

*Note: Product Name, Item Code and Pharma code Position & Orientation will be changed based on folding feasibility

2.1 Recommended Dose

The recommended dose of eribulin mesylate injection is 1.4 \mbox{mg}/\mbox{m}^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle

The recommended dose of eribulin mesylate injection in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/ 1² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle [see Use in Specific Populations

(8.6)]

E

Folding Pattern 50

The recommended dose of eribulin mesylate injection in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle [see Use in Specific Populations (8.6)1.

potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with eribulin mesylate and for at least 2 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with eribulin mesylate and for 3.5 months following the final dose [see Use in Specific Populations (8.1)].

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating eribulin mesylate and monitor these electrolytes periodically during therapy. Avoid eribulin mesylate in patients with congenital

njection in patients with moderate clearance (CLcr) 15 to 49 mL/min) is 1.1 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle [see Use in Specific Populations (8.7)].

2.2 Dose Modification

Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer eribulin mesylate injection on Day 1 or Day 8 for any of the following: $\Delta NC < 1.000/mm^3$
 - Platelets < 75,000/mm³
 - Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
- If toxicities do not resolve or improve to \leq Grade 2 severity by Day 15, omit the dose. If toxicities resolve or improve to \leq Grade 2 severity by Day 15, administer eribulin mesylate injection at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume eribulin
- mesulate injection at a reduced dose as set out in Table 1
- Do not re-escalate eribulin mesylate injection dose after it has been reduced.

Table 1: Recommended Dose Reductions

Event Description	Recommended Eribulin Mesylate Injection Dose	
Permanently reduce the 1.4 $\rm mg/m^2$ Eribulin Mesylate Injection dose for any of the following:		
ANC <500/mm ³ for >7 days		
ANC <1,000 /mm ³ with fever or infection	1.1 mg/m ²	
Platelets <25,000/mm ³		
Platelets <50,000/mm ³ requiring transfusion		
Non-hematologic Grade 3 or 4 toxicities		
Omission or delay of Day 8 eribulin mesylate injection dose in previous cycle for toxicity		
$\textbf{Occurrence}$ of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m ²	
$\textbf{Occurrence}$ of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue Eribulin Mesylate Injection	
ANC = absolute neutrophil count. Toxicities graded in accordance with National Cancer Institute (NCI) Comm	on Terminology Criteria for	

e (NCI) (Adverse Events (CTCAE) version 3.0.

2.3 Instructions for Preparation and Administration

Aseptically withdraw the required amount of eribulin mesylate injection from the single-dose vial and administer undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP.

Do not dilute in or administer through an intravenous line containing solutions with dextrose. Do not administer in the same intravenous line concurrent with the other medicinal products.

Store undiluted eribulin mesylate injection in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration at 4°C (40°F). Store diluted solutions of eribulin mesylate injection for up to 4 hours at room temperature or up to 24 hours under refrigeration at 4°C (40°F).

Discard unused portions of the vial

3 DOSAGE FORMS AND STRENGTHS

Injection: 1 mg/2 mL (0.5 mg/mL) eribulin mesylate is a clear, colorless, sterile solution in a single-dose vial. 4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

In Study 1, severe neutropenia (ANC < 500/mm³) lasting more than one week occurred in 12% (62/503) of patients with metastatic breast cancer, leading to discontinuation in <1% of patients. Febrile neutropenia (fever >38.5°C with Grade 3 or 4 neutropenia) occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia [see Adverse Reactions (6.1)].

In Study 1, patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin > 1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

In Study 2, severe neutropenia (ANC < 500/mm³) lasting more than one week occurred in 12% (26/222) of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 0.9% of patients treated with eribulin mesylate and fatal neutropenic sepsis in 0.9% [see Adverse Reactions (6.1)].

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of eribulin mesylate and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days [see Dosage and Administration (2.2)]. Clinical studies of eribulin mesylate did not include patients with baseline neutrophil counts below 1,500/mm³.

5.2 Peripheral Neuropathy

In Study 1, Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients with metastatic breast cancer (MBC). Peripheral neuropathy was the most common toxicity leading to discontinuation of eribulin mesylate (5% of patients; 24/503) in Study 1. Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25 to 662 days).

long QT syndrome 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in
- clinical practice.
- The following adverse reactions are discussed in detail in other sections of the labeling:
- Neutropenia [see Warnings and Precautions (5.1)] Peripheral neuropathy [see Warnings and Precautions (5.2)]
- QT prolongation [see Warnings and Precautions (5.4)]

In clinical trials, eribulin mesylate has been administered to 1963 patients including 467 patients exposed to eribulin mesylate for 6 months or longer. The majority of the 1963 patients were women (92%) with a median age of 55 years (range: 17 to 85 years). The racial and ethnic distribution was White (72%). Black (4%), Asian (9%), and other (3%)

Metastatic Breast Cancer

The most common adverse reactions (>25%) reported in patients receiving eribulin mesylate were neutropenia, anemia, astheni/attigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving enautheni/attigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving enautheni/attigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving enauthenia to the series of adverse reaction resulting in discontinuation of eribulin mesylate was peripheral neuropathy (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1 [see Clinical Studies (14.1)]. In Study 1, patients were randomized (2:1) to receive either eribulin mesylate (1.4 mg/m² 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 eribulin mesylate and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving eribulin mesylate and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2: Adverse Reactions^a with a Per-Patient Incidence of at Least 10% in Study 1

Adverse Reactions	Eribulin Mes	Eribulin Mesylate n=503		Control Group n=247	
	All Grades	\geq Grade 3	All Grades	≥ Grade 3	
Blood and lymphatic system disorders ^b	1				
Neutropenia	82%	57%	53%	23%	
Anemia	58%	2%	55%	4%	
Nervous system disorders					
Peripheral neuropathy ^c	35%	8%	16%	2%	
Headache	19%	<1%	12%	<1%	
General disorders			•		
Asthenia/Fatigue	54%	10%	40%	11%	
Pyrexia	21%	<1%	13%	<1%	
Mucosal inflammation	9%	1%	10%	2%	
Gastrointestinal disorders					
Nausea	35%	1%	28%	3%	
Constipation	25%	1%	21%	1%	
Vomiting	18%	1%	18%	1%	
Diarrhea	18%	0	18%	0	
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%	
Metabolism and nutrition disorders					
Decreased weight	21%	1%	14%	<1%	
Anorexia	20%	1%	13%	1%	
Respiratory, thoracic, and mediastinal	disorders				
Dyspnea	16%	4%	13%	4%	
Cough	14%	0	9%	0	
Skin and subcutaneous tissue disorders	3				
Alopecia	45%	NAd	10%	NAd	
Infections					
Urinary Tract Infection	10%	1%	5%	0	

peripheral sensory neuropathy, and paraesthesia not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received eribulin mesylate in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in 11% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm³) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte-macrophage colony stimulating factor) was used in 19% of patients who received eribulin mesylate.

- <u>Less Common Adverse Reactions</u>: The following additional clinically important adverse reactions were reported in \geq 5% to <10% of the eribulin mesylate-treated group:
- Blood and Lymphatic System Disorders: thrombocytopenia
- Eye Disorders: increased lacrimation Gastrointestinal Disorders: dyspepsia

Respiratory Disorders: cough (18%)

- Metabolism and Nutrition Disorders: hyperglycemia
- Musculoskeletal and Connective Tissue Disorders: muscle spasms, musculoskeletal pain Nervous System Disorders: dizziness, dysgeusia

Includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort. Not applicable; (grading system does not specify > Grade 2 for alopecia).

Gastrointestinal Disorders: nausea (41%); vomiting (19%), diarrhea (17%)

General Disorders: asthenia/fatique (62%); peripheral edema (12%)

Other clinically important adverse reactions occurring in \geq 10% of the eribulin mesylate-treated patients were:

Metabolism and Nutrition Disorders: decreased appetite (19%) Musculoskeletal and Connective Tissue Disorders: arthralgia/myalgia (16%); back pain (16%)

- Psychiatric Disorders: insomnia, anxiety Respiratory, Thoracic, and Mediastinal Disorders: oropharyngeal pain
- Vascular Disorders: hypotension

Table 4: Laboratory Abnormalities Occurring in ≥10% (all Grades) of Patients Treated on the Eribulin Mesylate arm and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4)^a (Study 2)[†]

	Eribulin Mesylate		Dacarbazine	
Laboratory Abnormality	All Grades	Grades 3 - 4	All Grades	Grades 3 – 4
Hematology				
Anemia	70%	4.1%	52%	6%
Neutropenia	63%	32%	30%	8.9%
Chemistry				
Increased alanine aminotransferase (ALT)	43%	2.3%	28%	2.3%
Increased aspartate aminotransferase (AST)	36%	0.9%	16%	0.5%
Hypokalemia	30%	5.4%	14%	2.8%
Hypocalcemia	28%	5%	18%	1.4%
Hypophosphatemia	20%	3.2%	11%	1.4%

[†] Laboratory results were graded per NCI CTCAE v4.03.

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of eribulin mesylate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Blood and Lymphatic System Disorders: lymphopenia
- Gastrointestinal Disorders: pancreatitis Hepatobiliary Disorders: hepatotoxicity
- Immune System Disorders: drug hypersensitivity
- Infections and Infestations: pneumonia, sepsis/neutropenic sepsis Metabolism and Nutrition Disorders: hypomagnesemia, dehydration
- Respiratory, thoracic and mediastinal disorders: interstitial lung disease
- Skin and Subcutaneous Tissue Disorders: pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis 7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Eribulin Mesylate

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-glycoprotein (P-gp) inhibitors. clinically meaningful differences in exposure (AUC) were not observed in patients with advanced solid tumors when eribulin mesylate was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a P-gp inhibitor) and when eribulin mesylate was administered with or without rifampin (a CYP3A4 inducer) [see Clinical Pharmacology (12.3)].

7.2 Effects of Eribulin Mesylate on Other Drugs

Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CVP2C9, CVP2C19 or CVP3A4 enzymes at relevant clinical concentrations. Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from an animal reproduction study and its mechanism of action, eribulin mesylate can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of eribulin mesylate during pregnancy. In an animal reproduction study, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose [see Data]. Advise pregnant women of the potential risk to a fetus.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area. Increased abortion and severe fetal external or soft tissue malformations, including the absence of a lower jaw and tongue, or stomach and spleen, were observed at doses 0.64 times the recommended human dose of 1.4 mg/m² based on body surface area. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at doses at or above a maternally toxic dose of approximately 0.43 times the recommended human dose.

8.2 Lactation

Risk Summary

There is no information regarding the presence of eribulin mesylate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. No lactation studies in animals were conducted. Because of the protection many of the cricks of the production in breastfeld infants from enbulin messiver conductor. Dodado in the protectial for serious adverse reactions in breastfeld infants from enbulin messiver, advise women not to breastfeed during treatment with eribulin messiver and for 2 weeks after the final dose.

Pharma Code: 437



8.3 Females and Males of Reproductive Potentia

Contraception

Females

Based on findings from an animal reproduction study and its mechanism of action, eribulin mesylate can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with eribulin mesylate and for at least 2 weeks following the final dose.

Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with eribulin mesylate and for 3.5 months following the final dose

Infertility

Males

Based on animal data, eribulin mesylate may result in damage to male reproductive tissues leading to impaired fertility of

unknown duration [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of eribulin mesylate in pediatric patients have not been established.

Pediatric use information describing clinical studies in which efficacy was not demonstrated is approved for Eisai Inc's HALAVEN® (eribulin mesylate) injection. However, due to Eisai Inc's marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use

Study 1 did not include sufficient numbers of subjects with metastatic breast cancer aged 65 years and older to determine whether they respond differently from younger subjects. Of the 827 subjects who received the recommended dose and schedule of eribulin mesylate in clinical studies with advanced breast cancer, 15% (121/827) were 65 and older, and 2%

(17/827) patients were 75 and older. No overall differences in safety were observed between these subjects and younger

Clinical studies of eribulin mesylate did not include a sufficient number of subjects in Study 2 aged 65 years and older to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

Administration of eribulin mesylate at a dose of 1.1 mg/m² to patients with mild hepatic impairment and 0.7 mg/m² to patients with moderate hepatic impairment resulted in similar exposure to eribbilin as a dose of 1.4 mg/m^2 to patients with mide hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate Pugh B). Eribulin mesylate was not studied in patients with severe hepatic impairment (Child-Pugh C) [see Dosage and stration (2.1), Člinical Pharmacology (12.3)].

8.7 Renal Impairment

For patients with moderate or severe renal impairment (CLcr 15 to 49 mL/min), reduce the starting dose to 1.1 mg/m² [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

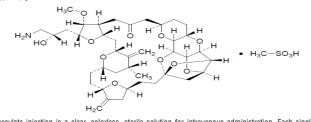
10 OVERDOSAGE

Overdosage of eribulin mesylate has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for eribulin mesylate overdose.

11 DESCRIPTION

Eribulin mesylate injection contains eribulin mesylate, a microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*. The chemical name for eribulin mesylate is 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9,H15H-furo]2,2-i]furo]2',3':5,6] pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one, 2-[(2S)-3-amino-2-hydroxypropy]]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-,(2R,3R,38,5,7R,88,59,10a,R,11S,12R,138,R,13b,5,15S,18S,21S,24S,26R,28R, 29aS)-, methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 for free base). The empirical formula is C40H59NO11•CH4O3S. Eribulin mesylate has the following structural formula



Fribulin mesulate injection is a clear colorless sterile solution for intravenous administration. Each sincle-dose vial contains 1 mg of eribulin mesylate in 2 mL of solution. Each mL of solution contains 0.5 mg of eribulin mesylate (equivalent to 0.44 mg eribulin) in dehydrated alcohol (5% v/v) and water for injection (95% v/v). Sodium hydroxide or hydrochloric acid may be used for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G_2M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of eribulin mesylate on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m² of eribulin mesylate on Days 1 and 8 of a

regimens in both arms. In Study 1, a statistically significant improvement in overall survival was observed in patients randomized to the eribulin

Table 5: Comparison of Overall Survival in Eribulin Mesylate and Control Arm - Study 1

Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitab

Figure 1: Updated Overall Survival Analysis for Study 1

Eribulin Mesylate (N=508)

CONTROL (N=254) -

18

The efficacy and safety of eribulin mesylate were evaluated in Study 2, an open-label, randomized (1:1), multicenter,

active-controlled trial. Eligible patients were required to have unresectable, locally advanced or metastatic liposarcoma or leiomyosarcoma, at least two prior systemic chemotherapies (one of which must have included an anthracycline), and disease progression within 6 months of the most recent chemotherapy regimen. Patients were randomized to eribuin mesylate 1.4 mg/m² administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of

850 mg/m², 1000 mg/m² or 1200 mg/m² administered intravenously every 21 days (dacarbazine dose was selected by the investigator prior to randomization). Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by histology (liposarcoma or leiomyosarcoma), number of prior therapies (2 vs. > 2), and geographic region (U.S. and Canada vs. Western Europe, Australia, and Israel vs. Eastern Europe, Latin America,

and Asia). The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were progression-free survival (PFS) and confirmed objective response rate (ORR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Patients in the dacarbazine arm were not offered eribulin

A total of 446 patients were randomized, 225 to the eribulin mesylate arm and 221 to the dacarbazine arm. The median

age was 56 years (range: 24 to 83); 33% were male; 73% were White; 44% had EOG performance status (FS) 0 and 53% had ECOG PS 1; 68% had leiomyosarcoma and 32% had liposarcoma; 39% were enrolled in U.S. and Canada (Region 1) and 46% were enrolled in Western Europe, Australia, and Israel (Region 2); and 47% received more than two

prior systemic chemotherapies. The most common (>40%) prior systemic chemotherapies were doxorubicin (90%),

Of the 143 patients with liposarcoma, the median age was 55 years (range: 32 to 83); 62% were male, 72% were White; 41% had ECOG PS of 0 and 53% had ECOG PS of 1; 35% were enrolled in Region 1 and 51% were enrolled in Region 2; and 44% received more than two prior systemic chemotherapies. The distribution of subtypes of liposarcoma, based on

local histologic assessment were 45% dedifferentiated 37% myxoid/round cell and 18% pleomorphic

142 61

24

54 26

30

11 5

0

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

Eribulin Mesvlate

(n=508)

274

13.1 (11.8, 14.3)

386

13.2 (12.1, 14.4)

duration was 4.2 months (95% CI: 3.8. 5.0 months)

Overall Survival

P value^t

therapy

Primary survival analysis

Median, months (95% CI)

Hazard Ratio (95% CI)^a

Updated survival analysis

Median, months (95% CI)

1.0

0.9

0.8

0.7

0.6

0.5

0.4

0.3

0.2

0.1

0.0

Number of 508 hts at Risk 254

mesylate at the time of disease progression.

14.2 Liposarcoma

406 178

ifosfamide (62%), gemcitabine (59%), trabectedin (50%), and docetaxel (48%).

274 106

Number of deaths

CI = confidence interval

Number of deaths

(positive: 16%, negative: 74%), triple negative status (ER',PR', HER2/neu': 19%), presence of visceral disease (82%, including 60% liver and 38% lung) and bone disease (61%), and number of sites of metastases (greater than two: 50%), were also similar in the eribulin mesylate and control arms. Patients received a median of four prior chemotherapy

0.81 (0.66, 0.99)

0.04

Control Arm

(n=254)

148

10.6 (9.3, 12.5)

203

10.6 (9.2, 12.0)

15 REFERENCES

Neutropenia

Embryo-Fetal Toxicity

Specific Populations (8.2)].

Visakhapatnam-530049, India.

Manufactured hv: Gland Pharma Limited

Manufactured for: Apotex Corp. Weston, FL USA 33326

Revised: 02/2024

o chills

Breast cancer

Liposarcoma

ncluding if you:

you have side effects.

What is Eribulin Mesylate Injection?

have liver or kidney problems

mesylate injection

1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 60505-6289-0

Eribulin Mesylate Injection: 1 mg/2 mL (0.5 mg/mL) single-dose vial.

Discard unused portion. One vial per carton.

Eribulin mesvlate injection is a clear, colorless solution,

mesylate arm compared to the control arm (see Table 5). An updated, unplanned survival analysis, conducted when 77% of events had been observed (see Figure 1), was consistent with the primary analysis. In patients randomized to eribulin mesylate, the objective response rate by the RECIST criteria was 11% (95% CI: 8.6%, 14.3%) and the median response

17 PATIENT COUNSELING INFORMATION

their original cartons. Eribulin mesylate injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

Store at 25°C (77°F); excursions permitted to 15° to 30° C (59° to 86°F). Do not freeze or refrigerate. Store the vials in

Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination [see Warnings and Precautions (5.1)].

<u>Peripheral Neuropathy</u> Advise patients to inform their healthcare providers of new or worsening numbness, tingling and pain in their extremities [see Warnings and Precautions (5.2)].

known or suspected pregnancy [see Warnings and Precautions (5.3), Use in Specific Populations (8.1)].

eribulin mesylate and for 3.5 months following the final dose [see Use in Specific Populations (8.3)].

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a

Advise females of reproductive potential to use effective contraception during treatment with eribulin mesylate and

Advise relates of the productive potential to use encode outside pluto using relation with encoding measure and for at least 2 weeks after the final does *[See Use in Specific Populations (8.3)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with

Lactation Advise women not to breastfeed during treatment with eribulin mesylate and for 2 weeks after the final dose [see Use in

PATIENT INFORMATION

FRIBULIN MESYLATE (ER-i-BUE-lin MES-i-late)

Low white blood cell count (neutropenia). This can lead to serious infections that could lead to death. Your

and during treatment. Call your healthcare provider right away if you develop any of these symptoms of

Numbness, tingling, or pain in your hands or feet (peripheral neuropathy). Peripheral neuropathy is com with eribulin mesylate injection and sometimes can be severe. Tell your healthcare provider if you have new or

Your healthcare provider may delay, decrease your dose, or stop treatment with eribulin mesylate injection if

See "What are possible side effects of Eribulin Mesylate Injection?" for more information about side effects.

who have already received certain types of anticancer medicines after the cancer has spread

Before you receive Eribulin Mesylate Injection, tell your healthcare provider about all of your medical conditions,

are pregnant or plan to become pregnant. Eribulin mesylate injection can harm your unborn baby. Tell your

healthcare provider right away if you become pregnant or think you are pregnant during treatment with eribulin

Females who are able to become pregnant should use an effective birth control during treatment with

eribulin mesylate injection and for at least 2 weeks after the final dose of eribulin mesylate injection. Males should use an effective form of birth control when having sex with female partners who are able to

become pregnant during treatment with eribulin mesylate injection and for 3 1/2 months (14 weeks) after

that cannot be treated with surgery or has spread to other parts of the body, and who have received treatment with a certain type of anticancer medicine

t is not known if eribulin mesylate injection is safe and effective in children under 18 years of age.

have heart problems, including a problem called congenital long QT syndrome have low potassium or low magnesium in your blood

healthcare provider will check your blood cell counts before you receive each dose of eribulin mesylate injection

cough

o burning or pain when you urinate

What is the most important information I should know about eribulin mesylate injection

Eribulin mesylate injection can cause serious side effects, including:

fever (temperature above 100.5°F) o

ribulin mesylate injection is a prescription medicine used to treat people with:

that has spread to other parts of the body. and

worsening symptoms of peripheral neuropathy.

Advise the patient to read the FDA-approved patient labeling (Patient Information).

21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of eribulin is linear with a mean elimination half-life of approximately 40 hours, a mean volume of distribution of 43 L/m² to 114 L/m² and mean clearance of 1.16 L/hr/m² to 2.42 L/hr/m² over the dose range of 0.25 mg/m² to 4.0 mg/m². The human plasma protein binding of eribulin at concentrations of 100 ng/m L to 1,000 ng/ mL ranges from 49% to 65%. Eribulin exposure after multiple dosing is comparable to that following a single dose. No accumulation of eribulin is observed with weekly administration

Elimination

Metabolism

Unchanged eribulin was the major circulating species in plasma following administration of ¹⁴C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin. Cytochrome P450 3A4 (CYP3A4) negligibly metabolizes eribulin in vitro.

Excretion

Eribulin is eliminated primarily in feces unchanged. After administration of ¹⁴C-eribulin to patients, approximately 82% of the dose was eliminated in feces and 9% in urine. Unchanged eribulin accounted for approximately 88% and 91% of total eribulin in feces and urine, respectively.

Specific Populations

Age, Sex, and Race/Ethnicity: Based on a population pharmacokinetic analysis, no clinically meaningful differences in the pharmacokinetics of eribulin were observed based on age, sex, or race.

Hepatic Impairment

In a study evaluating the effect of hepatic impairment on the PK of eribulin, eribulin exposures increased by 1.8-fold in patients with mild hepatic impairment (Child-Pugh A; n=7) and by 2.5-fold in patients with moderate (Child-Pugh B; n=5) hepatic impairment as compared to patients with normal hepatic function (n=6). Administration of eribulin mesylate at a dose of 1.1 mg/m² to patients with moderate hepatic impairment and 0.7 mg/m² to patients with moderate hepatic impairment resulted in similar exposure to eribulin at a dose of 1.4 mg/m² to patients with normal hepatic function (see Dosage and Administration (2.1), Use in Specific Populations (8.6)].

Renal Impairment

In a study evaluating the effect of renal impairment on the PK of eribulin, patients with moderate (CLcr 30 to 49 mL/min; n=7) and severe renal impairment (CLcr 15 to 29 mL/min; n=6) had 1.5-fold higher eribulin dose-normalized exposures compared to that in patients with normal renal function (CLcr ≥ 80 mL/min; n=6). There were no clinically meaningful changes in patients with mild renal impairment (CLcr 50 to 79 mL/min; n=27) [see Dosage and Administration (2.1), Use in Specific Populations (8.7)].

Drug Interaction Studies

Effect of Strong Inhibitors or Inducers of CYP3A4 on Eribulin: The effect of a strong CYP3A4 inhibitor and a P-gp inhibitor, ketoconazole, on the PK of eribulin was studied in a crossover trial of 12 patients with advanced solid tumors. No clinically relevant PK interaction was observed when eribulin mesylate was administered with or without ketoconazole (the geometric mean ratio of the AUC: 0.97; 90% CI: 0.83, 1.12).

The effect of a CYP3A4 inducer, rifampin, on the PK of eribulin was studied in a crossover trial of 14 patients with advanced solid tumors. No clinically relevant PK interaction was observed when eribulin mesylate was administered with or without rifampin (the geometric mean ratio of the AUC: 1.10; 90 CI%: 0.91, 1.34).

Effect of Eribulin on CYP Substrates: Eribulin shows no induction potential for CYP1A, CYP2B6, CYP2C9, CYP2C19, and CYP3A in primary human hepatocytes. Eribulin inhibits CVP3A4 activity in human liver microsomes, but it is unlikely that eribulin will substantially increase the plasma levels of CYP3A4 substrates. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected with eribulin concentrations up to 5 µM in pooled human liver micros In vitro drug interaction studies indicate that eribulin does not inhibit drugs that are substrates of these enzymes and it is unlikely that eribulin will affect plasma levels of drugs that are substrates of CYP enzymes.

Effect of Transporters on Eribulin: In vitro data suggest that eribulin at clinically relevant concentrations is a substrate of P-gp, but is not a substrate of breast cancer resistance protein (BCRP), multidrug resistance proteins (MRP2, MRP4), bile salt extrusion pump (BSEP), organic anion transporting polypeptides (OATP1B1, OATP1B3), organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or multidrug and toxin extrusion 1 (MATE1).

Effect of Eribulin on Transporters: In vitro data suggest that eribulin at clinically relevant concentrations may inhibit P-gp, but does not inhibit BCRP, OATP1B1, OCT1, OAT1, OAT3, or MATE1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with eribulin mesylate. Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Fertility studies have not been conducted with eribulin mesylate in humans or animals; however, nonclinical findings in repeat-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (based on body surface area) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (based on body surface area) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (based on body surface area) weekly for 3 out of 5 weeks, repeated for 6

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

Study 1 was an open-label, randomized, multicenter trial of 762 patients with metastatic breast cancer who received at least two chemotherapeutic regimens for the treatment of metastatic disease and experienced disease progression within 6 months of their last chemotherapeutic regimen. Patients were required to receive prior anthracycline- and taxane-based chemotherapy for adjuvant or metastatic disease. Patients were randomized (2:1) to receive eribulin mesylate (n=508) or a single agent therapy selected prior to randomization (control arm, n=254). Randomization was stratified by geographic a single agent analysis of the transmitted of the t 16% taxane, 9% anthracycline, 10% other chemotherapy), and 3% hormonal therapy. The main efficacy outcome was overall survival.

Patient demographic and baseline characteristics were comparable between the treatment arms. The median age was 55 (range: 27 to 85 years) and 92% were White. Sixty-four percent of patients were enrolled in North America/Western Europe/Australia, 25% in Eastern Europe/Russia, and 11% in Latin America/South Africa. Ninety-one percent of patients had a baseline ECOG performance status of 0 or 1. Tumor prognostic characteristics, including estrogen receptor status (positive: 67%, negative: 28%), progesterone receptor status (positive: 49%, negative: 39%), HER2/*neu* receptor status Study 2 demonstrated a statistically significant improvement in OS in patients randomized to eribulin mesylate compared with dacarbazine (see Table 6). There was no significant difference in progression-free survival in the overall population. Treatment effects of eribulin mesylate were limited to patients with liposarcoma based on pre-planned, exploratory subgroup analyses of OS and PFS (see Tables 6 and 7 and Figure 2). There was no evidence of efficacy of eribulin mesylate in patients with advanced or metastatic leiomyosarcoma in Study 2 (see Table 7).

Table 6: Efficacy Results for the Linosarcoma Stratum and All Patients* in Study 28

		Liposarcoma Stratum		ents*
	Eribulin Mesylate (n=71)	Dacarbazine (n=72)	Eribulin Mesylate (n=225)	Dacarbazine (n=221)
Overall survival	•			
Deaths, n (%)	52 (73)	63 (88)	173 (77)	179 (81)
Median, months (95% CI)	15.6 (10.2, 18.6)	8.4 (5.2, 10.1)	13.5 (11.1, 16.5)	11.3 (9.5, 12.6)
Hazard ratio (HR) (95% CI)	0.51 (0.35, 0.75)		0.75 (0.61, 0.94)	
Stratified log-rank p value	N/A†		0.011	
Progression-free survival				
Events, n (%)	57 (80)	59 (82)	194 (86)	185 (84)
Disease progression	53	52	180	170
Death	4	7	14	15
Median, months (95% CI)	2.9 (2.6, 4.8)	1.7 (1.4, 2.6)	2.6 (2.0, 2.8)	2.6 (1.7, 2.7)
HR (95% CI)	0.52 (0.35, 0.78)		0.86 (0.69, 1.06)	
Objective response rate				
Objective response rate (%) (95% Cl)	1.4 (0, 7.6)	0 (0, 4.2)	4.0 (1.8, 7.5)	5.0 (2.5, 8.7)

^a Efficacy data from one study site enrolling six patients were excluded.

* All patients = liposarcoma and leiomyos † N/A = not applicable

Figure 2: Kaplan-Meier Curves of Overall Survival in the Liposarcoma Stratum in Study 2

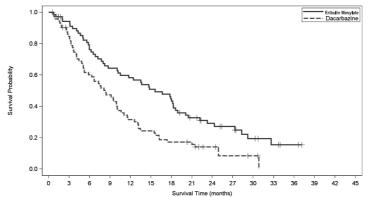


Table 7: Efficacy Results for the Leiomyosarcoma Stratum in Study 2ª

		Leiomyosarcoma Stratum		
	Eribulin Mesylate (n=154)	Dacarbazine (n=149)		
Overall survival	· · ·			
Deaths, n (%)	121 (79)	116 (78)		
Median, months (95% CI)	12.8 (10.3, 14.8)	12.3 (11.0, 15.1)		
HR (95% CI)	0.90 (0.6	0.90 (0.69, 1.18)		
Progression-free survival	·			
Events, n (%)	137 (89)	126 (85)		
Disease progression	127	118		
Death	10	8		
Median, months (95% CI)	2.2 (1.5, 2.7)	2.6 (2.2, 2.9)		
HR (95% CI)	1.05 (0.8	1.05 (0.81, 1.35)		
Objective response rate (%) (95% CI)	5.2 (2.3, 10)	7.4 (3.7, 12.8)		

^a Efficacy data from one study site enrolling six patients were excluded.

- are breastfeeding or plan to breastfeed. It is not known if eribulin mesylate passes into your breast milk. Do not breastfeed during treatment with eribulin mesylate injection and for 2 weeks after the final dose of eribulin
- mesylate injection.
- Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter edicines, vitamins, and herbal supplen

How will I receive Eribulin Mesylate Injection?

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- Eribulin mesylate injection is given by intravenous (IV) injection in your vein
- Eribulin mesylate injection is given in "cycles" of treatment, with each cycle lasting 21 days. Eribulin mesylate injection is usually given on day 1 and day 8 of a treatment cycle

What are the possible side effects of Eribulin Mesylate Injection?

Eribulin mesylate injection may cause serious side effects, including:

- See "What is the most important information I should know about Eribulin Mesulate Injection?"
- Ilin Mesylate Injection can cause changes in your heartbeat (called QT prolongation). This can cause irregular heartbeats. Your healthcare provider may do heart monitoring (electrocardiogram or ECG) or blood tests during your treatment with eribulin mesylate injection to check for heart problems. The most common side effects of eribulin mesylate injection in people with breast cancer include:
- low red blood cell count (anemia) constipation
- weakness or tiredness hair loss (alopecia)

nausea

- The most common side effects of eribulin mesylate injection in people with liposarcoma include tiredness
 - stomach pain fever
- hair loss (alopecia) constipation

Your healthcare provider will do blood tests before and during treatment while you are taking eribulin mesylate injection. The most common changes to blood tests in people with liposarcoma include

- low white blood cell count (neutropenia)
- decreased blood levels of potassium or calcium
- Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of eribulin mesylate injection. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about Eribulin Mesylate Injection

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about eribulin mesylate injection that is written for health ofessionals.

What are the ingredients in Eribulin Mesylate Injection?

Active Ingredient: eribulin mesylat

Inactive Ingredients: dehydrated alcohol, water for injection, and sodium hydroxide or hydrochloric acid may be used for pH adjustment.

For more information, contact Apotex Corp. at 1-800-706-5575.

Manufactured by: Gland Pharma Limited

Visakhapatnam-530049, India.

Manufactured for:

Apotex Corp. Weston, FL USA 33326

Revised: 02/2024

This Patient Information has been approved by the U.S. Food and Drug Administration.

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