



# IXEMPRA<sup>®</sup> (ixabepilone) dosing and administration guide

For patients with metastatic or locally advanced breast cancer resistant or refractory to an anthracycline, a taxane, and capecitabine

## Indications

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.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

## Safety information<sup>1</sup>

### **WARNING: toxicity in hepatic impairment**

- **IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT  $>2.5 \times$  ULN or bilirubin  $>1 \times$  ULN due to increased risk of toxicity and neutropenia-related death**
- In combination with capecitabine, the overall frequency of grades 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater in patients with hepatic impairment
- Caution should be used when using IXEMPRA as monotherapy in patients with AST or ALT  $>5 \times$  ULN; use of IXEMPRA in patients with AST or ALT  $>10 \times$  ULN or bilirubin  $>3 \times$  ULN is not recommended
- With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment

Please [click here](#) for Important Safety Information, including **boxed WARNING regarding hepatic impairment**, and [click here](#) for Full Prescribing Information.

**IXEMPRA<sup>®</sup>**  
(ixabepilone) for injection,  
for intravenous infusion

# IXEMPRA<sup>®</sup> (ixabepilone) dosing<sup>1</sup>

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 greater than 2.2 m<sup>2</sup> should be calculated based on 2.2 m<sup>2</sup>
- The dose of IXEMPRA is the same for monotherapy and for combination therapy with capecitabine
- For certain toxicities, an initial 20% dose reduction should be made, followed by an additional 20% dose reduction if toxicities recur

## Recommended dosage

40 mg/m<sup>2</sup> IV over 3 hours  
every 3 weeks

## Initial 20% dose reduction in the presence of toxicities

32 mg/m<sup>2</sup> IV over 3 hours  
every 3 weeks

## Additional 20% dose reduction if toxicities recur

25 mg/m<sup>2</sup> IV over 3 hours  
every 3 weeks

### Safety information: contraindications

- IXEMPRA is contraindicated in patients:
  - With a known history of a severe (CTC grades 3/4) hypersensitivity reaction to agents containing Cremophor<sup>®</sup> EL or its derivatives, such as polyoxyethylated castor oil
  - Who have a baseline neutrophil count <1,500 cells/mm<sup>3</sup> or a platelet count <100,000 cells/mm<sup>3</sup>

CTC, common terminology criteria.

- 2 Please [click here](#) for Important Safety Information, including **boxed WARNING regarding hepatic impairment**, and [click here](#) for Full Prescribing Information.

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**For certain toxicities, an initial dose reduction of 20% should be made, followed by an additional 20% dose reduction if toxicities recur**

- Patients should be evaluated during treatment by periodic clinical observation and laboratory tests, including complete blood cell counts
- Depending on the type and severity of the toxicity, patients may require treatment discontinuation or no dose adjustment; if toxicities are present, treatment should be delayed to allow recovery
- Dosing adjustment guidelines for monotherapy and combination therapy are shown in the table below

**Dose adjustment for toxicities\***

| <b>IXEMPRA® (ixabepilone) (combination therapy or monotherapy)</b>                               | <b>IXEMPRA dose modification</b>   |
|--|--|
| <b>Nonhematologic</b>  |  |
| 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  | No change in the dose of IXEMPRA   |
| Grade 3 palmar-plantar erythrodysesthesia (hand-foot) syndrome                                   | No change in the dose of IXEMPRA   |
| Any grade 4 toxicity (disabling)   | Discontinue treatment  |
| <b>Hematologic</b>   |  |
| Neutrophils <500 cells/mm <sup>3</sup> for ≥7 days   | Decrease the dose by 20%   |
| Febrile neutropenia  | Decrease the dose by 20%   |
| Platelets <25,000 cells/mm <sup>3</sup> or platelets <50,000 cells/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>  |  |
| <b>Follow capecitabine label</b>   |  |
| <b>Hematologic</b>   |  |
| Platelets <25,000 cells/mm <sup>3</sup> or platelets <50,000 cells/mm <sup>3</sup> with bleeding | Hold for concurrent diarrhea or stomatitis until platelet count is >50,000 cells/mm <sup>3</sup> , then continue at the same dose  |
| Neutrophils <500 cells/mm <sup>3</sup> for ≥7 days or febrile neutropenia                        | Hold for concurrent diarrhea or stomatitis until neutrophil count is >1,000 cells/mm <sup>3</sup> , then continue at the same dose |

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

**Safety information: peripheral neuropathy**

- Peripheral neuropathy was common; patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles; patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity; caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

3 Please [click here](#) for Important Safety Information, including boxed **WARNING regarding hepatic impairment**, and [click here](#) for Full Prescribing Information.



## Re-treatment criteria<sup>1</sup>

- 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 the “Dose adjustment for toxicities” table on the previous page
- Patients should not begin a new cycle of treatment unless the neutrophil count is  $\geq 1,500$  cells/mm<sup>3</sup>, the platelet count is  $\geq 100,000$  cells/mm<sup>3</sup>, and nonhematologic toxicities have improved to grade 1 (mild) or resolved

## Dose modification for patients with hepatic impairment<sup>1</sup>

- Assessment of hepatic function is recommended before initiation of IXEMPRA<sup>®</sup> (ixabepilone) and periodically thereafter
- Patients with baseline AST or ALT  $>2.5$  x ULN or bilirubin  $>1.5$  x ULN experienced greater toxicity than patients with baseline AST or ALT  $\leq 2.5$  x ULN or bilirubin  $\leq 1.5$  x ULN when treated with IXEMPRA at 40 mg/m<sup>2</sup> in combination with capecitabine or as monotherapy in breast cancer studies

### For 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  $\leq 2.5$  x ULN and bilirubin  $\leq 1$  x ULN may receive the standard dose of IXEMPRA (40 mg/m<sup>2</sup>)

### For monotherapy

- Patients with hepatic impairment should be dosed with IXEMPRA based on the table below
- Patients with moderate hepatic impairment should be started at 20 mg/m<sup>2</sup>; the dosage in subsequent cycles may be escalated up to, but should not exceed, 30 mg/m<sup>2</sup> 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 AST or ALT  $>5$  x ULN; caution should be used when treating these patients

### Dose adjustments for IXEMPRA monotherapy in patients with hepatic impairment

|          | Transaminase levels          |     | Bilirubin levels*                        | IXEMPRA (mg/m <sup>2</sup> ) <sup>†</sup> |
|----------|------------------------------|-----|--|---|
| Mild     | AST and ALT $\leq 2.5$ x ULN | and | Bilirubin $\leq 1$ x ULN                 | 40  |
|          | AST and ALT $\leq 10$ x ULN  | and | Bilirubin $\leq 1.5$ x ULN               | 32  |
| Moderate | AST and ALT $\leq 10$ x ULN  | and | Bilirubin $>1.5$ x ULN to $\leq 3$ x ULN | 20-30                                     |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

\*Excluding patients whose total bilirubin is elevated due to Gilbert syndrome.

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

### Safety information: myelosuppression

- Myelosuppression is dose-dependent and primarily manifested as neutropenia
- Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced; neutropenia-related deaths occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine; neutropenia-related death occurred in 0.4% of 240 patients treated with IXEMPRA as monotherapy

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# Dose modification: inhibitors and inducers of CYP3A4<sup>1</sup>

## CYP3A4 inhibitors

- Avoid the use of concomitant strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, or voriconazole)
- Grapefruit juice may also increase plasma concentrations of IXEMPRA<sup>®</sup> (ixabepilone) and should be avoided
- Based on pharmacokinetic studies, if a strong CYP3A4 inhibitor must be coadministered, a dose reduction to 20 mg/m<sup>2</sup> is predicted to adjust the IXEMPRA 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
- Patients receiving CYP3A4 inhibitors during treatment with IXEMPRA should be monitored closely for acute toxicities (eg, frequent monitoring of peripheral blood counts between cycles of IXEMPRA)

## CYP3A4 inducers

- IXEMPRA is a CYP3A4 substrate; avoid the use of concomitant strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital)
- Selection of an alternative concomitant medication with no or minimal enzyme induction potential should be considered
- 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 become maintained on a strong CYP3A4 inducer, the dose of IXEMPRA may be gradually increased from 40 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup>, depending on tolerance
  - If the dose is increased, IXEMPRA should be given as a 4-hour intravenous infusion
  - There are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers; however, it is predicted to adjust the AUC to the range observed without inducers
  - Patients whose dose is increased above 40 mg/m<sup>2</sup> 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
- St. John's wort may decrease ixabepilone plasma concentrations unpredictably and should be avoided

## Safety information: hypersensitivity reaction

- Premedicate with an H<sub>1</sub> and an H<sub>2</sub> antagonist approximately 1 hour before IXEMPRA infusion, and observe for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm)
- In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started
- Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H<sub>1</sub> and H<sub>2</sub> antagonists, and extension of the infusion time should be considered

AUC, area under the curve.

## Premedication<sup>1</sup>

- To minimize the chance of occurrence of a hypersensitivity reaction, all patients must be premedicated approximately 1 hour before the infusion of IXEMPRA<sup>®</sup> (ixabepilone) 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

## Overdosage<sup>1</sup>

- Experience with overdose of IXEMPRA is limited to isolated cases; the adverse reactions reported in these cases included peripheral neuropathy, fatigue, musculoskeletal pain/myalgia, and gastrointestinal symptoms (nausea, anorexia, diarrhea, abdominal pain, and stomatitis)
- The highest dose mistakenly received was 100 mg/m<sup>2</sup> (total dose, 185 mg)
- There is no known antidote for overdosage of IXEMPRA; in case of overdosage, the patient should be closely monitored, and supportive treatment should be administered
- Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations

## Use in specific populations<sup>1</sup>

### Hepatic impairment

- IXEMPRA in combination with capecitabine must not be given to patients with AST or ALT >2.5 × ULN or bilirubin >1 × ULN
- Dose reduction is recommended when administering IXEMPRA as monotherapy to patients with hepatic impairment
- Because there is a need for dosage adjustment based upon hepatic function, assessment of hepatic function is recommended before initiation of IXEMPRA and periodically thereafter

### Geriatric use

- Clinical studies of IXEMPRA did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently than younger subjects
- Forty-five of 431 patients treated with IXEMPRA in combination with capecitabine were ≥65 years of age, and 3 patients were ≥75 years of age
  - Overall, the incidence of grades 3/4 adverse reactions was higher in patients ≥65 years of age versus those <65 years of age (82% vs 68%), including grades 3/4 stomatitis (9% vs 1%), diarrhea (9% vs 6%), palmar-plantar erythrodysesthesia (hand-foot) syndrome (27% vs 20%), peripheral neuropathy (24% vs 22%), febrile neutropenia (9% vs 3%), fatigue (16% vs 12%), and asthenia (11% vs 6%)
  - Toxicity-related deaths occurred in 2 of 43 patients (4.7%) ≥65 years of age with normal baseline hepatic function or mild impairment
- Thirty-two of 240 breast cancer patients treated with IXEMPRA as monotherapy were ≥65 years of age, and 6 patients were ≥75 years of age; no overall differences in safety were observed in these patients compared to those <65 years of age

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

## Use in specific populations<sup>1</sup> (cont'd)

### Renal impairment

- IXEMPRA® (ixabepilone) is minimally excreted via the kidney
- No controlled pharmacokinetic studies were conducted with IXEMPRA in patients with renal impairment
- IXEMPRA in combination with capecitabine has not been evaluated in patients with calculated creatinine clearance of <50 mL/min
- IXEMPRA as monotherapy has not been evaluated in patients with creatinine >1.5 x ULN
- In a population pharmacokinetic analysis of IXEMPRA as monotherapy, there was no meaningful effect of mild or moderate renal insufficiency (CrCl >30 mL/min) on the pharmacokinetics of IXEMPRA

### Pregnant women and nursing mothers

- Pregnancy Category D: IXEMPRA may cause fetal harm when administered to pregnant women
- There are no adequate and well-controlled studies with IXEMPRA in pregnant women
- Women should be advised not to become pregnant when taking IXEMPRA
- If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- It is not known whether IXEMPRA is excreted into human milk
- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IXEMPRA, a decision must be made whether to discontinue nursing or to discontinue IXEMPRA, taking into account the importance of the drug to the mother

### Pediatric use

- The safety and effectiveness of IXEMPRA in pediatric patients have not been established

CrCl, creatinine clearance; ULN, upper limit of normal.

## How supplied

### A 2-vial kit, IXEMPRA® (ixabepilone) for injection and diluent, which must be refrigerated<sup>1</sup>

IXEMPRA is supplied as a kit containing one vial of IXEMPRA and one vial of diluent for IXEMPRA; a sufficient excess of drug is provided in the respective vials to allow for withdrawal losses.

- IXEMPRA Kit must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original package to protect from light

### Additional supplies needed<sup>1,2</sup>

| Required materials for dose preparation and administration |  |
|--|--|
| For preparation  | <ul style="list-style-type: none"><li>Qualified infusion fluid (DEHP-free)*</li><li>Sterile, disposable syringes/needles</li><li>Impervious gloves, gown</li><li>Other safety precautions required by your institution</li></ul> |
| For administration   | <ul style="list-style-type: none"><li>One IV administration set (DEHP-free)</li><li>One IV catheter</li><li>Alcohol pads</li><li>In-line filter (0.2 to 1.2 microns)</li></ul>   |

DEHP, di-(2-ethylhexyl) phthalate.

\* See page 9 for the qualified infusion fluids.

## Handling guidelines

As with all antineoplastic agents, care should be taken when preparing and handling IXEMPRA for injection.

- To minimize the risk of dermal exposure, impervious gloves should be worn when handling vials containing IXEMPRA, regardless of setting, including unpacking and inspection, transport within a facility, and dose preparation and administration<sup>1</sup>
- If IXEMPRA comes into contact with skin or mucosa, immediately and thoroughly wash with soap and water, as appropriate<sup>2</sup>
- IXEMPRA should be prepared in a class II vertical laminar airflow safety cabinet using standard precautions for the safe handling of antineoplastic agents<sup>2</sup>
- The preparation area should be isolated and equipped with a hand-wash sink and an eye-wash station<sup>2</sup>

### Other important considerations when preparing IXEMPRA

- Only personnel trained in the handling of antineoplastic agents should be involved in preparing IXEMPRA<sup>1</sup>
- Please follow procedures for proper handling, preparation, and administration of antineoplastic agents

### Safety information: pregnancy<sup>1</sup>

- Women should be advised not to become pregnant when taking IXEMPRA; if this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus



## Constitution of IXEMPRA® (ixabepilone)<sup>1</sup>

The IXEMPRA Kit should be removed from the refrigerator and allowed to stand at room temperature for approximately 30 minutes before constitution. 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 constitute IXEMPRA, with a suitable syringe, aseptically withdraw 8 mL of diluent and slowly inject into the 15-mg IXEMPRA vial or withdraw 23.5 mL of diluent and inject into the 45-mg IXEMPRA vial; once constituted with diluent, the concentration of IXEMPRA is 2 mg/mL
  - To allow for withdrawal losses, the vial labeled 15-mg IXEMPRA for injection contains 16 mg of drug, and the vial labeled 45-mg IXEMPRA for injection contains 47 mg of drug
- Gently swirl and invert the vial until the powder in IXEMPRA is completely dissolved; do not shake
- After constitution, the constituted solution should be further diluted with infusion fluid as soon as possible, but may be stored in the vial (not the syringe) for a maximum of 1 hour at room temperature and room light

## Dilution of IXEMPRA<sup>1</sup>

- Before IV administration, the constituted solution must be further diluted with one of the specified infusion fluids listed below; the IXEMPRA infusion must be prepared in a DEHP-free bag
  - Lactated Ringer's Injection, USP
  - 0.9% Sodium Chloride Injection, USP
    - When using a 250-mL or a 500-mL bag of 0.9% Sodium Chloride Injection to prepare the infusion, the pH must be adjusted to between 6.0 and 9.0 by adding 2 mEq (ie, 2 mL of an 8.4% w/v solution or 4 mL of a 4.2% w/v solution) of Sodium Bicarbonate Injection prior to the addition of the constituted IXEMPRA solution
  - PLASMA-LYTE® A Injection pH 7.4
- For most doses, a 250-mL bag of infusion fluid is sufficient; however, it is necessary to check the final infusion concentration of each dose based on the volume of infusion fluid to be used
- To calculate the final infusion concentration of IXEMPRA (which must range between 0.2 mg/mL and 0.6 mg/mL), use the following formulas:



Total infusion volume = mL of constituted solution + mL of infusion fluid

Final infusion concentration = dose of IXEMPRA (mg) / total infusion volume (mL)

### Safety information: cardiac adverse reactions

- Caution should be exercised in patients with a history of cardiac disease; discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction); the frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the group treated with IXEMPRA in combination with capecitabine (1.9%) than in the group treated with capecitabine alone (0.3%)

DEHP, di-(2-ethylhexyl) phthalate; w/v, weight/volume.

PLASMA-LYTE is a registered trademark of Baxter Laboratories, Inc.

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## Dilution of IXEMPRA® (ixabepilone)<sup>1</sup> (cont'd)

- Aseptically, withdraw the appropriate volume of constituted solution (2 mg of IXEMPRA per mL) to achieve the required dose based on patient's body surface area
- Aseptically, transfer to an IV bag containing the appropriate volume of infusion fluid to achieve the desired final concentration of IXEMPRA
- Thoroughly mix the infusion by manual rotation; do not shake
- Once diluted with infusion fluid, the solution is stable at room temperature and room light for a maximum of 6 hours; administration must be completed within this 6-hour period

## IV administration of IXEMPRA

- Infusion must be administered through an appropriate in-line filter with a microporous membrane of 0.2 to 1.2 microns; DEHP-free containers and administration sets must be used<sup>1</sup>
- Syringes, infusion sets, and pumps should have Luer-lock fittings and should be observed for leakage; a plastic-backed absorbent pad should be placed under the tubing during administration to contain any leakage<sup>2</sup>
- Syringes, IV containers, and pumps should be wiped clean of any drug contamination with an alcohol gauze pad<sup>2</sup>
- Infusion should be given over 3 hours while patient is closely monitored for adverse reactions<sup>1</sup>
- Once diluted with one of the specified infusion fluids, the solution is stable at room temperature and room light for a maximum of 6 hours; administration must be completed within this 6-hour period<sup>1</sup>
- Any remaining solution should be discarded according to institutional procedures for antineoplastic agents<sup>1</sup>

### Safety information: potential for cognitive impairment from excipients<sup>1</sup>

- IXEMPRA contains dehydrated alcohol USP; consideration should be given to the possibility of central nervous system and other effects of alcohol

DEHP, di-(2-ethylhexyl) phthalate.

## FAQs<sup>1</sup>

### How is IXEMPRA® (ixabepilone) supplied?

IXEMPRA is supplied as a 2-vial kit (IXEMPRA for injection and diluent).

### How is IXEMPRA stored?

Both IXEMPRA and diluent must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F).

### Why do I need to use one of the specified infusion fluids?

IXEMPRA requires a pH range of 6.0 to 9.0, which is required to maintain the stability of IXEMPRA. Other infusion fluids should not be used with IXEMPRA. The qualified infusion fluids have the suitable pH range.

### What is the usual size of the infusion fluid bag?

For most doses, a 250-mL bag of infusion fluid is sufficient. However, it is necessary to check the final infusion concentration of each dose based on the volume of infusion fluid to be used.

### What is the final infusion concentration of IXEMPRA?

IXEMPRA must be administered at a final infusion concentration of 0.2 mg/mL to 0.6 mg/mL.

### Are in-line filters required to administer IXEMPRA?

The infusion must be administered through an appropriate in-line filter with a microporous membrane of 0.2 to 1.2 microns.

### What is the stability/use time of IXEMPRA?

After constitution, the constituted solution should be further diluted with infusion fluid as soon as possible, but may be stored in the vial (not the syringe) for a maximum of 1 hour at room temperature and room light. Once diluted with infusion fluid, IXEMPRA is stable at room temperature and room light for a maximum of 6 hours. Administration of IXEMPRA must be completed within this 6-hour period.

## Additional resources for information on safe handling of antineoplastic agents

American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-1191. <http://www.ashp.org/DocLibrary/BestPractices/PrepGdlHazDrugs.aspx>. Accessed February 9, 2016.

National Institute for Occupational Safety and Health. *NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings*. Cincinnati, OH: National Institute for Occupational Safety and Health, US Dept of Health and Human Services; 2004. NIOSH publication 2004-165.

Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. In: *OSHA Technical Manual*. Washington, DC: Occupational Safety and Health Administration. [https://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](https://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html). Accessed February 9, 2016.

Polovich M, White JM, Kelleher LO, eds. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. 2nd ed. Pittsburgh, PA: Oncology Nursing Society; 2005.

## IMPORTANT SAFETY INFORMATION

### WARNING: Toxicity in hepatic impairment

- IXEMPRA® (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT  $>2.5 \times \text{ULN}$  or bilirubin  $>1 \times \text{ULN}$  due to increased risk of toxicity and neutropenia-related death
- In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater in patients with hepatic impairment
- Caution should be used when using IXEMPRA as monotherapy in patients with AST or ALT  $>5 \times \text{ULN}$ . Use of IXEMPRA in patients with AST or ALT  $>10 \times \text{ULN}$  or bilirubin  $>3 \times \text{ULN}$  is not recommended
- With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment

### Contraindications

- IXEMPRA is contraindicated in patients:
  - with a known history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives such as polyoxyethylated castor oil
  - who have a baseline neutrophil count  $<1500 \text{ cells/mm}^3$  or a platelet count  $<100,000 \text{ cells/mm}^3$

### Peripheral neuropathy

- Peripheral neuropathy was common. Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

### Myelosuppression

- Myelosuppression is dose-dependent and primarily manifested as neutropenia
- Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced. Neutropenia-related deaths occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine. Neutropenia-related death occurred in 0.4% of 240 patients with IXEMPRA as monotherapy

### Hypersensitivity reaction

- Premedicate with an  $H_1$  and an  $H_2$  antagonist approximately 1 hour before IXEMPRA infusion and observe for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm)
- In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started
- Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the  $H_1$  and  $H_2$  antagonists, and extension of the infusion time should be considered

### Pregnancy

- Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus

## IMPORTANT SAFETY INFORMATION (cont'd)

### Cardiac adverse reactions

- Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA® (ixabepilone) should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group

### Potential for cognitive impairment from excipients

- IXEMPRA contains dehydrated alcohol USP. Consideration should be given to the possibility of central nervous system and other effects of alcohol

### Adverse reactions

#### *Monotherapy*

- The most common adverse reactions ( $\geq 20\%$ ) reported by patients receiving IXEMPRA monotherapy were peripheral sensory neuropathy, 62% (grade 3/4: 14%); fatigue/asthenia, 56% (grade 3/4: 13%); myalgia/arthralgia, 49% (grade 3/4: 8%); alopecia, 48% (grade 3/4: 0%); nausea, 42% (grade 3/4: 2%); stomatitis/mucositis, 29% (grade 3/4: 6%); vomiting, 29% (grade 3/4: 1%); diarrhea, 22% (grade 3/4: 1%); and musculoskeletal pain, 20% (grade 3/4: 3%). Drug-associated hematologic abnormalities ( $>40\%$ ) included neutropenia, leukopenia, anemia, and thrombocytopenia. Grade 3/4 hematologic adverse reactions included neutropenia, 54%; leukopenia, 49%; anemia, 8%; and thrombocytopenia, 7%

#### *Combination with capecitabine*

- The most common adverse reactions ( $\geq 20\%$ ) reported by patients receiving IXEMPRA in combination with capecitabine compared to capecitabine alone, respectively, were peripheral sensory neuropathy, 65% vs. 16% (grade 3/4: 21% vs. 0%); palmar-plantar erythrodysesthesia (hand-foot) syndrome, 64% vs. 63% (grade 3/4: 18% vs. 17%); fatigue/asthenia, 60% vs. 29% (grade 3/4: 16% vs. 4%); nausea, 53% vs. 40% (grade 3/4: 3% vs. 2%); diarrhea, 44% vs. 39% (grade 3/4: 6% vs. 9%); vomiting, 39% vs. 24% (grade 3/4: 4% vs. 2%); myalgia/arthralgia, 39% vs. 5% (grade 3/4: 8% vs.  $<1\%$ ); anorexia, 34% vs. 15% (grade 3/4: 3% vs. 1%); stomatitis/mucositis, 31% vs. 20% (grade 3/4: 4% vs. 3%); alopecia, 31% vs. 3% (grade 3/4: 0% vs. 0%); abdominal pain, 24% vs. 14% (grade 3/4: 2% vs. 1%); nail disorder, 24% vs. 10% (grade 3/4: 2% vs.  $<1\%$ ); musculoskeletal pain, 23% vs. 5% (grade 3/4: 2% vs. 0%); and constipation, 22% vs. 6% (grade 3/4: 0% vs.  $<1\%$ ). Drug-associated hematologic abnormalities ( $>40\%$ ) with IXEMPRA in combination with capecitabine and capecitabine alone, respectively, included neutropenia, leukopenia, anemia, and thrombocytopenia. Grade 3/4 hematologic adverse reactions included neutropenia, 68% vs. 11%; leukopenia, 57% vs. 6%; anemia, 10% vs. 5%; and thrombocytopenia, 8% vs. 4%

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AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; CTC = common terminology criteria.

**References:** 1. IXEMPRA (ixabepilone) Prescribing Information. 2. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2006;63(12):1172-1191. <http://www.ashp.org/DocLibrary/BestPractices/PrepGdlHazDrugs.aspx>. Accessed February 9, 2016.



## ACCESS + SUPPORT™

Committed to patients. Committed to care.

### Access and support for eligible, commercially insured patients

The R-Pharm US Access and Support co-pay program is designed to assist eligible patients who have been prescribed R-Pharm US products with out-of-pocket deductibles, co-pays, or coinsurance requirements.

#### Assistance for eligible patients—IXEMPRA® (ixabepilone)

##### ENROLLED PATIENTS

pay the first **\$25** of their co-pay per infusion

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the remaining amount up to **\$25,000** per year

Restrictions may apply. Final determination of program eligibility is based on review of completed application.

**Please note:** The program will cover the out-of-pocket expenses of the R-Pharm US product only. It does not cover the costs of any other healthcare provider charges or any other treatment costs. Patients may be responsible for non-drug-related out-of-pocket costs, depending on their specific healthcare benefits.

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#### For more information about R-Pharm US Access and Support:



Call the Support Center at  
**1-855-991-7277**, 8 AM to 8 PM ET,  
Monday-Friday



Visit [rpharm-us.enrollsource.com](http://rpharm-us.enrollsource.com)  
for resources to help your patients  
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Please [click here](#) for Important Safety Information, including **boxed WARNING regarding hepatic impairment**, and [click here](#) for Full Prescribing Information.



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**IXEMPRA®**  
(ixabepilone) for injection,  
for intravenous infusion