ERIBULIN MESYLATE- eribulin mesylate injection
HIKMA PHARMACEUTICALS USA INC.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ERIBULIN MESYLATE INJECTION safely and effectively. See full prescribing information for ERIBULIN MESYLATE INJECTION.

ERIBULIN MESYLATE injection, for intravenous use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE

Eribulin mesylate injection is a microtubule inhibitor indicated for the treatment of patients with:

- Metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. (1.1)
- Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. (1.2)

DOSAGE AND ADMINISTRATION

- Administer 1.4 mg/m^2 intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. (2.1)
- Reduce dose in patients with hepatic impairment or with moderate or severe renal impairment. (2.1)
- Do not mix with other drugs or administer with dextrose-containing solutions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 1 mg per 2 mL (0.5 mg per mL) eribulin mesylate in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Neutropenia: Monitor peripheral blood cell counts and adjust dose as appropriate. (5.1)
- Peripheral Neuropathy: Monitor for signs of neuropathy. Manage with dose delay and adjustment. (5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.3, 8.1, 8.3)
- QT Prolongation: Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid in patients with congenital long QT syndrome. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) in metastatic breast cancer were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. (6.1)
The most common adverse reactions (≥25%) in liposarcoma and leiomyosarcoma were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. The most common (≥5%) Grade 3-4 laboratory abnormalities in liposarcoma and leiomyosarcoma were neutropenia, hypokalemia, and hypocalcemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at (1-877-845-0689) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed. (8.2)
- Hepatic Impairment: A lower starting dose is recommended for patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) were not studied. (8.6)
- Renal Impairment: A lower starting dose is recommended for patients with moderate (CLcr 30-49 mL/min) or severe (CLcr 15-29 mL/min) renal impairment. (8.7)

See 17 for FDA-approved patient labeling.

Revised: 5/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer

Eribulin mesylate injection is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting *[see Clinical Studies (14.1)]*.

1.2 Liposarcoma

Eribulin mesylate injection is indicated for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of eribulin mesylate injection is 1.4 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 mesylate injection in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle *[see Use in Specific Populations (8.6)]*.

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

The recommended dose of eribulin mesylate injection in patients with moderate or severe renal impairment (creatinine clearance (CLcr) 15-49 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 *[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:
  - ANC < 1,000/mm^3
  - Platelets < 75,000/mm^3
  - 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 ≤ Grade 2 severity by Day 15, omit the

dose.
- If toxicities resolve or improve to ≤ 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 mesylate 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 mg/m^2 eribulin mesylate injection dose for any of the following:	1.1 mg/m^2
ANC <500/mm^3 for >7 days	
ANC <1,000 /mm^3 with fever or infection	
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	
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
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) Common Terminology Criteria for 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/mm^3) 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 injection 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 injection 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 injection did not include patients with baseline neutrophil counts below 1,500/mm^3.

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 injection (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 25-662 days).

In Study 2, Grade 3 peripheral neuropathy occurred in 3.1% (7/223) of eribulin mesylate injection - treated patients. Peripheral neuropathy led to discontinuation of eribulin

mesylate injection in 0.9% of patients. The median time to first occurrence of peripheral neuropathy of any severity was 5 months (range: 3.5 months to 9 months). Neuropathy lasting more than 60 days occurred in 58% (38/65) of patients. Sixty three percent (41/65) had not recovered within a median follow-up duration of 6.4 months (range: 27 days to 29 months).

Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold Eribulin mesylate injection in patients who experience Grade 3 or 4 peripheral neuropathy, until resolution to Grade 2 or less *[see Dosage and Administration (2.2)]*.

5.3 Embryo-Fetal Toxicity

Based on findings from an animal reproduction study and its mechanism of action, eribulin mesylate injection can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of eribulin mesylate injection in pregnant women. In animal reproduction studies, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with eribulin mesylate injection 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 injection 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 injection and monitor these electrolytes periodically during therapy. Avoid eribulin mesylate injection in patients with congenital 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 injection has been administered to 1963 patients including 467 patients exposed to eribulin mesylate injection 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 injection were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving eribulin mesylate injection were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of eribulin mesylate injection 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 injection (1.4 mg/m^{2}on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received eribulin mesylate injection 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 injection 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 Mesylate Injection n=503**		**Control Group n=247**	
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Blood and lymphatic system disorders[b]				
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				
Alopecia	45%	NA[d]	10%	NA[d]
Infections				
Urinary Tract Infection	10%	1%	5%	0%

[a]adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.0.
[b]based upon laboratory data.
[c]includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[d]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 injection 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 <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) 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 injection.

Peripheral Neuropathy: In Study 1, 17% of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received eribulin mesylate injection. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

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

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the eribulin mesylate injection-treated group:

- **Eye Disorders:** increased lacrimation
- **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth
- **General Disorders and Administration Site Conditions:** peripheral edema

- **Infections and Infestations:** upper respiratory tract infection
- **Metabolism and Nutrition Disorders:** hypokalemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness
- **Nervous System Disorders:** dysgeusia, dizziness
- **Psychiatric Disorders:** insomnia, depression
- **Skin and Subcutaneous Tissue Disorders:** rash

Liposarcoma

The safety of eribulin mesylate injection was evaluated in Study 2, an open-label, randomized, multicenter, active-controlled trial, in which patients were randomized (1:1) to receive either eribulin mesylate injection 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle or dacarbazine at doses of 850 mg/m^2 (20%), 1000 mg/m^2 (64%), or 1200 mg/m^2 (16%) every 3 weeks. A total of 223 patients received eribulin mesylate injection and 221 patients received dacarbazine. Patients were required to have received at least two prior systemic chemotherapy regimens. The trial excluded patients with pre-existing ≥ Grade 3 peripheral neuropathy, known central nervous system metastasis, elevated serum bilirubin or significant chronic liver disease, history of myocardial infarction within 6 months, history of New York Heart Association Class II or IV heart failure, or cardiac arrhythmia requiring treatment. The median age of the safety population in Study 2 was 56 years (range: 24 to 83 years); 67% female; 73% White, 3% Black or African American, 8% Asian/Pacific Islander, and 15% unknown; 99% received prior anthracycline-containing regimen; and 99% received ≥ 2 prior regimens. The median duration of exposure was 2.3 months (range: 21 days to 26 months) for patients receiving eribulin mesylate injection *[see Clinical Studies (14.2)]*.

The most common adverse reactions (≥25%) reported in patients receiving eribulin mesylate injection were fatigue, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia. The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving eribulin mesylate injection were neutropenia, hypokalemia, and hypocalcemia. The most common serious adverse reactions reported in patients receiving eribulin mesylate injection were neutropenia (4.9%) and pyrexia (4.5%). Permanent discontinuation of eribulin mesylate injection for adverse reactions occurred in 8% of patients. The most common adverse reactions resulting in discontinuation of eribulin mesylate injection were fatigue and thrombocytopenia (0.9% each). Twenty-six percent of patients required at least one dose reduction. The most frequent adverse reactions that led to dose reduction were neutropenia (18%) and peripheral neuropathy (4.0%).

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients in the eribulin mesylate injection - treated arm in Study 2.

Table 3: Adverse Reactions[a] Occurring in ≥10% (all Grades) of Patients Treated on the eribulin mesylate injection 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) (Study 2)[b]

	Eribulin Mesylate Injection	Control Group n=221

	n=223		n=221	
Adverse Reactions	**All Grades**	**Grades 3-4**	**All Grades**	**Grade 3-4**
Nervous system disorders				
Peripheral neuropathy[c]	29%	3.1%	8%	0.5%
Headache	18%	0%	10%	0%
General disorders				
Pyrexia	28%	0.9%	14%	0.5%
Gastrointestinal disorders				
Constipation	32%	0.9%	26%	0.5%
Abdominal pain[d]	29%	1.8%	23%	4.1%
Stomatitis	14%	0.9%	5%	0.5%
Skin and subcutaneous tissue disorders				
Alopecia	35%	NA[e]	2.7%	NA[e]
Infections				
Urinary Tract Infection	11%	2.2%	5%	0.5%

[a] Adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).
[b] Safety data from one study site enrolling six patients were excluded.
[c]Includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[d] Includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort.
[e] Not applicable; (grading system does not specify > Grade 2 for alopecia).

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

- **Gastrointestinal Disorders:** nausea (41%); vomiting (19%), diarrhea (17%)
- **General Disorders:** asthenia/fatigue(62%); peripheraledema(12%)
- **Metabolism and Nutrition Disorders:** decreased appetite (19%)
- **Musculoskeletal and Connective Tissue Disorders:** arthralgia/myalgia (16%); back pain (16%)
- **Respiratory Disorders:** cough (18%)

Less Common Adverse Reactions: The following additional clinically important adverse reactions were reported in ≥5% to <10% of the eribulin mesylate injection-treated group:

- **Blood and Lymphatic System Disorders:** thrombocytopenia
- **Eye Disorders:** increased lacrimation
- **Gastrointestinal Disorders:** dyspepsia
- **Metabolism and Nutrition Disorders:** hyperglycemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, musculoskeletal pain
- **Nervous System Disorders:** dizziness, dysgeusia
- **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 injection 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 Injection		Dacarbazine	
Laboratory Abnormality	**All Grades**	**Grades 3-4**	**All Grades**	**Grade 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%

[a]Each test incidence is based on the number of patients who had both baseline and at least one on-study measurement and at least 1 grade increase from baseline. Eribulin mesylate injection group (range 221-222) and dacarbazine group (range 214-215).
[†] 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 injection. 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 Injection

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 injection was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a P-gp inhibitor) and when eribulin mesylate injection was administered with or without rifampin (a CYP3A4 inducer) *[see Clinical Pharmacology (12.3)].*

7.2 Effects of Eribulin Mesylate Injection on Other Drugs

Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes *[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 injection 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 injection 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/m^2 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 potential for serious adverse reactions in breastfed infants from eribulin mesylate, advise women not to breastfeed during treatment with eribulin mesylate injection and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on findings from an animal reproduction study and its mechanism of action, eribulin mesylate injection 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 injection and for at least 2 weeks following the final dose**.**

Males

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

Infertility

Males

Based on animal data, eribulin mesylate injection 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 injection 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 injection 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 subjects.

Clinical studies of eribulin mesylate injection 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 injection at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal 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 B). eribulin mesylate injection was not studied in patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].*

8.7 Renal Impairment

For patients with moderate or severe renal impairment (CLcr 15-49 mL/min), reduce the starting dose to 1.1 mg/m^2*[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].*

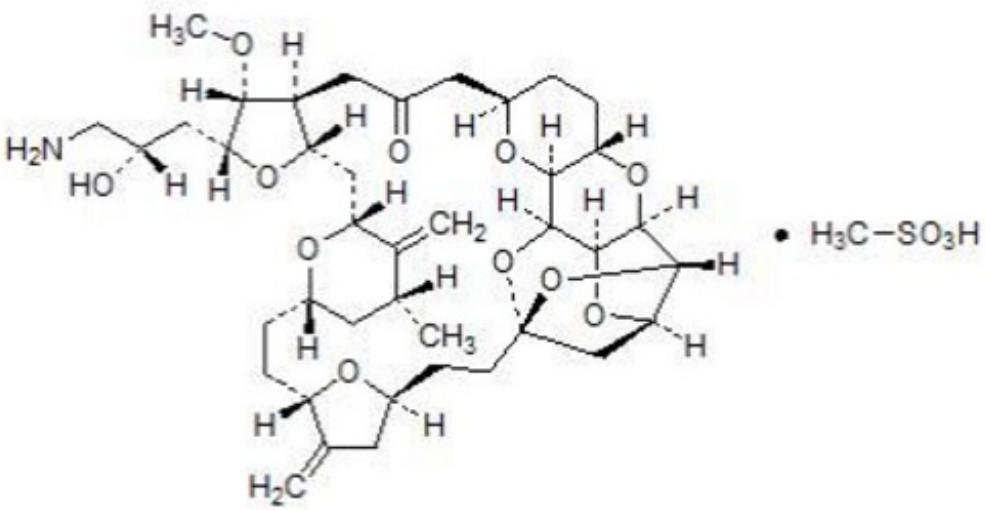
10 OVERDOSAGE

Overdosage of eribulin mesylate injection 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 eribulin mesylate injection 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*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 for free base). The empirical formula is $C_{40}H_{59}NO_{11}\bullet CH_4O_3S$. Eribulin mesylate has the following structural formula:



Eribulin mesylate injection is a clear, colorless, sterile solution for intravenous administration. Each single-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_2/M 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 injection 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/m^2 of eribulin mesylate injection on Days 1 and 8 of a 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/m^2 to 114 L/m^2 and mean clearance of 1.16 L/hr/m^2 to 2.42 L/hr/m^2 over the dose range of 0.25 mg/m^2 to 4.0 mg/m^2. The human plasma protein binding of eribulin at concentrations of 100 ng/mL 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 ^{14}C-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 ^{14}C-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 injection at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin at a dose of 1.4 mg/m^2 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 30-49 mL/min; n=7) and severe renal impairment (CLcr 15-29 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 50-79 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 injection 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 injection 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 CYP3A4 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 microsomes. 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 cycles.

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 injection (n=508) or a single agent therapy selected prior to randomization (control arm, n=254). Randomization was stratified by geographic region, HER2/*neu* status, and prior capecitabine exposure. Eribulin mesylate injection was administered at a dose of 1.4 mg/m2 on Days 1 and 8 of a 21-day cycle. Eribulin mesylate injection-treated patients received a median of 5 cycles (range: 1 to 23 cycles) of therapy. Control arm therapy consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 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 (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 injection and control arms. Patients received a median of four prior chemotherapy regimens in both arms.

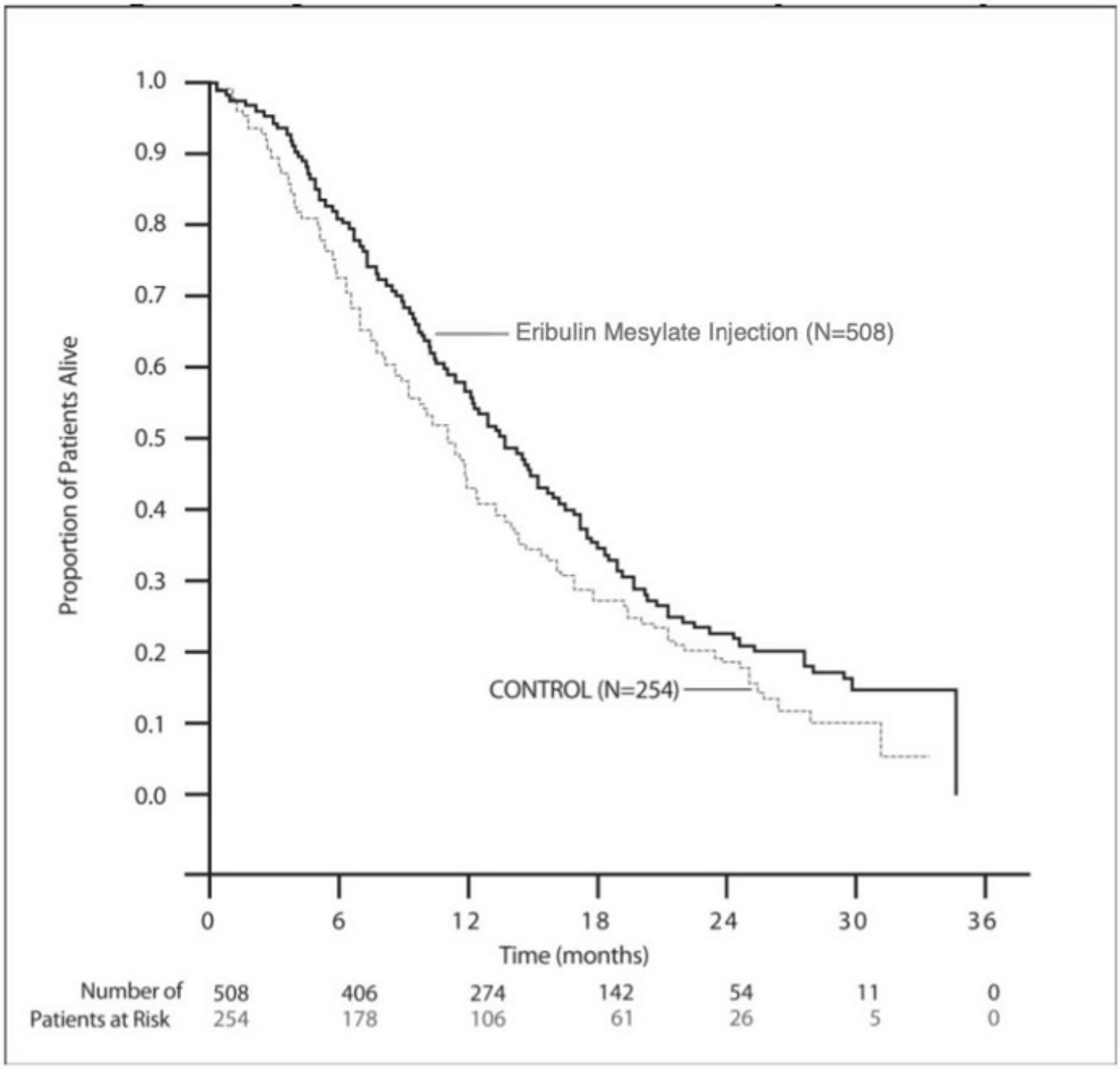
In Study 1, a statistically significant improvement in overall survival was observed in patients randomized to the eribulin mesylate injection arm compared to the control arm (see Table 5). An updated, unplanned survival analysis, conducted when 77% of events had been observed (see Figure 1), was consistent with the primary analysis. In patients randomized to eribulin mesylate injection, the objective response rate by the RECIST criteria was 11% (95% CI: 8.6%, 14.3%) and the median response duration was 4.2 months (95% CI: 3.8, 5.0 months).

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

Overall Survival	**Eribulin Mesylate Injection (n=508)**	**Control Arm (n=254)**
Primary survival analysis		
Number of deaths	274	148
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI)[a]	0.81 (0.66, 0.99)	
P value [b]	0.041	
Updated survival analysis		
Number of deaths	386	203
Median, months (95% CI)	13.2 (12.1, 14.4)	10.6 (9.2, 12.0)

CI = confidence interval
[a] Based on Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.
[b] Based on a log-rank test stratified by geographic region, HER2 status, and prior capecitabine therapy.

Figure 1: Updated Overall Survival Analysis for Study 1



14.2 Liposarcoma

The efficacy and safety of eribulin mesylate injection 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 eribulin mesylate injection 1.4 mg/m^2 administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of 850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 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 mesylate injection at the time of disease progression.

A total of 446 patients were randomized, 225 to the eribulin mesylate injection 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 ECOG performance status (PS) 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%), ifosfamide (62%), gemcitabine (59%), trabectedin (50%), and docetaxel (48%).

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.

Study 2 demonstrated a statistically significant improvement in OS in patients randomized to eribulin mesylate injection compared with dacarbazine (see Table 6). There was no significant difference in progression-free survival in the overall population. Treatment effects of eribulin mesylate injection 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 injection in patients with advanced or metastatic leiomyosarcoma in Study 2 (see Table 7).

Table 6: Efficacy Results for the Liposarcoma Stratum and All Patients* in Study 2[a]

	Liposarcoma Stratum		**All Patients***	
	Eribulin Mesylate Injection (n=71)	**Dacarbazine (n=72)**	**Eribulin Mesylate Injection (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% CI)	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 leiomyosarcoma.
[†]N/A = not applicable

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

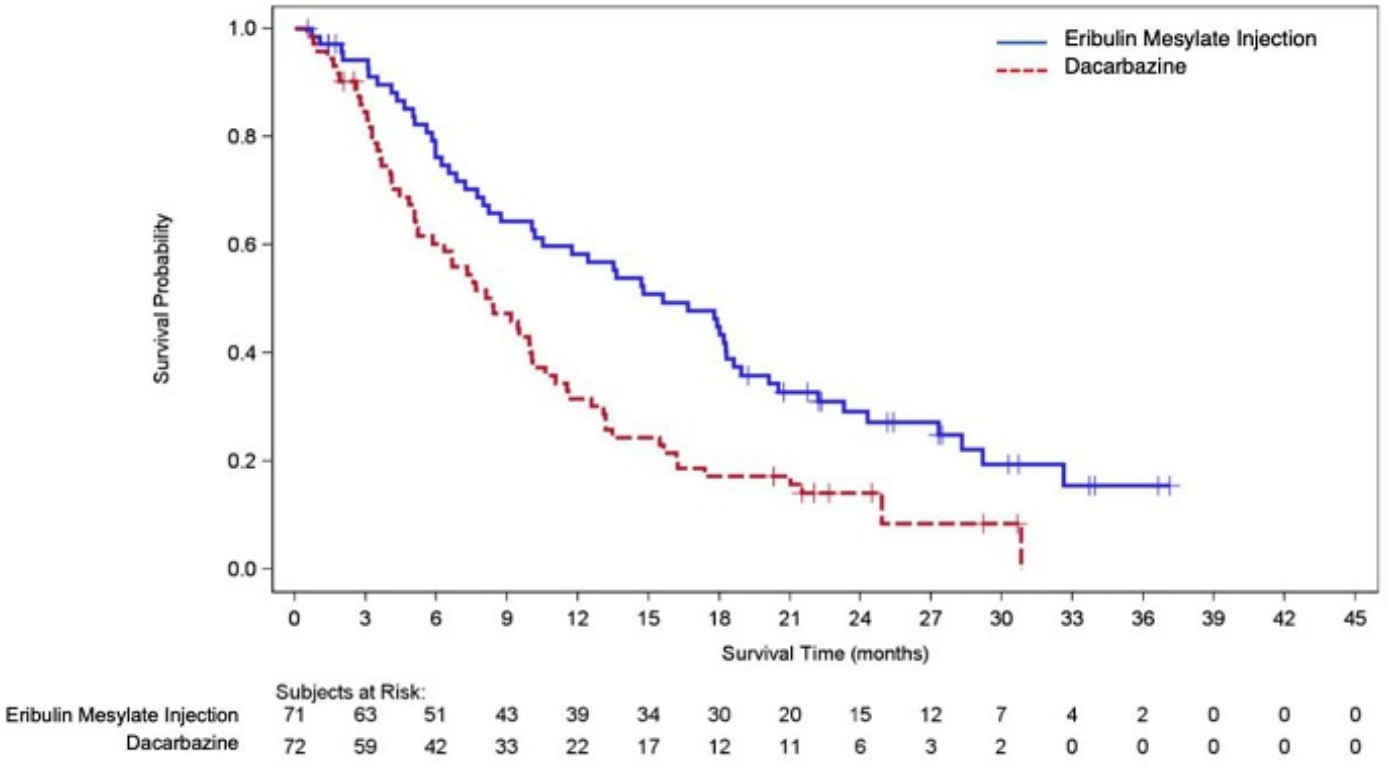


Table 7: Efficacy Results for the Leiomyosarcoma Stratum in Study 2[a]

	Leiomyosarcoma Stratum	
	Eribulin Mesylate Injection (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 (0.69, 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 (0.81, 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.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 0143-9167-01

Injection: 1 mg/2 mL, in a single-dose vial. One vial per carton.

Eribulin mesylate injection is a clear, colorless, sterile solution for intravenous administration.

Store at 25°C (77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. Do not freeze or refrigerate. Store the vials in their original cartons.

Eribulin mesylate injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

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

Neutropenia

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)]***.**

Peripheral Neuropathy

Advise patients to inform their healthcare providers of new or worsening numbness, tingling and pain in their extremities *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)].*
- Advise females of reproductive potential to use effective contraception during treatment with eribulin mesylate injection and for at least 2 weeks after the final dose *[see Use in Specific Populations (8.3)].*
- Advise males with female partners of reproductive potential to use effective contraception during treatment with eribulin mesylate injection and for 3.5 months following the final dose *[see Use in Specific Populations (8.3)].*

Lactation

Advise women not to breastfeed during treatment with eribulin mesylate injection and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)].*

Manufactured for:
Jiangxi Qingfeng Pharmaceutical Co., Ltd.
Ganzhou, Jiangxi 341000, China

Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922
Made in China

PATIENT INFORMATION
Eribulin Mesylate Injection
(er " i bue ' lin mes ' i late**)**
Injection, for intravenous use

What is the most important information I should know about eribulin mesylate injection?
Eribulin mesylate injection can cause serious side effects, including:

- **Low white blood cell count (neutropenia)**. This can lead to serious infections that could lead to death. Your healthcare provider will check your blood cell counts before you receive each dose of eribulin mesylate injection and during treatment. Call your healthcare provider right away if you develop any of these symptoms of infection:
  ° fever (temperature above 100.5°F)
  ° chills
  ° cough
  ° burning or pain when you urinate
- **Numbness, tingling, or pain in your hands or feet (peripheral neuropathy)**. Peripheral neuropathy is common with eribulin mesylate injection and sometimes can be severe. Tell your healthcare provider if you have new or worsening symptoms of peripheral neuropathy.
- Your healthcare provider may delay, decrease your dose, or stop treatment with eribulin mesylate injection if you have side effects.

See "**What are possible side effects of eribulin mesylate injection?"** for more

information about side effects.

What is eribulin mesylate injection?

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

- Breast cancer
  - ° that has spread to other parts of the body, **and**
  - ° who have already received certain types of anticancer medicines after the cancer has spread
- Liposarcoma
  - ° 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

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

Before you receive eribulin mesylate injection, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have heart problems, including a problem called congenital long QT syndrome
- have low potassium or low magnesium in your blood
- 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 mesylate injection.
  - ° **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 the final dose of eribulin mesylate injection.
- 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 medicines, vitamins, and herbal supplements.

How will I receive eribulin mesylate injection?

- 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 mesylate injection?”**
- **Eribulin 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 white blood cell count (neutropenia)
- low red blood cell count (anemia)
- weakness or tiredness
- hair loss (alopecia)
- nausea
- constipation

The most common side effects of eribulin mesylate injection in people with liposarcoma include:

- tiredness
- nausea
- hair loss (alopecia)
- constipation
- stomach pain
- fever

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 professionals.

What are the ingredients in eribulin mesylate injection?
Active Ingredient: eribulin mesylate
Inactive Ingredients: dehydrated alcohol, water for injection, and sodium hydroxide or hydrochloric acid may be used for pH adjustment.
Manufactured for:
Jiangxi Qingfeng Pharmaceutical Co., Ltd.
Ganzhou, Jiangxi 341000, China
Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922
Made in China

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

Revised: 05/2023

PRINCIPAL DISPLAY PACKAGE - Eribulin Mesylate Injection 1 mg/2 mL Vial Label

NDC 0143-**9167**-01

Rx only

Eribulin Mesylate Injection

1 mg/2 mL

(0.5 mg/mL)

For Intravenous Use

PRINCIPAL DISPLAY PACKAGE - Eribulin Mesylate Injection 1 mg/2 mL Carton

NDC 0143-**9167**-01

Rx only

Eribulin Mesylate Injection

1 mg/2 mL

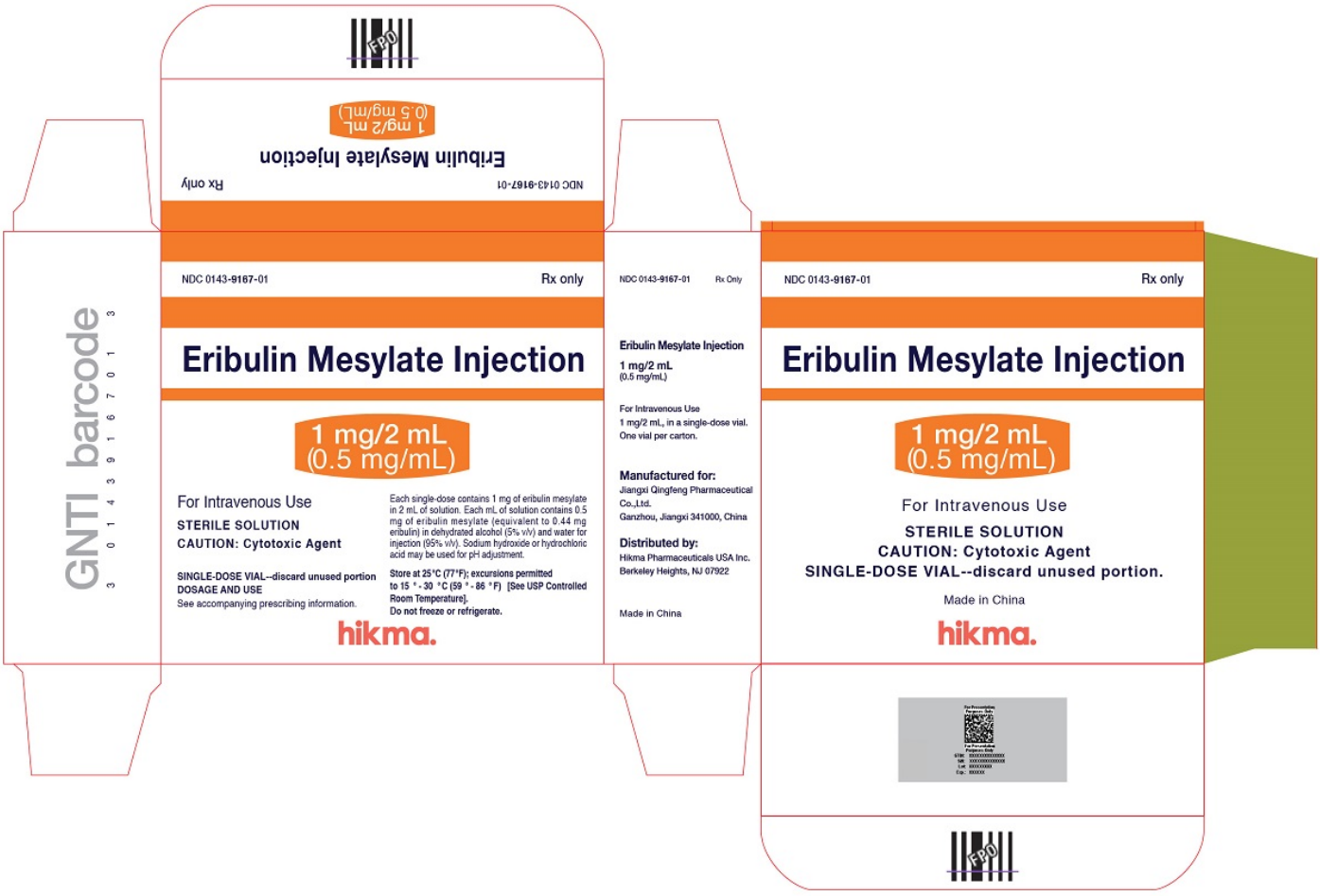
(0.5 mg/mL)

For Intravenous Use

STERILE SOLUTION

CAUTION: Cytotoxic Agent

SINGLE-DOSE VIAL--discard unused portion.



ERIBULIN MESYLATE

eribulin mesylate injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9167
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ERIBULIN MESYLATE (UNII: AV9U0660CW) (ERIBULIN - UNII:LR24G6354G)	ERIBULIN MESYLATE	0.5 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
ALCOHOL (UNII: 3K9958V90M)	0.05 mL in 1 mL
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9167-01	1 in 1 CARTON	06/28/2024	
1		2 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA218281	06/28/2024	

Labeler - HIKMA PHARMACEUTICALS USA INC. (001230762)

Registrant - Jiangxi Qingfeng Pharmaceutical Co., Ltd. (420618530)

Establishment

Name	Address	ID/FEI	Business Operations
Kindos Pharmaceuticals Co., Ltd.		529111185	manufacture(0143-9167)

Revised: 7/2024 HIKMA PHARMACEUTICALS USA INC.