APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Halaven (solution for injection)

COMPOSITION

Each 2 ml vial contains eribulin mesilate equivalent to 0,88 mg of eribulin.

Inactive ingredients:

5 % (v/v) ethanol in water for injections.

Sugar free

CATEGORY AND CLASS

A. 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Eribulin mesilate is a synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai* that inhibits tubulin formation and mitotic spindle function, leading to phase G2/M cell-cycle arrest.

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.

Pharmacokinetic properties

Distribution

Eribulin is rapidly and widely distributed, hence has a large volume of distribution of 43 to 114 l/m2.

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 of 1,16 to 2,42 l/h/m^2 with a terminal half-life of approximately 40 h. No significant accumulation of eribulin was observed on weekly administration. The pharmacokinetic properties are not dose or time dependent in the range of eribulin doses of 0,22 to 3,53 mg/m^2.

Eribulin is eliminated primarily by biliary excretion.

After administration of 14^C-eribulin to patients, approximately 82 % of the dose was eliminated in faeces and only 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 eribulin 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. Eribulin 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 “Dosage and Directions for

Use”.

Renal impairment

Increased Halaven exposure was seen in patients with moderately or severely impaired renal function, with high between-subject variability. The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with

normal renal function (Creatinine clearance: ≥ 80 ml/min; n=6), moderate (30-50 ml/min; n=7) or severe (15 to <30

ml/min; n=6) renal impairment. Creatinine clearance was estimated with the Cockcroft-Gault formula. A 1,5-fold (90

% CI: 0,9-2,5) higher dose-normalised $AUC_{(0\text{-}inf)}$ was observed in patients with moderate and severe renal impairment.

See “Dosage and Directions for Use” for treatment recommendations.

INDICATIONS

Halaven is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see “Pharmacodynamic properties”). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

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

CONTRAINDICATIONS

- Hypersensitivity to eribulin or to any of the excipients of Halaven.
- Pregnancy and lactation (see “Human Reproduction”).

WARNINGS AND SPECIAL PRECAUTIONS

Haematology

Myelosuppression is dose dependent and primarily manifested as neutropenia (see “Side effects”). 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 Absolute Neutrophil Count (ANC) values ≥ 1,5 x 10^9/l and platelets > 100 x
10^9/l.

Febrile neutropenia occurred in < 5 % of breast cancer patients treated with Halaven. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommendations in section “Dosage and Directions for Use”.
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 medical practitioner’s discretion in accordance with relevant guidelines (see “Pharmacodynamic properties”).

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 “Dosage and Directions for Use”).

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 Halaven concentration. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradydysrhythmias and electrolyte abnormalities.

Concomitant treatment with medicines known to prolong the QT interval, including Class Ia and III antidysrhythmics is not recommended.

Hypokalaemia or hypomagnesaemia 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.

Effects on ability to drive and use machines

Halaven may cause tiredness and dizziness which may influence the ability to drive or use machines. Patients should be advised not to drive or use machines when receiving Halaven.

INTERACTIONS

Formal interaction studies have not been done.

Halaven is mainly (up to 70 %) eliminated through biliary excretion. The transport protein involved in this process is unknown.

Halaven 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 interactions are expected with CYP3A4 inhibitors and inducers.

Halaven exposure (AUC and C_{max}) was unaffected by rifampicin, a CYP3A4 inducer.

Effects of Halaven on the pharmacokinetics of other medicine

Halaven may inhibit CYP3A4 according to *in vitro* data.

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, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus,

tacrolimus).

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

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

HUMAN REPRODUCTION

Pregnancy

Halaven is contraindicated in pregnancy and lactation.

There are no data from the use of Halaven in pregnant women.

Halaven is embryotoxic, foetotoxic, and teratogenic in rats.

Halaven should not be used during pregnancy (see “Contraindications”).

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.

Lactation

There is no information on the excretion of Halaven or its metabolites in human or animal breast milk.

Mothers on Halaven must not breastfeed their infants (see “Contraindications”).

Fertility

Testicular toxicity has been observed in rats and dogs.

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

DOSAGE AND DIRECTIONS FOR USE

Halaven should be administered in units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a qualified medical practitioner experienced in the appropriate

use of cytotoxic medicines.

Dosage

The recommended dose of Halaven as ready-to-use solution is 1,23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Day 1 and 8 of every 21-day cycle.

IMPORTANT:

PLEASE NOTE:

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 recommendation 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 US and Switzerland, the recommended dose is based on the salt form (eribulin mesilate).

Patients may experience nausea or vomiting. Anti-emetic 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-haematological 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 Halaven
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

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

Patients with hepatic impairment

Impaired liver function due to metastases:

The recommended dose of Halaven in patients with mild hepatic impairment (Child-Pugh A) is 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 Halaven 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 Halaven is used in these patients.

Impaired liver function due to cirrhosis:

This patient group has not been studied. The doses given 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 moderately or severely impaired renal function (creatinine clearance < 50 ml/min) will have increased Halaven exposure.

The recommended dose of Halaven in patients with moderate renal impairment (creatinine clearance (CLcr) 30-50 ml/min) is 1,1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The safety of Halaven was not studied in patients with severe renal impairment (CrCl < 30 ml/min). For all patients with renal impairment, caution and close safety monitoring is advised. (See "Pharmacokinetic Properties").

Elderly patients

No specific dose adjustments are recommended based on the age of the patient.

Paediatric population

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 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 % NaCl) solution for injection. It should not be diluted in glucose 5 % infusion solution.

In the absence of compatibility studies Halaven must not be mixed with other medicines except sodium chloride 9 mg/ml (0,9 % NaCl) solution for injection.

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.

Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0,9 % NaCl) solution for injection to ensure administration of the complete dose. Halaven is a cytotoxic anticancer medicine and 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 Halaven solution, the skin should be washed immediately and thoroughly with soap and water. If the Halaven solution comes into contact with 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 medicines.
Pregnant staff should not handle Halaven.

Discard any unused portion of the vial.

SIDE EFFECTS

Summary of safety profile

The most commonly reported adverse reactions related to Halaven, are bone marrow suppression manifested as neutropenia, leukopenia, anaemia and 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 the undesirable effects reported. Other undesirable effects include fatigue, alopecia, increased liver enzymes, sepsis and musculoskeletal pain syndrome.

Tabulated list of adverse reactions

Unless otherwise noted, the table below shows the incidence 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) and uncommon (≥ 1/1000 to < 1/100). 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**
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 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 %)	

Metabolism and nutrition disorders	Decreased appetite (22,5 %) (G3/4: 0,7 %)	Hypokalaemia (6,8 %) (G3/4: 2,0 %) Hypomagnesaemia (2,8 %) (G3/4: 0,3 %) Dehydration (2,8 %) (G3/4: 0,5 %) Hyperglycaemia Hypophosphataemia	
Psychiatric disorders		Insomnia Depression	
Nervous system disorders	Peripheral neuropathy[b] (35,9 %) (G3/4: 7,3 %) Headache (17,5 %) (G3/4: 0,7 %)	Dysgeusia Dizziness (9,0 %) (G3/4: 0,4 %) Hypoaesthesia Lethargy Neurotoxicity	
Eye disorders		Lacrimation increased (5,8 %) (G3/4: 0,1 %) 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 %)	Oropharyngeal pain Epistaxis Rhinorrhoea	Interstitial lung disease (0,2 %) (G3/4: 0,1 %)
Gastrointestinal disorders	Nausea (35,7 %) (G3/4: 1,1 %) Constipation (22,3 %) (G3/4: 0,7 %) Diarrhoea (18,7 %) (G3/4: 0,8 %) Vomiting (18,1 %) (G3/4: 1,0 %)	Abdominal pain Stomatitis (11,1 %) (G3/4: 1,0 %) Dry mouth Dyspepsia (6,5 %) (G3/4: 0,3 %) Gastrooesophageal reflux disease Abdominal distension	Mouth ulceration Pancreatitis
Hepatobiliary disorders		Aspartate aminotransferase increased (7,7 %) (G3/4: 1,4 %) Alanine aminotransferase increased (7,6 %) (G3/4: 1,9 %) Gamma glutamyl transferase increased (1,7 %) (G3/4: 0,9 %) 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 %) Nail disorder Night sweats Dry skin Erythema Hyperhidrosis Palmar plantar erythrodysaesthesia (1,0 %) (G3/4: 0,1 %)	Angioedema
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 %)	Bone pain (6,7 %) (G3/4: 1,2 %) Muscle spasms (5,3 %) (G3/4: 0,1 %) 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 %) Peripheral oedema Pain Chills Influenza-like illness Chest pain	
Investigations	Weight decreased (11,4 %) (G3/4: 0,4 %)		

[a] Includes Grade 5 events

[b] Includes preferred terms of peripheral neuropathy, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy, peripheral sensorimotor neuropathy and demyelinating polyneuropathy

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

Description of selected adverse reactions

Neutropenia

The neutropenia 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 Halaven.

Neutropenia was reported as a Treatment Emergent Adverse Event (TEAE) in 151/404 (37,4 % for all grades) in the sarcoma population, compared with 902/1559 (57,9 % for all grades) in the breast cancer population. The combined grouped TEAE and neutrophil laboratory abnormality frequencies

were 307/404 (76,0 %) and 1314/1559 (84,3 %), respectively. The median duration of treatment was 12,0 weeks for sarcoma patients and 15,9 weeks for breast cancer patients.

Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported. Out of 1 963 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 %).

Severe neutropenia may be managed by the use of G-CSF or equivalent at the medical practitioner's discretion in accordance with relevant guidelines.
18 % and 13 % of Halaven-treated patients received G-CSF in the two phase 3 breast cancer studies.
In the phase 3 sarcoma study, 26 % of the Halaven-treated patients received G-CSF.
Neutropenia resulted in discontinuation in < 1 % of patients receiving Halaven.

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 Halaven was peripheral neuropathy (3,4 %). The median time to Grade 2 peripheral neuropathy was 12,6 weeks
(post 4 cycles). Out of the 404 sarcoma patients, 2 patients discontinued treatment with 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 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 Halaven, increased levels of liver enzymes were reported with initiation of Halaven treatment. Such elevations appeared to have occurred early with Halaven treatment in cycle 1 – 2 for the majority of these patients and, whilst thought likely to be a phenomenon of adaptation to Halaven treatment by the liver and not a sign of significant liver toxicity in most patients, hepatotoxicity has also been reported.

Post-marketing experience

Post-marketing spontaneous side effects include disseminated intravascular coagulation and Stevens-Johnson syndrome/toxic epidermal necrolysis. The frequencies are not known.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdosage reported were hypersensitivity reactions and neutropenia.
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.

IDENTIFICATION

Clear, colourless aqueous solution for injection essentially free from visible particles of foreign matter.

PRESENTATION

5 ml Type I clear glass vial, with teflon-coated, grey butyl rubber stopper and blue flip-off aluminium over seal, containing a sufficient volume to allow the withdrawal of 2 ml of solution.
The pack sizes are cartons of 1 or 6 vials.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

In-use instructions

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 to 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

48/26/0047

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