEN tidak direkomendasikan untuk anak berusia kurang dari 18 tahun dengan sarkoma pediatrik karena belum diketahui seberapa efektif obat ini pada kelompok usia tersebut.

Obat lain dan HALAVEN
Beritahukan dokter Anda jika Anda sedang menggunakan, baru saja atau kemungkinan akan menggunakan obat lain.

Kehamilan, menyusui, dan kesuburan
HALAVEN dapat menyebabkan cacat lahir yang berat dan tidak boleh digunakan jika Anda sedang hamil, kecuali dianggap sangat perlu setelah mempertimbangkan semua risiko terhadap Anda dan janin. HALAVEN juga dapat menyebabkan gangguan kesuburan permanen pada laki-laki jika mereka menggunakannya dan mereka perlu mendiskusikan hal ini dengan dokter sebelum memulai terapi. Wanita berusia subur harus menggunakan kontrasepsi yang efektif selama dan hingga 3 bulan setelah menyelesaikan terapi HALAVEN.

HALAVEN tidak boleh digunakan selama menyusui karena mungkin membawa risiko untuk bayi.

Mengemudi dan mengoperasikan mesin
HALAVEN dapat menyebabkan efek samping seperti kelelahan (sangat lazim) dan pusing (lazim). Jangan mengemudi atau mengoperasikan mesin jika Anda merasa lelah atau pusing.

HALAVEN mengandung etanol (alkohol)
Obat ini mengandung sedikit etanol (alkohol), kurang dari 100 mg per satu vial.

3. Bagaimana cara menggunakan HALAVEN
HALAVEN akan disuntikkan oleh dokter atau perawat ke dalam pembuluh darah balik (vena) Anda selama periode 2-5 menit. Dosis yang akan Anda terima bergantung pada luas permukaan tubuh Anda (dinyatakan dalam meter persegi, atau m^2) yang dihitung dari tinggi badan dan berat badan Anda. Dosis HALAVEN yang lazim digunakan adalah 1,23 mg/m^2, tetapi dapat disesuaikan oleh dokter Anda berdasarkan hasil pemeriksaan darah Anda atau faktor lainnya. Untuk memastikan bahwa seluruh dosis HALAVEN sudah masuk, dianjurkan agar dokter menyuntikkan larutan normal salin ke dalam vena setelah HALAVEN disuntikkan.

Seberapa sering Anda akan mendapatkan HALAVEN
HALAVEN biasanya diberikan pada Hari 1 dan 8 dalam siklus 21 hari. Dokter Anda akan menentukan jumlah siklus terapi yang Anda perlukan. Bergantung pada hasil pemeriksaan darah Anda, dokter mungkin perlu menunda pemberian obat hingga hasil pemeriksaan darah kembali ke angka normal. Dokter juga mungkin akan menurunkan dosis obat yang Anda terima.

Apabila Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, silahkan tanyakan pada dokter Anda.

4. Efek samping yang mungkin timbul
Seperti halnya semua obat, HALAVEN dapat menimbulkan efek samping, meskipun tidak semua orang akan mengalaminya.

Jika Anda mengalami salah satu di antara gejala serius berikut, hentikan HALAVEN dan segeralah cari bantuan medis:
- Demam, disertai peningkatan denyut jantung, napas cepat dan dangkal, kulit dingin, pucat, berkeringat dingin atau berbintik, dan/atau kebingungan. Hal-hal tersebut mungkin merupakan tanda dari sepsis – suatu reaksi berat dan serius akibat infeksi. Sepsis tidak lazim ditemukan (dapat dialami oleh hingga 1 di antara 100 orang), dapat mengancam nyawa, dan dapat menyebabkan kematian.
- Kesulitan bernapas, atau bengkak pada wajah, mulut, lidah, atau tenggorokan. Hal-hal tadi mungkin merupakan tanda reaksi alergi yang tidak lazim (dapat dialami oleh hingga 1 di antara 100 orang).
- Ruam kulit yang serius disertai lepuh pada kulit, mulut, mata, dan alat kelamin. Hal-hal tadi mungkin merupakan tanda dari sindrom Stevens Johnson/nekrolisis epidermal toksik. Frekuensi kejadian ini tidak diketahui, tetapi dapat mengancam nyawa.

Efek samping lainnya:

Efek samping yang sangat lazim (dapat terjadi pada lebih dari 1 di antara 10 orang) adalah:
- Penurunan jumlah sel darah putih atau sel darah merah.
- Lelah atau lemas.
- Mual, muntah, konstipasi, diare.
- Kebas, kesemutan, atau rasa seperti ditusuk-tusuk.
- Demam.
- Hilangnya nafsu makan, penurunan berat badan.
- Kesulitan bernapas, batuk.
- Nyeri sendi, otot, dan punggung.
- Nyeri kepala.
- Kerontokan rambut.

Efek samping yang lazim (dapat terjadi hingga 1 di antara 10 orang) adalah:
- Penurunan jumlah platelet (yang dapat menyebabkan memar atau luka lambat berhenti).
- Infeksi dengan demam, pneumonia, menggigil.
- Detak jantung cepat, *flushing*/kemerahan.
- Vertigo, pusing.
- Meningkatnya produksi air mata, konjungtivitis (kemerahan dan nyeri pada permukaan mata), mimisan.
- Dehidrasi, mulut kering, lepuh/luka pada mulut, *oral thrush*, gangguan cerna, rasa terbakar di ulu hati, nyeri atau bengkak pada perut.
- Pembengkakan jaringan lunak, nyeri (terutama nyeri di dada, punggung, dan tulang), kejang atau kelemahan otot.
- Infeksi mulut, saluran napas, dan saluran kemih, nyeri saat berkemih.
- Sakit tenggorokan, pilek atau nyeri pada hidung, gejala seperti flu, nyeri tenggorokan.
- Kelainan hasil pemeriksaan fungsi hati, kadar gula, bilirubin, fosfat, kalium atau magnesium dalam darah.
- Sulit tidur, depresi, perubahan sensasi rasa.
- Ruam, gatal, kelainan pada kuku, kulit kering atau merah.
- Berkeringat berlebihan (termasuk keringat malam).
- Telinga berdenging.
- Bekuan darah di paru-paru.
- *Shingles*/penyakit ruam saraf.
- Bengkak pada kulit dan kebas pada tangan dan kaki.

Efek samping yang tidak lazim (dapat terjadi hingga 1 di antara 100 orang) adalah:
- Bekuan darah.
- Hasil pemeriksaan fungsi hati yang abnormal (hepatotoksisitas).
- Gagal ginjal, adanya darah atau protein dalam urin.
- Radang pada paru yang meluas dan dapat menyebabkan terbentuknya jaringan ikat.
- Radang pankreas.
- Sariawan.

Efek samping yang jarang (dapat terjadi hingga 1 di antara 1000 orang) adalah:
- Gangguan pada sistem pembekuan darah yang serius, yang menyebabkan terbentuknya bekuan darah yang sistemik dan perdarahan internal.

Pelaporan efek samping
Apabila ada keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat, konsultasikan ke dokter, apoteker, atau perawat. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut: PT Eisai Indonesia di (021) 21684107 atau *email*: ptei-safety@hhc.eisai.co.jp. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

5. Bagaimana cara menyimpan HALAVEN
Jauhkan obat ini dari penglihatan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada dus dan vial setelah tulisan EXP. Tanggal kedaluwarsa tersebut merujuk pada hari terakhir bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan membuang obat atau sisa obat melalui sistem pembuangan sampah atau limbah rumah tangga. Mintalah bantuan apoteker Anda untuk membuang obat yang sudah tidak Anda gunakan. Tindakan seperti ini dapat membantu perlindungan lingkungan.

6. Isi kemasan dan informasi lain
Apa isi HALAVEN
- Zat aktifnya adalah eribulin. Setiap vial 2 mL mengandung eribulin mesilate yang setara dengan 0,88 mg eribulin.
- Komposisi lainnya adalah etanol anhidrat dan *water for injections*, dengan asam klorida dan natrium hidroksida mungkin ada dalam jumlah yang sangat sedikit.

Seperti apa tampilan HALAVEN dan apa isi kemasan
HALAVEN berupa larutan injeksi yang bening, encer, dan tidak berwarna yang dikemas dalam vial kaca berisi 2 mL larutan. Setiap dus berisi 1 vial.

HARUS DENGAN RESEP DOKTER

Reg. No.: XXXXXXXXXXXXXXX

DISETUJUI OLEH BPOM : 24/07/2025 ID : EREG17180812500002

Dibuat oleh: **BSP Pharmaceuticals S.p.A., Latina (LT), Italy**

Dikemas oleh:
Eisai Manufacturing Limited
UNITED KINGDOM

Diimpor oleh:
PT Eisai Indonesia
BOGOR, INDONESIA

Untuk informasi lebih lanjut Anda dapat menghubungi:

PT Eisai Indonesia
Trinity Tower Lt 10. Suites 09-15
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Tel: +62-21-21684107

DISETUJUI OLEH BPOM : 24/07/2025 ID : EREG17180812500002