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: 2007

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^2 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 one of the specified fluids, 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^3 or a platelet count <100,000 cells/mm^3 (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_1 antagonist and an H_2 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

----------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: XX/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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 (ixabepilone) 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^2 administered intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2 m^2 should be calculated based on 2.2 m^2.

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[a]

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

[a] 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^3, the platelet count is at least 100,000 cells/mm^3, 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 x ULN or bilirubin >1 x ULN. Patients receiving combination treatment who have AST and ALT ≤2.5 x ULN and bilirubin ≤1 x ULN may receive the standard dose of ixabepilone (40 mg/m^2) *[see Boxed Warning, Contraindications (4), Warnings and Precautions (5.3), and 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 mg/m^2, the dosage in subsequent cycles may be escalated up to, but not exceeding, 30 mg/m^2 if tolerated. Use in patients with AST or ALT >10 x ULN or bilirubin >3 x ULN is not recommended. Limited data are available for patients with baseline AST or ALT >5 x ULN. Caution should be used when treating these patients *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

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

	Transaminase Levels		Bilirubin Levels[a]	IXEMPRA[b] (mg/m^2)
Mild	AST and ALT ≤2.5 x ULN	and	≤1 x ULN	40
	AST and ALT ≤10 x ULN	and	≤1.5 x ULN	32
Moderate	AST and ALT ≤10 x ULN	and	>1.5 x ULN - ≤3 x ULN	20 - 30

[a] Excluding patients whose total bilirubin is elevated due to Gilbert's disease.

[b] 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 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)]*.

Strong CYP3A4 Inducers

The use of concomitant strong CYP3A4 inducers should be avoided (eg, phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital). Selection of an alternative concomitant medication with no or minimal enzyme induction potential should be considered. Based on extrapolation from a drug interaction study with rifampin, the following guidance may be considered for dosing in patients requiring coadministration of a strong CYP3A4 inducer, if no alternatives are feasible. Once patients have been maintained on a strong CYP3A4 inducer, the dose of IXEMPRA may be gradually increased from 40 mg/m^2 to 60 mg/m^2 depending on tolerance. If the dose is increased, IXEMPRA should be given as a 4-hour intravenous infusion. This 60 mg/m^2 dose given intravenously over 4 hours is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. Patients whose dose is increased above 40 mg/m^2 should be monitored carefully for toxicities associated with IXEMPRA. If the strong inducer is discontinued, the IXEMPRA dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[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_1 antagonist (eg, diphenhydramine 50 mg orally or equivalent) and
- An H_2 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_1 and H_2 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

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