

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IXEMPRA™ safely and effectively. See full prescribing information for IXEMPRA™.

**IXEMPRA™ Kit (ixabepilone) for Injection, for intravenous infusion only**  
**Initial U.S. Approval: Year**

### WARNING: TOXICITY IN HEPATIC IMPAIRMENT

See full prescribing information for complete boxed warning.

**IXEMPRA™ in combination with capecitabine must not be given to patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death. (4, 5.3)**

### INDICATIONS AND USAGE

IXEMPRA, a microtubule inhibitor, in combination with capecitabine is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane (1).

IXEMPRA as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine (1).

### DOSAGE AND ADMINISTRATION

- The recommended dose of IXEMPRA is 40 mg/m<sup>2</sup> infused intravenously over 3 hours every 3 weeks (2.1).
- Dose reduction is required in certain patients with elevated AST, ALT, or bilirubin (2.2, 8.6).

IXEMPRA (ixabepilone) for injection must be constituted with supplied DILUENT. The ixabepilone concentration in constituted solution is 2 mg/mL. Constituted solution must be diluted with Lactated Ringer's Injection, USP, to a final ixabepilone concentration of 0.2 mg/mL to 0.6 mg/mL. The final solution must be used within 6 hours of preparation. (2.4)

### DOSAGE FORMS AND STRENGTHS

- IXEMPRA for injection, 15 mg supplied with DILUENT for IXEMPRA, 8 mL (3)
- IXEMPRA for injection, 45 mg supplied with DILUENT for IXEMPRA, 23.5 mL (3)

### CONTRAINDICATIONS

- Hypersensitivity to drugs formulated with Cremophor® EL (4).
- Baseline neutrophil count <1500 cells/mm<sup>3</sup> or a platelet count <100,000 cells/mm<sup>3</sup> (4).

- Patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN must not be treated with IXEMPRA in combination with capecitabine (4).

### WARNINGS AND PRECAUTIONS

- Peripheral Neuropathy:** Monitor for symptoms of neuropathy, primarily sensory. Neuropathy is cumulative, generally reversible and should be managed by dose adjustment and delays (2.2, 5.1).
- Myelosuppression:** Primarily neutropenia. Monitor with peripheral blood cell counts and adjust dose as appropriate (2.2, 5.2).
- Hypersensitivity reaction:** Must premedicate all patients with an H<sub>1</sub> antagonist and an H<sub>2</sub> antagonist before treatment (2.3, 5.4).
- Fetal harm can occur when administered to a pregnant woman.** Women should be advised not to become pregnant when taking IXEMPRA (5.5, 8.1).

### ADVERSE REACTIONS

- The most common adverse reactions (≥20%) are peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. Additional reactions occurred in ≥20% in combination treatment: palmar-plantar erythrodysesthesia syndrome, anorexia, abdominal pain, nail disorder, and constipation (6).
- Drug-associated hematologic abnormalities (>40%) include neutropenia, leukopenia, anemia, and thrombocytopenia (6).

**To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### DRUG INTERACTIONS

- Inhibitors of CYP3A4 may increase plasma concentrations of ixabepilone; dose of IXEMPRA must be reduced with strong CYP3A4 inhibitors (7.1).
- Inducers of CYP3A4 may decrease plasma concentrations of ixabepilone; alternative therapeutic agents with low enzyme induction potential should be considered (7.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: Month/Year

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

## FULL PRESCRIBING INFORMATION

**WARNING: TOXICITY IN HEPATIC IMPAIRMENT**  
**IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death [see *Contraindications (4)* and *Warnings and Precautions (5.3)*].**

### 1 INDICATIONS AND USAGE

IXEMPRA is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

IXEMPRA is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 General Dosing Information

The recommended dosage of IXEMPRA is 40 mg/m<sup>2</sup> administered intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2 m<sup>2</sup> should be calculated based on 2.2 m<sup>2</sup>.

#### 2.2 Dose Modification

##### Dose Adjustments During Treatment

Patients should be evaluated during treatment by periodic clinical observation and laboratory tests including complete blood cell counts. If toxicities are present, treatment should be delayed to allow recovery. Dosing adjustment guidelines for monotherapy and combination therapy are shown in Table 1. If toxicities recur, an additional 20% dose reduction should be made.

**Table 1: Dose Adjustment Guidelines**

<b>IXEMPRA (Monotherapy or Combination Therapy)</b>	<b>IXEMPRA Dose Modification</b>
<b>Nonhematologic:</b>	
Grade 2 neuropathy (moderate) lasting $\geq 7$ days	Decrease the dose by 20%
Grade 3 neuropathy (severe) lasting $< 7$ days	Decrease the dose by 20%
Grade 3 neuropathy (severe) lasting $\geq 7$ days or disabling neuropathy	Discontinue treatment
Any grade 3 toxicity (severe) other than neuropathy	Decrease the dose by 20%
Transient grade 3 arthralgia/myalgia or fatigue	No change in dose of IXEMPRA
Grade 3 hand-foot syndrome (palmar-plantar erythrodysesthesia)	
Any grade 4 toxicity (disabling)	Discontinue treatment
<b>Hematologic:</b>	
Neutrophil $< 500$ cells/mm <sup>3</sup> for $\geq 7$ days	Decrease the dose by 20%
Febrile neutropenia	Decrease the dose by 20%
Platelets $< 25,000$ /mm <sup>3</sup> or platelets $< 50,000$ /mm <sup>3</sup> with bleeding	Decrease the dose by 20%
<b>CAPECITABINE (when used in combination with IXEMPRA)</b>	<b>Capecitabine Dose Modification</b>
<b>Nonhematologic:</b>	Follow Capecitabine Label
<b>Hematologic:</b>	
Platelets $< 25,000$ /mm <sup>3</sup> or $< 50,000$ /mm <sup>3</sup> with bleeding	Hold for concurrent diarrhea or stomatitis until platelet count $> 50,000$ /mm <sup>3</sup> , then continue at same dose.
Neutrophils $< 500$ cells/mm <sup>3</sup> for $\geq 7$ days or febrile neutropenia	Hold for concurrent diarrhea or stomatitis until neutrophil count $> 1,000$ cells/mm <sup>3</sup> , then continue at same dose.

Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v3.0).

**Re-treatment Criteria:** Dose adjustments at the start of a cycle should be based on nonhematologic toxicity or blood counts from the preceding cycle following the guidelines in Table 1. Patients should not begin a new cycle of treatment unless the neutrophil count is at least 1500 cells/mm<sup>3</sup>, the platelet count is at least 100,000 cells/mm<sup>3</sup>, and nonhematologic toxicities have improved to grade 1 (mild) or resolved.

**Dose Adjustments in Special Populations - Hepatic Impairment**

**Combination Therapy:**

IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT  $>2.5 \times$  ULN or bilirubin  $>1 \times$  ULN. Patients receiving combination treatment who have AST and ALT  $\leq 2.5 \times$  ULN and bilirubin  $\leq 1 \times$  ULN may receive the standard dose of ixabepilone ( $40 \text{ mg/m}^2$ ). [See *Boxed Warning*, *Contraindications (4)*, *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.6)*.]

**Monotherapy:**

Patients with hepatic impairment should be dosed with IXEMPRA based on the guidelines in Table 2. Patients with moderate hepatic impairment should be started at  $20 \text{ mg/m}^2$ , the dosage in subsequent cycles may be escalated up to, but not exceeding,  $30 \text{ mg/m}^2$  if tolerated. Use in patients with AST or ALT  $>10 \times$  ULN or bilirubin  $>3$  is not recommended. Limited data are available for patients with baseline AST or ALT  $>5 \times$  ULN. Caution should be used when treating these patients. [See *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.6)*.]

**Table 2: Dose Adjustments for IXEMPRA as Monotherapy in Patients with Hepatic Impairment**

	Transaminase Levels		Bilirubin Levels <sup>a</sup>	IXEMPRA <sup>b</sup> (mg/m <sup>2</sup> )
Mild	AST and ALT $\leq 2.5 \times$ ULN	and	$\leq 1 \times$ ULN	40
	AST or ALT $\leq 10 \times$ ULN	and	$\leq 1 \times$ ULN	32
Moderate	AST and ALT $\leq 10 \times$ ULN	and	$>1.5 \times$ ULN - $\leq 3 \times$ ULN	20 - 30

<sup>a</sup> Excluding patients whose total bilirubin is elevated due to Gilbert’s disease.

<sup>b</sup> Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance.

**Strong CYP3A4 Inhibitors**

The use of concomitant strong CYP3A4 inhibitors should be avoided (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, or voriconazole). Grapefruit juice may also increase plasma concentrations of IXEMPRA and should be avoided. Based on pharmacokinetic studies, if a strong CYP3A4 inhibitor must be coadministered, a dose reduction to  $20 \text{ mg/m}^2$  is predicted to adjust the ixabepilone AUC to the range observed without inhibitors and should be considered. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the IXEMPRA dose is adjusted upward to the indicated dose. [See *Drug Interactions (7.1)*.]

## 2.3 Premedication

To minimize the chance of occurrence of a hypersensitivity reaction, all patients must be premedicated approximately 1 hour before the infusion of IXEMPRA with:

- An H<sub>1</sub> antagonist (eg, diphenhydramine 50 mg orally or equivalent) and
- An H<sub>2</sub> antagonist (eg, ranitidine 150 - 300 mg orally or equivalent).

Patients who experienced a hypersensitivity reaction to IXEMPRA require premedication with corticosteroids (eg, dexamethasone 20 mg intravenously, 30 minutes before infusion or orally, 60 minutes before infusion) in addition to pretreatment with H<sub>1</sub> and H<sub>2</sub> antagonists.

## 2.4 Instructions for Preparation and IV Administration

IXEMPRA *Kit* contains two vials, a vial labeled IXEMPRA (ixabepilone) for injection which contains ixabepilone powder and a vial containing DILUENT for IXEMPRA. Only supplied DILUENT must be used for constituting IXEMPRA (ixabepilone) for injection. IXEMPRA *Kit* must be stored in a refrigerator at 2° C - 8° C (36° F - 46° F) in the original package to protect from light. Prior to constituting IXEMPRA for injection, the *Kit* should be removed from the refrigerator and allowed to stand at room temperature for approximately 30 minutes. When the vials are first removed from the refrigerator, a white precipitate may be observed in the DILUENT vial. This precipitate will dissolve to form a clear solution once the DILUENT warms to room temperature. To allow for withdrawal losses, the vial labeled as 15 mg IXEMPRA for injection contains 16 mg of ixabepilone and the vial labeled as 45 mg IXEMPRA for injection contains 47 mg of ixabepilone. The 15-mg IXEMPRA *Kit* is supplied with a vial providing 8 mL of the DILUENT and the 45-mg IXEMPRA *Kit* is supplied with a vial providing 23.5 mL of the DILUENT. After constituting with the DILUENT, the concentration of ixabepilone is 2 mg/mL.

*Please refer to Preparation and Handling Precautions [See Dosage and Administration (2.5)] before preparation.*

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