Indications

IXEMPRA® (ixabepilone) 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.

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.

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.

- 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 x ULN. Use of IXEMPRA in patients with AST or ALT >10 x ULN or bilirubin >3 x ULN is not recommended.
- With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment.

Please see Important Safety Information, including boxed WARNING regarding hepatic impairment, on pages 5-6.
Contraindications
IXEMPRA® (ixabepilone) 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 (eg, polyoxyethylated castor oil). Who have a neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³. In combination with capcitabine 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.

How Supplied
IXEMPRA is supplied as a kit containing one vial of IXEMPRA for injection and one vial of diluent for IXEMPRA. To allow for withdrawal losses, the vials labeled as 15-mg and 45-mg IXEMPRA for injection contain 16 mg and 47 mg of ixabepilone, respectively. The diluent for IXEMPRA is a sterile, non-pyrogenic solution of 52.8% (w/v) purified polyoxyethylated castor oil and 39.8% (w/v) dehydrated alcohol, USP.

Table 1. Dose adjustments for toxicities*

<table>
<thead>
<tr>
<th>IXEMPRA (monotherapy or combination therapy)</th>
<th>IXEMPRA dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonhematologic</td>
<td></td>
</tr>
<tr>
<td>Grade 2 neuropathy (moderate) lasting ≥7 days</td>
<td>Decrease the dose by 20%</td>
</tr>
<tr>
<td>Grade 3 neuropathy (severe) lasting &lt;7 days</td>
<td>Decrease the dose by 20%</td>
</tr>
<tr>
<td>Grade 3 neuropathy (severe) lasting ≥7 days or disabling neuropathy</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Any grade 3 toxicity (severe) other than neuropathy</td>
<td>Decrease the dose by 20%</td>
</tr>
<tr>
<td>Transient grade 3 arthralgia/myalgia or fatigue</td>
<td>No change in dose of IXEMPRA</td>
</tr>
<tr>
<td>Grade 3 hand-foot syndrome (palmar-plantar erythrodysesthesia)</td>
<td>No change in dose of IXEMPRA</td>
</tr>
<tr>
<td>Any grade 4 toxicity (disabling)</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Neutrophils &lt;500 cells/mm³ for ≥7 days</td>
<td>Decrease the dose by 20%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Decrease the dose by 20%</td>
</tr>
<tr>
<td>Platelets &lt;25,000/mm³ or platelets &lt;50,000/mm³ with bleeding</td>
<td>Decrease the dose by 20%</td>
</tr>
<tr>
<td>Capcitabine (when used in combination with IXEMPRA)</td>
<td>Capcitabine dose modification</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;25,000/mm³ or &lt;50,000/mm³ with bleeding</td>
<td>Hold for concurrent diarrhea or stomatitis until platelet count &gt;50,000/mm³, then continue at same dose</td>
</tr>
<tr>
<td>Neutrophils &lt;500 cells/mm³ for ≥7 days or febrile neutropenia</td>
<td>Hold for concurrent diarrhea or stomatitis until neutrophil count &gt;1,000 cells/mm³, then continue at same dose</td>
</tr>
</tbody>
</table>

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

Recommended Dosage
The recommended dosage of IXEMPRA is 40 mg/m² administered intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2 m² should be calculated based on 2.2 m².

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 H₁ antagonist (eg, diphenhydramine 50 mg orally or equivalent)
- An H₂ 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 H₁ and H₂ antagonists.

Dose Modifications
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. Depending on the type and severity of the toxicity, patients may require treatment discontinuation or no dose adjustment.

Please see Important Safety Information, including boxed WARNING regarding hepatic impairment, on pages 5-6.
Retreatment Criteria
Dose adjustments at the start of a cycle should be based on w/w 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
Assessment of hepatic function is recommended before initiation of IXEMPRA® (ixabepilone) and periodically thereafter.

- Patients with baseline AST or ALT >2.5 $\times$ ULN or bilirubin >1.5 $\times$ ULN experienced greater toxicity than patients with baseline AST or ALT $\leq$ 2.5 $\times$ ULN or bilirubin $\leq$ 1.5 $\times$ ULN when treated with IXEMPRA at 40 mg/m$^2$ 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 $\times$ 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 IXEMPRA (40 mg/m$^2$).

For 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 exceed, 30 mg/m$^2$ if tolerated. Use in patients with AST or ALT >10 $\times$ ULN or bilirubin >3 $\times$ ULN 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.

### Table 2. Dose adjustments for IXEMPRA as monotherapy in patients with hepatic impairment

<table>
<thead>
<tr>
<th>Transaminase levels</th>
<th>Bilirubin levels*</th>
<th>IXEMPRA (mg/m$^2$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>AST and ALT $\leq$ 2.5 $\times$ ULN and $\leq$ 1 $\times$ ULN</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>AST and ALT $\leq$ 10 $\times$ ULN and $\leq$ 1.5 $\times$ ULN</td>
<td>32</td>
</tr>
<tr>
<td>Moderate</td>
<td>AST and ALT $\leq$ 10 $\times$ ULN and &gt;1.5 $\times$ ULN to $\leq$ 3 $\times$ ULN</td>
<td>20-30</td>
</tr>
</tbody>
</table>

*Excluding patients whose total bilirubin was elevated due to Gilbert’s disease.

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

Dose Adjustments for 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 IXEMPRA AUC to the range observed without inhibitors and should be considered. If the 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).

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.
- The following guidance may be considered for dosing in patients requiring coadministration of a strong CYP3A4 inducer. 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. 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.
- St. John’s wort may decrease plasma concentrations of IXEMPRA unpredictably and should be avoided.

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

Please see Important Safety Information, including boxed WARNING regarding hepatic impairment, on pages 5-6.
Preparation and Handling Precautions

Procedures for proper handling and disposal of antineoplastic drugs should be followed. To minimize the risk of dermal exposure, impervious gloves should be worn when handling vials containing IXEMPRA (ixabepilone), regardless of the setting, including unpacking and inspection, transport within a facility, and dose preparation and administration.

Nine Steps to Prepare and Administer IXEMPRA® (ixabepilone)

1. 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.

2. With a suitable syringe, aseptically withdraw the diluent and slowly inject it into the IXEMPRA for injection vial. The 15-mg IXEMPRA vial is constituted with 8 mL of diluent and the 45-mg IXEMPRA vial is constituted with 23.5 mL of diluent.

3. Gently swirl and invert the vial until the powder in IXEMPRA is completely dissolved. Do not shake.

4. Before administration, the constituted solution must be further diluted as soon as possible with one of the specified infusion fluids listed below:
   - 0.9% Sodium Chloride Injection, USP (pH adjusted with Sodium Bicarbonate 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 a pH 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

The infusion fluid must be supplied in DEHP [di-(2-ethylhexyl)phthalate]-free bags. 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. Any remaining solution should be discarded according to institutional procedures for antineoplastics.

5. The final concentration for infusion must be between 0.2 mg/mL and 0.6 mg/mL. To calculate the final infusion concentration, use the following formulas:
   \[
   \text{Total Infusion Volume} = \text{mL of Constituted Solution} + \text{mL of infusion fluid}
   \]
   \[
   \text{Final Infusion Concentration} = \frac{\text{Dose of IXEMPRA (mg)}}{\text{Total Infusion Volume (mL)}}
   \]

6. Aseptically, withdraw the appropriate volume of constituted solution containing 2 mg of IXEMPRA per mL.

7. Aseptically, transfer to an intravenous (IV) bag containing an appropriate volume of infusion fluid to achieve the final desired concentration of IXEMPRA.

8. Thoroughly mix the infusion by manual rotation. Do not shake.

9. The 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

Procedures for proper handling and disposal of antineoplastic drugs should be followed.¹

Stability

After constituting IXEMPRA for injection, the constituted solution should be further diluted with one of the specified infusion fluids 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, the solution is stable at room temperature and room light for a maximum of 6 hours. Administration of diluted IXEMPRA must be completed within this 6-hour period. IXEMPRA requires a pH range of 6 to 9 to maintain IXEMPRA’s stability. The qualified infusion fluids have the suitable pH range. Other infusion fluids should not be used with IXEMPRA.

Special Storage Requirements

IXEMPRA Kit must be stored refrigerated at 2°C to 8°C (36°F to 46°F). Retain in original package to protect from light.

Reimbursement information: 1-800-861-0048
For additional information, please call 1-888-IXEMPRA (493-6772) or visit www.IXEMPRA.com.

Toxicity in hepatic impairment

- IXEMPRA® (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 ULN or bilirubin >1 x 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 x ULN.
- Use of IXEMPRA in patients with AST or ALT >10 x ULN or bilirubin >3 x 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 cells/mm$^3$ or a platelet count <100,000 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.

Please see accompanying full Prescribing Information, including boxed WARNING regarding hepatic impairment, following this document.
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

The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA were peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthritis, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional events occurred in ≥20% in combination treatment: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation. Drug-associated hematologic abnormalities (>40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

Cremophor is a registered trademark of BASF AG.

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

Please see accompanying full Prescribing Information, including boxed WARNING regarding hepatic impairment, following this document.
WARNINGS AND PRECAUTIONS

7.4 Effect of Ixabepilone on Other Drugs

7.3 Hypersensitivity Reactions

7.2 Fever/Neutropenia

7.1 Peripheral Neuropathy

6.3 Pharmacokinetics

6.2 Postmarketing Experience

6.1 Clinical Trials Experience

5.1 Hypersensitivity Reactions

5.2 Myelosuppression

5.3 Hepatic Impairment

5.4 Pregnancy

5.5 Cardiac Adverse Reactions

5.6 Hypersensitivity Reaction

5.5 Pregnancy

5.4 Myelosuppression

5.3 Hepatic Impairment

5.2 Myelosuppression

5.1 Peripheral Neuropathy

4.1 Radiation Injury

4.1 Radiation Injury

3.3 Hematologic

3.2 Pharmacodynamics

3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

2.5 Preparation and Handling Precautions

2.4 Instructions for Preparation and IV Administration

2.3 Premedication

2.2 Dose Modification

2.1 General Dosing Information

1.4 How Supplied/Storage and Handling

1.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

1.1 Description

1.1 Description

1. INDICATIONS AND USAGE

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**DOSAGE AND ADMINISTRATION**

**2. General Dosing Information**

The recommended dosage of IXEMPRA is 40 mg/m² administered intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2 m² should be calculated based on 2.2 m².

**2.2 Dose Modification**

**Dose Adjustments During Treatment**

Patients should be evaluated during treatment by periodic clinical observation and laboratory tests of hematologic and nonhematologic toxicity. If toxicities recur, additional dose reduction should be made.

<table>
<thead>
<tr>
<th>Table 1: Dose Adjustment Guidelines*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IXEMPRA (Monotherapy or Combination Therapy)</strong></td>
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<td><strong>Hematologic:</strong>*</td>
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<tr>
<td>Neutrophils &lt;500 cells/mm³ for ≥7 days</td>
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<tr>
<td>Neutrophils &lt;25,000 cells/mm³ or platelets &lt;50,000 cells/mm³ with bleeding</td>
</tr>
<tr>
<td><strong>Carcinoblast (when used in combination with IXEMPRA):</strong>*</td>
</tr>
<tr>
<td><strong>Nonhematologic:</strong>*</td>
</tr>
<tr>
<td><strong>Hematologic:</strong>*</td>
</tr>
<tr>
<td>Platelets &lt;50,000 cells/mm³ or &lt;50,000/mm³ with bleeding</td>
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<td>Neutrophils &lt;500 cells/mm³ for ≥7 days or febrile neutropenia</td>
</tr>
</tbody>
</table>

*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/mm³, the platelet count is at least 100,000 cells/mm³, 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/m²) [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/m², the dosage in subsequent cycles may be escalated up to, but not exceeding, 30 mg/m² 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**

<table>
<thead>
<tr>
<th>Transaminase Levels</th>
<th>Bilirubin Levels</th>
<th>IXEMPRA Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST and ALT ≤2.5 x ULN</td>
<td>≤1 x ULN</td>
<td>40</td>
</tr>
<tr>
<td>AST and ALT ≤3 x ULN</td>
<td>≤1.5 x ULN</td>
<td>32</td>
</tr>
<tr>
<td>AST and ALT ≤4 x ULN</td>
<td>≤2 x ULN</td>
<td>20 - 30</td>
</tr>
</tbody>
</table>

*Excluding patients whose total bilirubin is elevated due to Gilbert's disease. 

**Strong CYP3A4 Inhibitors**

The use of concomitant strong CYP3A4 inhibitors should be avoided (eg, ketoconazole, itraconazole, clarithromycin, azithromycin, cimetidine, lovastatin, itraconazole, rifapentine, indinavir, nelfinavir, delavirdine, or voriconazole). Grapefruit juice may also increase plasma concentrations of IXEMPRA and should be avoided. Based on pharmacokinetic studies, close monitoring of IXEMPRA AUC and toxicities associated with IXEMPRA should be expected in patients taking concomitant strong CYP3A4 inhibitors. If IXEMPRA dose is reduced to 20 mg/m², it is recommended 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/m² to 60 mg/m² depending on tolerance. If the dose is increased, IXEMPRA should be given as a 4-hour intravenous infusion. This 60 mg/m² dose given intravenously over 4 hours is predicted to adjust the IXEMPRA AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. Patients whose dose is increased above 40 mg/m² 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 H₁ antagonist (eg, diphenhydramine 50 mg orally or equivalent) and
- An H₂ 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 H₁ and H₂ 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 vial containing IXEMPRA is 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 vial is opened. To avoid for withdrawal losses, the vial labeled as 15 mg IXEMPRA contains 16 mg of ixabepilone and the vial labeled as 45 mg IXEMPRA 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.**

**A. To constitute:**

1. With a suitable syringe, aseptically withdraw the DILUENT and slowly inject it into the IXEMPRA for injection vial. The 15-mg IXEMPRA is constituted with 8 mL of DILUENT and the 45-mg IXEMPRA is constituted with 23.5 mL of DILUENT.

2. Gently swirl and invert the vial until the powder in IXEMPRA is completely dissolved.
B. To dilute:

Before 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- (di(2-ethylhexyl) phthalate) free bag.

The following infusion fluids have been qualified for use in the dilution of IXEMPRA:

- Lactated Ringer's Injection, USP
- 0.9% Sodium Chloride Injection, USP (pH adjusted with Sodium Bicarbonate Injection, USP)
- o When reconstituting a 250 mL or a 500 mL bag of 0.9% Sodium Chloride Injection to prepare the infusion, the pH must be adjusted to a pH between 6.0 and 7.0 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 IXEMPRA infusion concentration of each dose based on the volume of infusion fluid to be used. The final concentration for infusion must be between 0.2 mg/mL and 0.6 mg/mL. To calculate the final infusion concentration, 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)

1. Aseptically, withdraw the appropriate volume of constituted solution containing 2 mg of IXEMPRA per mL.
2. Aseptically, transfer to an intravenous (IV) bag containing an appropriate volume of infusion fluid to achieve the final desired concentration of IXEMPRA.
3. Thoroughly mix the IV bag by manual rotation.

The infusion solution must be administered through an appropriate in-line filter with a microporous membrane of 0.2 to 1.2 microns. DEHP-free infusion containers and administration sets must be used. Any remaining solution should be discarded according to institutional procedures for antineoplastics.

Stability

After constituting IXEMPRA, 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, the solution is stable at room temperature and room light for a maximum of 6 hours. Administration of diluted IXEMPRA must be completed within this 6-hour period. The infusion fluids previously mentioned are specified because their pH is in the range of 6.0 to 9.0, which is required to maintain IXEMPRA stability. Other infusion fluids should not be used with IXEMPRA.

2.5 Preparation and Handling Precautions

Procedures for proper handling and disposal of antineoplastic drugs [see References (15)] should be followed. To minimize the risk of dermal exposure, impervious gloves should be worn when handling vials containing IXEMPRA, regardless of the setting, including unpacking and inspection, transport within a facility, and dose preparation and administration.

3 DOSAGE FORMS AND STRENGTHS

IXEMPRA for injection, 15 mg supplied with DILUENT for IXEMPRA, 8 mL.

IXEMPRA for injection, 45 mg supplied with DILUENT for IXEMPRA, 23.5 mL.

4 CONTRAINDICATIONS

IXEMPRA is contraindicated in patients with a history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives (eg, polyoxyethylated castor oil) [see Warnings and Precautions (5.4)].

IXEMPRA is contraindicated in patients who have a neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³ [see Warnings and Precautions (5.2)].

IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >10 x ULN when treated with IXEMPRA at 40 mg/m² in combination with capecitabine as monotherapy in breast cancer studies. In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater [see Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

Peripheral neuropathy was common (see Table 3). 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 symptoms may require a reduction or delay in the dose of IXEMPRA [see Dosage and Administration (2.2)]. In clinical studies, peripheral neuropathy was managed through dose reductions, dose delays, and treatment discontinuation. Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. In Studies 046 and 081, 80% and 87%, respectively, of patients with peripheral neuropathy who received IXEMPRA had improvement or no worsening of their neuropathy following dose reduction. For patients with grade 3/4 neuropathy in Studies 046 and 081, 76% and 79%, respectively, had documented improvement to baseline or grade 1, twelve weeks after onset.

5.3 Hepatic Impairment

Patients with baseline AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN experienced greater toxicity than patients with baseline AST ≤2.5 x ULN or bilirubin ≤1.5 x ULN when treated with IXEMPRA at 40 mg/m² in combination with capecitabine as monotherapy in breast cancer studies. In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater [see Warnings and Precautions (5.2)].

5.4 Hypersensitivity Reactions

Patients with a history of a severe hypersensitivity reaction to agents containing Cremophor® EL or its derivatives (eg, polyoxyethylated castor oil) should not be treated with IXEMPRA. All patients should be premedicated with an H₁ and an H₂ antagonist approximately 1 hour before IXEMPRA infusion and be observed 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. Of the 1232 patients treated with IXEMPRA in clinical studies, 9 patients (1%) had experienced severe hypersensitivity reactions (including anaphylaxis). Three of the 9 patients were able to be retreated. Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H₁ and H₂ antagonists, and extension of the infusion time should be considered [see Dosage and Administration (2.3) and Contraindications (4)].

5.5 Pregnancy

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 if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Table 4: Nonhematologic Drug-related Adverse Reactions Occurring in at Least 5% of Patients with Metastatic or Locally Advanced Breast Cancer Treated with IXEMPRA

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>IXEMPRA with capcitabine</th>
<th>Capcitabine</th>
<th>IXEMPRA monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=369</td>
<td>n=368</td>
<td>n=126</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush^a</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea^a</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cough^a</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
<td>3^b</td>
<td>40</td>
<td>2^b</td>
</tr>
<tr>
<td>Vomiting^a</td>
<td>39</td>
<td>4^b</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis/mucositis^a</td>
<td>31</td>
<td>4^b</td>
<td>20</td>
<td>3^b</td>
</tr>
<tr>
<td>Diarrhea^a</td>
<td>44</td>
<td>6^b</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>Constipation</td>
<td>22</td>
<td>0</td>
<td>6</td>
<td>&lt;1^c</td>
</tr>
<tr>
<td>Abdominal pain^b</td>
<td>24</td>
<td>2^b</td>
<td>14</td>
<td>1^i</td>
</tr>
<tr>
<td><strong>Gastroesophageal reflux disease^b</strong></td>
<td>7</td>
<td>1^i</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia^a</td>
<td>31</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash^a</td>
<td>17</td>
<td>1^i</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail disorder^d</td>
<td>24</td>
<td>2^b</td>
<td>10</td>
<td>&lt;1^i</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome^d</td>
<td>64</td>
<td>18^b</td>
<td>63</td>
<td>17^b</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin exfoliation^d</td>
<td>5</td>
<td>&lt;1^i</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Skin hyperpigmentation^b</td>
<td>11</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue, and Bone Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>39</td>
<td>8^b</td>
<td>5</td>
<td>&lt;1^i</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue, and Bone Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain^b</td>
<td>23</td>
<td>2^b</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia^a</td>
<td>60</td>
<td>16</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema^a</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>&lt;1^i</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia^a</td>
<td>10</td>
<td>1^i</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pain^a</td>
<td>9</td>
<td>1^i</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain^a</td>
<td>4</td>
<td>1^i</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decrease</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

^a System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Informative on Drugs by the Council for International Organizations of Medical Sciences (CIOMS).
^b A composite of multiple MedDRA Preferred Terms.
^c NCI CTC grading for febrile neutropenia ranges from Grade 3 to 5. Three patients (1%) experienced Grade 5 (fatal) febrile neutropenia, Other neutropenia-related deaths (9) occurred in the absence of reported febrile neutropenia (see Warnings and Precautions (5.2)).
^d No grade 4 reports.
^e Peripheral sensory neuropathy (graded with the NCI CTC scale) was defined as the occurrence of any of the following: areflexia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, hyperreflexia, neuralgia, neuritis, neuropathy, peripheral neuropathy, pain, response to normal stimuli, paresthesia, paresthesia, peripheral sensory neuropathy, polymyalgia, polymyalgia toxic and sensorimotor disorder. Peripheral motor neuropathy was defined as the occurrence of any of the following: multifocal motor neuropathy, neuromuscular toxicity, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.
^f Palmar-plantar erythrodysesthesia (hand-foot syndrome) was graded on a 1-3 severity scale in Study 046.

Table 3: Hematologic Abnormalities in Patients with Metastatic or Locally Advanced Breast Cancer Treated with IXEMPRA

<table>
<thead>
<tr>
<th>Hematology Parameter</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia^a</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Leukopenia (WBC)</td>
<td>41</td>
<td>16</td>
</tr>
<tr>
<td>Anemia (Hgb)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

^a G-CSF (granulocyte colony stimulating factor) or GM-CSF (granulocyte macrophage colony stimulating factor) was used in 20% and 17% of patients who received IXEMPRA in Study 046 and Study 081, respectively.

Table 4 (Continued):

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>IXEMPRA with capcitabine</th>
<th>Capcitabine</th>
<th>IXEMPRA monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=369</td>
<td>n=368</td>
<td>n=126</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection^a</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5</td>
<td>4^c</td>
<td>1</td>
<td>1^d</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Hyperosensitivity</td>
<td>2</td>
<td>1^e</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia^a</td>
<td>34</td>
<td>3^d</td>
<td>15</td>
<td>1^e</td>
</tr>
<tr>
<td>Dehydration^a</td>
<td>2</td>
<td>2</td>
<td>&lt;1^i</td>
<td>2</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia^a</td>
<td>9</td>
<td>&lt;1^i</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>65</td>
<td>21</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Motor neuropathy^a</td>
<td>16</td>
<td>5^b</td>
<td>&lt;1^i</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>&lt;1^i</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Taste disorder^a</td>
<td>12</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>1^i</td>
<td>5</td>
<td>1^i</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>&lt;1^i</td>
</tr>
<tr>
<td><strong>(Continued)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The following serious adverse reactions were also reported in 1323 patients treated with IXEMPRA as monotherapy or in combination with other therapies in Phase 2 and 3 studies.

**Infections and Infestations:** sepsis, pneumonia, infection, neutropenic infection, urinary tract infection, bacterial infection, enterocolitis, laryngitis, lower respiratory tract infection

**Blood and Lymphatic System Disorders:** coagulopathy, lymphopenia

**Metabolism and Nutrition Disorders:** hypoglycemia, metabolic acidosis, hypokalemia, hypovolemia

**Nervous System Disorders:** cognitive disorder, syncope, cerebral hemorrhage, acute pulmonary edema, dyspnea, pharyngolaryngeal pain

**Cardiac Disorders:** myocardial infarction, supraventricular arrhythmia, left ventricular dysfunction, angina pectoris, atrial flutter, cardiomyopathy, myocardial ischemia

**Vascular Disorders:** hypotension, thrombosis, embolism, hemorrhage, hypovolemic shock, vasculitis

**Respiratory, Thoracic, and Mediastinal Disorders:** pneumonitis, hypoxia, respiratory failure

**Cognitive Disorders, Syncope, Cerebral Hemorrhage:**

**Maximal Tolerated Dose (MTD):** was evaluated in one Phase 1 and one Phase 2 trial. The pediatric patients had a safety evaluation. IXEMPRA in pediatric patients has not been established. IXEMPRA was administered at a dose of 8 mg/m² IV daily for 5 days every 21 days. This trial was terminated early due to lack of efficacy.

### 8.5 Geriatric Use

Clinical studies of IXEMPRA did not include sufficient numbers of subjects aged sixty-five and over to determine whether they respond differently from younger subjects.

Forty-five of 431 patients treated with IXEMPRA in combination with capecitabine were ≥65 years of age and 3 patients were ≥75. Overall, the incidence of grade 3/4 adverse reactions was higher in patients ≥65 years of age versus those <65 years of age (82% versus 68%) including grade 3/4 stomatitis (9% versus 1%), diarrhea (9% versus 6%), palmar-planar erythrodysesthesia syndrome (27% versus 20%), peripheral neuropathy (24% versus 22%), febrile neutropenia (9% versus 3%), fatigue (16% versus 12%), and anemia (11% versus 6%). Toxicity-related deaths occurred in 2 (4.7%) of 43 patients ≥65 years 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. No overall differences in safety were observed in these patients compared to those <65 years of age.

### 8.6 Hepatic Impairment

IXEMPRA was evaluated in 56 patients with mild to severe hepatic impairment defined by bilirubin levels and AST levels. Compared to patients with normal hepatic function (n=17), the area under the curve (AUC) [0-12 h] of ixabepilone increased by:

- 22% in patients with a) bilirubin >1–1.5 x ULN or b) AST > ULN but bilirubin <1.5 x ULN.
- 30% in patients with bilirubin >1.5 – 3 x ULN and any AST level; and
- 81% in patients with bilirubin >3 x ULN and any AST level.

Doses of 10 and 20 mg/m² as monotherapy were tolerated in 17 patients with severe hepatic impairment (bilirubin >3 x ULN).

IXEMPRA in combination with capecitabine must not be given to patients with AST or ALT ≥2.5 x ULN or bilirubin >1 x ULN [see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.3)]. Dose reduction is recommended when administering IXEMPRA as monotherapy to patients with hepatic impairment [see Dosage and Administration (2.3)]. 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.

### 8.7 Renal Impairment

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 times ULN. In a population pharmacokinetic analysis of IXEMPRA as monotherapy, there was no meaningful effect of mild and moderate renal insufficiency (CrCL ≥30 mL/min) on the pharmacokinetics of ixabepilone.

### 10 OVERDOSAGE

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, stomach pain). The highest dose exposure received was 100 mg/m² (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.

### DESCRIPTION

IXEMPRA® (ixabepilone) is a microtubule inhibitor belonging to a class of antineoplastic agents, the epothilones and their analogs. The epothilones are isolated from the myxobacterium Sorangium cellulosum. Ixabepilone is a semisynthetic analog of epothilone B, a 16-membered polyketal macrolide, with a chemically modified lactam substitution for the naturally occurring lactone. The chemical name for ixabepilone is (1R,2S,5S)-7-[(2R,4R)-4-[(Z)-2-methyl-4-[(1,2-oxathiolylidene)-2-yl]ethylidene]-2-oxa-4-azabicyclo[14.1.0] heptadecane-5,9-dione, and it has a molecular weight of 506.7. Ixabepilone has the following structural formula:
IXEMPRA® (ixabepilone) for injection is intended for intravenous infusion only after consultation with the supplied DILUENT and after further dilution with a specified infusion fluid [see Instructions for Preparation and IV Administration (2.4)]. IXEMPRA (ixabepilone) for injection is supplied as a sterile, non-pyrogenic, single-use vial providing 15 mg or 45 mg ixabepilone as a lyophilized white powder. The DILUENT for IXEMPRA is a sterile, non-pyrogenic, solution of 52.8% (w/v) purified polyethylene-castor oil and 39.8% (w/v) dehydrated alcohol, USP. The IXEMPRA (ixabepilone) for injection and the DILUENT for IXEMPRA are copackaged and supplied as IXEMPRA kit.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ixabepilone is a semi-synthetic analog of epothilone B. Ixabepilone binds directly to β-tubulin subunits on microtubules, leading to suppression of microtubule dynamics. Ixabepilone suppresses the dynamic instability of α-β II and α-β III microtubules. Ixabepilone possesses low in vitro susceptibility to multiple tumor resistance mechanisms including efflux transporters, such as MRP-1 and P-glycoprotein (P-gp). Ixabepilone blocks cells in the mitotic phase of the cell division cycle, leading to cell death.

12.2 Pharmacodynamics

In cancer patients, ixabepilone has a plasma concentration-dependent effect on tubulin dynamics in peripheral blood mononuclear cells that is observed as the formation of microtubule bundles. Ixabepilone has antitumor activity in vivo against multiple human tumor xenografts, including drug-resistant types that overexpress P-gp, MRP-1, and β III tubulin isoforms, or harbor tubulin mutations. Ixabepilone is active in xenografts that are resistant to multiple agents including taxanes, anthracyclines, and vinca alkaloids. Ixabepilone demonstrated synergistic antitumor activity in combination with capecitabine in vivo. In addition to direct antitumor activity, ixabepilone has antiangiogenic activity.

12.3 Pharmacokinetics

Absorption

Following administration of a single 40 mg/m² dose of IXEMPRA in patients with cancer, the mean Cmax was 252 ng/mL (coefficient of variation, CV 56%) and the mean AUC was 2143 ng•h/mL (CV 48%). Typically, Cmax occurred at the end of the 3-hour infusion. In cancer patients, the pharmacokinetics of ixabepilone were linear at doses of 15 to 57 mg/m².

Distribution

The mean volume of distribution of 40 mg/m² ixabepilone at steady-state was in excess of 1000 L. In vitro, the binding of ixabepilone to human serum proteins ranged from 67% to 77%, and the blood-to-plasma concentration ratios in human blood ranged from 0.65 to 0.65 over a concentration range of 50 to 5000 ng/mL.

Metabolism

Ixabepilone is extensively metabolized in the liver. In vitro studies indicated that the main route of oxidative metabolism of ixabepilone is via CYP3A4. More than 30 metabolites of ixabepilone are excreted into human urine and feces. No single metabolite accounted for more than 6% of the administered dose. The biotransformation products generated from ixabepilone by human liver microsomes were not active when tested for in vitro cytotoxicity against a human tumor cell line. In vitro studies using human liver microsomes indicate that clinically relevant concentrations of ixabepilone do not inhibit CYP3A4, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP2D6. Ixabepilone does not induce the activity or the expression of CYP enzymes.

Elimination

Ixabepilone is eliminated primarily as metabolized drug. After an intravenous [3H]-ixabepilone dose to patients, approximately 86% of the dose was eliminated within 7 days in feces (65% of the dose) and in urine (21% of the dose). Unchanged ixabepilone has a terminal elimination half-life of approximately 52 hours. No accumulation in plasma is expected for ixabepilone administered every 3 weeks.

Drug Transport Systems

Ixabepilone is a substrate and a weak inhibitor for the drug efflux transporter P-glycoprotein (P-gp) in vitro. Ixabepilone is not a substrate for the breast cancer resistance protein (BCRP) in vitro.

Effects of Age, Gender, and Race

Based upon a population pharmacokinetic analysis in 676 cancer patients, gender, race, and age do not have meaningful effects on the pharmacokinetics of ixabepilone.

12.4 Effect of Ixabepilone on QT/QTc Interval

The QT prolongation potential of ixabepilone was assessed as part of an uncontrolled, open-label single-dose study in advanced cancer patients. Fourteen patients received a single dose of IXEMPRA 40 mg/m² intravenously over 3 hours and serial ECGs were collected over 24 hours. The maximum mean ΔQTcF was observed 1 hour after the end of infusion and was 8 ms (upper 95% CI: 12 ms). No patients had a QTcF interval >450 ms or ΔQTc >30 ms after IXEMPRA administration. However, small increases in QTc interval with the use of ixabepilone cannot be excluded due to study design limitations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with ixabepilone have not been conducted. Ixabepilone did not induce mutations in the microbial mutagenesis Ames assay and was not clastogenic in an in vitro cytogenetic assay using primary human lymphocytes. Ixabepilone was clastogenic (induction of micronuclei) in the in vivo rat micronucleus assay at doses ≥0.625 mg/kg/day.

13.2 Animal Toxicology

Overdose

In rats, single intravenous doses of ixabepilone from 60 to 180 mg/m² (mean AUC values ≥8156 ng•h/mL) were associated with mortality occurring between 5 and 14 days after dosing, and toxicity was principally manifested in the gastrointestinal, hematopoietic (bone-marrow), lymphatic, peripheral-nervous, and male-reproductive systems. In dogs, a single intravenous dose of 100 mg/m² (mean AUC value of 6925 ng•h/mL) was markedly toxic, inducing severe gastrointestinal toxicity and death 3 days after dosing.

14 CLINICAL STUDIES

Combination Therapy

In an open-label, multicenter, multinational, randomized trial of 752 patients with metastatic or locally advanced breast cancer, the efficacy and safety of IXEMPRA (40 mg/m² every 3 weeks) in combination with capecitabine (at 1000 mg/m² twice daily for 2 weeks followed by 1 week rest) were assessed in combination with capcitabine as monotherapy (at 1250 mg/m² twice daily for 2 weeks followed by 1 week rest). Patients were previously treated with anthracyclines and taxanes. Patients were required to have demonstrated tumor progression or resistance to taxanes and anthracyclines as follows:

- tumor progression within 3 months of the last anthracycline dose in the metastatic setting or recurrence within 6 months in the adjuvant or neoadjuvant setting, and
- tumor progression within 4 months of the last taxane dose in the metastatic setting or recurrence within 12 months in the adjuvant or neoadjuvant setting.

For anthracyclines, patients who received a minimum cumulative dose of 240 mg/m² of doxorubicin or 360 mg/m² of epirubicin were also eligible. Sixty-seven percent of patients were White, 23% were Asian, and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (47%).

Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2-negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6.

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>IXEMPRA with capecitabine</th>
<th>Capcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>316 (84%)</td>
<td>231 (61%)</td>
</tr>
<tr>
<td>Lymph</td>
<td>245 (65%)</td>
<td>174 (46%)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>190 (49%)</td>
<td>174 (46%)</td>
</tr>
<tr>
<td>Bone</td>
<td>249 (66%)</td>
<td>249 (66%)</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>316 (16%)</td>
<td>62 (16%)</td>
</tr>
</tbody>
</table>

| Number of prior chemotherapy regimens in metastatic setting* | 1 | 2 | 3 | 0
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>179 (48%)</td>
<td>152 (41%)</td>
<td>17 (5%)</td>
<td>23 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

| Anthracycline resistance* | 104 (44%) | 105 (44%) |

| Taxane Resistance* | 40 (11%) | 44 (12%) |

| Metastatic setting | 327 (87%) | 319 (85%) |

*For IXEMPRA plus capecitabine versus capecitabine alone, prior treatment in the metastatic setting included taxanes (23%) and/or taxanes plus anthracyclines (25%) in 23% of patients. Ixabepilone decreased tumor necrosis and prolonged progression-free survival compared to capecitabine treatment (HODR=0.002). No difference in the rate of disease recurrence was observed. Baseline characteristics were similar for the two groups.

The patients in the combination treatment group received a median of 5 cycles of treatment and patients in the capecitabine monotherapy treatment group received a median of 4 cycles of treatment.

The primary endpoint of the study was progression-free survival (PFS) defined as time from randomization to radiologic progression as determined by Independent Radiologic Review (IRR), clinical progression of measurable skin lesions or death from any cause. Other study endpoints included objective tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST), time to response, response duration, and overall survival.

IXEMPRA in combination with capecitabine resulted in a statistically significant improvement in PFS compared to capecitabine. The results of the study are presented in Table 7 and Figure 1.
IXEMPRA with capecitabine

Table 7: Efficacy of IXEMPRA in Combination with Capecitabine vs Capecitabine Alone—Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>IXEMPRA with capecitabine (n=375)</th>
<th>Capecitabine Alone (n=377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>242</td>
<td>256</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(4.8 - 6.7)</td>
<td>(3.1 - 4.3)</td>
</tr>
<tr>
<td>Median</td>
<td>5.7 months</td>
<td>4.1 months</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.69 (0.58 - 0.83)</td>
<td></td>
</tr>
<tr>
<td>p-value (Log rank)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Objective Tumor Response Rate (95% CI)</td>
<td>34.7% (29.9 - 39.7)</td>
<td>14.3% (10.9 - 18.3)</td>
</tr>
<tr>
<td>p-value (CMH)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Duration of Response, Median (95% CI)</td>
<td>6.4 months</td>
<td>5.6 months</td>
</tr>
<tr>
<td></td>
<td>(5.6 - 7.1)</td>
<td>(4.2 - 7.5)</td>
</tr>
</tbody>
</table>

• Patients were censored for PFS at the last date of tumor assessment prior to the start of subsequent therapy. In patients where independent review was not available PFS was censored at the randomization date.

• For the hazard ratio, a value less than 1.00 favors combination treatment.

• Stratified by visceral metastasis in liver/lung, prior chemotherapy in metastatic setting, and anthracycline resistance.

• Cochran-Mantel-Haenszel test.

There was no statistically significant difference in overall survival between treatment arms in this study, as well as in a second similar study. In the study described above, the median overall survivals were 12.9 months (95% CI: 11.5, 14.2) in the combination therapy arm and 11.1 months (95% CI: 10.0, 12.5) in the capecitabine alone arm [Hazard Ratio 0.90 (95% CI: 0.77, 1.05), p-value=0.19].

In the second trial, comparing IXEMPRA in combination with capecitabine versus capecitabine alone, conducted in 1221 patients pretreated with an anthracycline and a taxane, the median overall survivals were 16.4 months (95% CI: 15.0, 17.9) in the combination therapy arm and 15.6 months (95% CI: 13.9, 17.0), in the capecitabine alone arm [Hazard Ratio 0.90 (95% CI: 0.78, 1.03), p-value=0.12].

Monotherapy

IXEMPRA was evaluated as a single agent in a multicenter single-arm study in 126 women with metastatic or locally advanced breast cancer. The study enrolled patients whose tumors had recurred or had progressed following two or more chemotherapy regimens including an anthracycline, a taxane, and capecitabine. Patients who had received a cumulative minimum dose of 240 mg/m² of doxorubicin or 360 mg/m² of epirubicin were also eligible. Tumor progression or recurrence were prospectively defined as follows:

• Disease progression while on therapy in the metastatic setting (defined as progression while on treatment or within 8 weeks of last dose),
• Recurrence within 6 months of the last dose in the adjuvant or neoadjuvant setting (only for anthracycline and taxane),
• HER2-positive patients must also have progressed during or after discontinuation of trastuzumab.

IXEMPRA was administered at a dose of 40 mg/m² intravenously over 3 hours every 3 weeks. Patients received a median of 4 cycles (range 1 to 18) of IXEMPRA therapy.

IXEMPRA® (ixabepilone)

Objective tumor response was determined by independent radiologic and investigator review using RECIST. Efficacy results are presented in Table 8.

Table 8: Efficacy of IXEMPRA in Metastatic and Locally Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective tumor response rate (95% CI)</td>
<td>12.4% (6.9 - 19.9)</td>
</tr>
<tr>
<td>Investigator Assessment (n=126)</td>
<td>18.3% (11.9 - 26.1)</td>
</tr>
<tr>
<td>Time to response (n=14)</td>
<td>Median, weeks (min - max)</td>
</tr>
<tr>
<td>6.1 (5 - 54.4)</td>
<td></td>
</tr>
<tr>
<td>Duration of response (n=14)</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>6.0 (5.0 - 7.6)</td>
<td></td>
</tr>
</tbody>
</table>

IXEMPRA® Kit must be stored in a refrigerator at 2° C to 8° C (36° F to 46° F). Retain in original package until time of use to protect from light.

Procedures for proper handling and disposal of antineoplastic drugs [see References (15)] should be followed. To minimize the risk of dermal exposure, impervious gloves should be worn when handling vials containing IXEMPRA, regardless of the setting, including unpacking and inspection, transport within a facility, and dose preparation and administration.

15 REFERENCES
1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
**IXEMPRA** (ixabepilone)

**FDA-Approved Patient Labeling**

**Patient Information**

**IXEMPRA® Kit** (pronounced as ɪk-ˈsɛm-prə) (ixabepilone)

*for Injection, for intravenous infusion only*

Read the Patient Information that comes with IXEMPRA before you start receiving it and before each injection. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about IXEMPRA?

Your healthcare provider should do blood tests to check your liver function:

- before you begin receiving IXEMPRA
- as needed while you are receiving IXEMPRA

If blood tests show that you have liver problems, do not receive injections of IXEMPRA along with the medicine capcitabine. Taking these two medicines together if you have liver problems increases your chance of serious problems. These include: serious infection and death due to a very low white blood cell count (neutropenia).

What is IXEMPRA?

IXEMPRA is a cancer medicine. IXEMPRA is used alone or with another cancer medicine called capcitabine. IXEMPRA is used to treat breast cancer, when certain other medicines have not worked or no longer work.

Who should not receive IXEMPRA?

Do not receive injections of IXEMPRA if you:

- are allergic to a medicine, such as TAXOL®, that contains Cremophor® EL or polyoxyethylated castor oil.
- have low white blood cell or platelet counts. Your healthcare provider will check your blood counts.
- are also taking a cancer medicine called capcitabine and you have liver problems. See “What is the most important information I should know about IXEMPRA?”

What should I tell my healthcare provider before receiving IXEMPRA?

IXEMPRA may not be right for you. Before you receive IXEMPRA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have heart problems or a history of heart problems
- have had an allergic reaction to IXEMPRA. You will receive medicines before each injection of IXEMPRA to decrease the chance of an allergic reaction. See “How will I receive IXEMPRA?”
- are pregnant or plan to become pregnant. You should not receive IXEMPRA during pregnancy because it may harm your unborn baby. Talk with your healthcare provider about how to prevent pregnancy while receiving IXEMPRA. Tell your healthcare provider right away if you become pregnant or think you are pregnant while receiving IXEMPRA.
- are breast-feeding. It is not known if IXEMPRA passes into breast milk. You and your healthcare provider should decide if you will receive IXEMPRA or breast-feed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. IXEMPRA and certain other medicines may affect each other causing side effects. IXEMPRA may affect the way other medicines work, and other medicines may affect how IXEMPRA works. Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider.

How will I receive IXEMPRA?

IXEMPRA is given by an injection directly into your vein (intravenous infusion). IXEMPRA is usually given once every three weeks. Each treatment with IXEMPRA will take about 3 hours. Your healthcare provider will decide how much IXEMPRA you will receive and how often you will receive it.

To lower the chance of an allergic reaction, you will receive other medicines about 1 hour before each treatment with IXEMPRA. See “What are the possible side effects of IXEMPRA?”

What should I avoid while receiving IXEMPRA?

IXEMPRA contains alcohol. If you are dizzy or drowsy, avoid activities that may be dangerous, such as driving or operating machinery. Do not drink grapefruit juice while receiving IXEMPRA. Drinking grapefruit juice may cause you to have too much IXEMPRA in your blood and lead to side effects.

What are the possible side effects of IXEMPRA?

IXEMPRA may cause serious side effects including:

- Numbness, tingling, or burning in the hands or feet can occur while receiving IXEMPRA (neuropathy). These symptoms may be new or get worse while you are receiving IXEMPRA. These symptoms often occur early during treatment with IXEMPRA. Tell your healthcare provider if you have any of these symptoms. Your dose of IXEMPRA may need to be decreased, stopped until your symptoms get better, or totally stopped.
- Low white blood cell count (neutropenia). White blood cells help protect the body from infections caused by bacteria. If you get a fever or infection when your white blood cells are very low, you can become seriously ill and die. You may need treatment in the hospital with antibiotic medicines. Your healthcare provider will monitor your white blood cell count often with blood tests. Tell your healthcare provider right away or go to the nearest hospital emergency room if you have a fever (temperature above 100.5°F) or other sign of infection, such as chills, cough, burning or pain when you urinate, any time between treatments with IXEMPRA.
- Allergic Reactions. Severe allergic reactions can occur with IXEMPRA and may cause death in rare cases. Allergic reactions are most likely to occur while IXEMPRA is being injected into your vein. Tell your healthcare provider right away if you get any of the following signs and symptoms of an allergic reaction:
  - itching, hives (raised itchy welts), rash
  - flushed face
  - sudden swelling of face, throat or tongue
  - chest tightness, trouble breathing
  - feel dizzy or faint
  - feel your heart beating (palpitations)
- Harm to an unborn child. See “What should I tell my healthcare provider before receiving IXEMPRA?”
- Heart problems. IXEMPRA might cause decreased blood flow to the heart, problems with heart function, and abnormal heart beat. This is seen more often in patients who also take capcitabine. Tell your healthcare provider right away if you have any of the following symptoms:
  - chest pain,
  - difficulty breathing,
  - feel your heart beating (palpitations), or
  - unusual weight gain.

The most common side effects with IXEMPRA used alone or with capcitabine may include:

- tiredness
- loss of appetite
- disorders of toenails and fingernails
- hair loss
- fever
- decreased red blood cells (anemia)
- joint and muscle pain
- headache
- decreased platelets (thrombocytopenia)
- nausea, vomiting, diarrhea, constipation, and abdominal pain
- sores on the lip, in the mouth and esophagus
- tender, red palms and soles of feet (hand-foot syndrome) that looks like a sunburn; the skin may become dry and peel. There may also be numbness and tingling.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all of the side effects of IXEMPRA. Ask your healthcare provider or pharmacist for more information if you have questions or concerns.

**General Information about IXEMPRA**

This patient information leaflet summarizes the most important information about IXEMPRA. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you would like more information about IXEMPRA, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about IXEMPRA that is written for health professionals. For more information about IXEMPRA, call 1-844-586-8953.

IXEMPRA® (ixabepilone) for injection Manufactured by: Baxter Oncology GmbH, 33790 Halle/Westfalen, Germany

DILUENT for IXEMPRA Manufactured by: Baxter Oncology GmbH, 33790 Halle/Westfalen, Germany

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