

A nurse's guide to IXEMPRA® (ixabepilone) therapy

An overview of dosing, preparation, administration, and management of adverse reactions for IXEMPRA



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.

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Safety information¹

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

IXEMPRA®
(ixabepilone) for injection,
for intravenous infusion



Therapy as strong as her spirit

Determination in the face
of resistance

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When to use IXEMPRA® (ixabepilone)

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.

Safety information: contraindications¹

IXEMPRA is contraindicated in patients:

- With a known history of a severe (CTC grades 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives, such as polyoxyethylated castor oil
- Who have a baseline neutrophil count $<1,500$ cells/mm³ or a platelet count $<100,000$ cells/mm³
- In combination with capecitabine when AST or ALT is $>2.5 \times$ ULN or bilirubin is $>1 \times$ ULN due to increased risk of toxicity and neutropenia-related death

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

Defined resistance criteria used in IXEMPRA® (ixabepilone) registrational studies¹

Neoadjuvant/adjuvant setting

Study 046: IXEMPRA + capecitabine

Recurrence within 6 months
of anthracycline therapy

and

Recurrence within 12 months
of taxane therapy

or

Recurrence within 12 months
of taxane therapy when
further anthracycline therapy
is contraindicated*

Study 081: IXEMPRA monotherapy

Recurrence within 6 months
of the last dose (only for
anthracyclines and taxanes)

or

Recurrence within 6 months
of last taxane dose when
further anthracycline therapy
is contraindicated*

HER2-positive patients must
also have progressed during
or after discontinuation
of trastuzumab

Metastatic setting

Study 046: IXEMPRA + capecitabine

Progression
within 3 months of
last anthracycline dose

and

Progression within
4 months of last taxane dose

or

Progression within
4 months of last taxane dose
when further anthracycline
therapy is contraindicated*

Study 081: IXEMPRA monotherapy

Progression while on therapy
or within 8 weeks of last dose
of anthracycline, taxane,
and capecitabine therapy

or

Progression on a taxane
and capecitabine when
further anthracycline therapy
is contraindicated*

HER2-positive patients must
also have progressed during
or after discontinuation
of trastuzumab

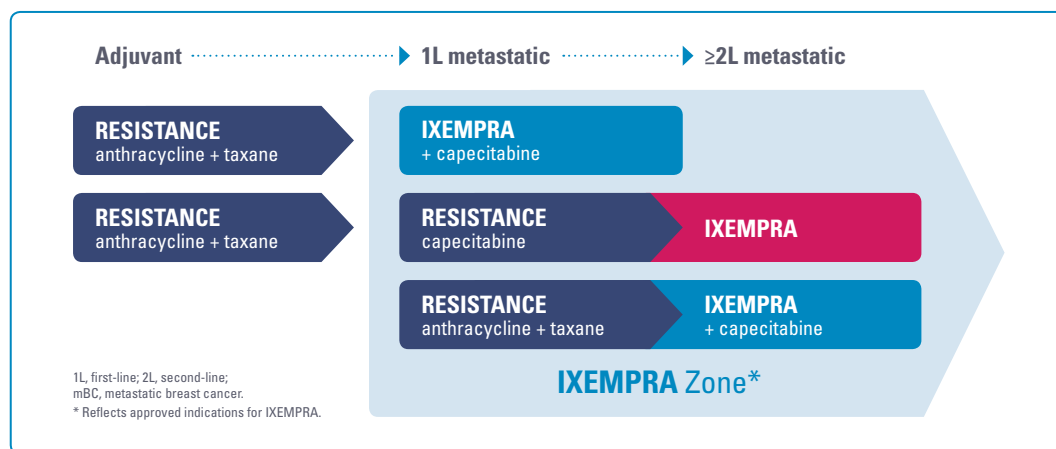
HER2, human epidermal growth factor receptor 2.

*For anthracyclines, patients who received a minimum cumulative dose of 240 mg/m² of doxorubicin or 360 mg/m² of epirubicin were also eligible.

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Think IXEMPRA® (ixabepilone) when resistance emerges in mBC

For patients with metastatic or locally advanced breast cancer resistant or refractory to an anthracycline, a taxane, and capecitabine¹



When resistance emerges in the adjuvant setting¹

- Consider IXEMPRA + capecitabine in patients resistant to an anthracycline (progressing while on therapy or within 6 months) and a taxane (progressing while on therapy or within 12 months) or in patients whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated

When resistance emerges in the metastatic setting¹

- Consider IXEMPRA + capecitabine in patients who are resistant to an anthracycline (progressing within 3 months) or in whom further anthracycline use is contraindicated and who progress within 4 months of taxane therapy
- Consider IXEMPRA as monotherapy in patients resistant or refractory to an anthracycline, a taxane, and capecitabine

IXEMPRA, in combination with capecitabine, is the only FDA-approved, non-taxane microtubule-targeting agent indicated as first-line therapy for the treatment of patients with metastatic or locally advanced breast cancer resistant to an anthracycline and a taxane^{1,2}

Safety information: peripheral neuropathy¹

Monitor for symptoms of neuropathy, primarily sensory. Neuropathy is cumulative, is generally reversible, and should be managed by dose adjustment and delays. Please see pages 18-20 for more information.

IXEMPRA[®] (ixabepilone) dosing¹

The recommended dosage of IXEMPRA is 40 mg/m² administered intravenously over 3 hours every 3 weeks

- Doses for patients with body surface area greater than 2.2 m² should be calculated based on 2.2 m²
- The dose of IXEMPRA is the same for monotherapy and 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/m² IV over 3 hours
every 3 weeks

Initial 20% dose reduction in the presence of toxicities

32 mg/m² IV over 3 hours
every 3 weeks

Additional 20% dose reduction if toxicities recur

25 mg/m² IV over 3 hours
every 3 weeks

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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 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*

IXEMPRA® (ixabepilone) (combination therapy or monotherapy)	IXEMPRA dose modification
Nonhematologic	
Grade 2 neuropathy (moderate) lasting ≥7 days	Decrease the dose by 20%
Grade 3 neuropathy (severe) lasting <7 days	Decrease the dose by 20%
Grade 3 neuropathy (severe) lasting ≥7 days or disabling neuropathy	Discontinue treatment
Any grade 3 toxicity (severe) other than neuropathy	Decrease the dose by 20%
Transient grade 3 arthralgia/myalgia or fatigue	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
Hematologic	
Neutrophils <500 cells/mm ³ for ≥7 days	Decrease the dose by 20%
Febrile neutropenia	Decrease the dose by 20%
Platelets <25,000 cells/mm ³ or platelets <50,000 cells/mm ³ with bleeding	Decrease the dose by 20%
Capecitabine (when used in combination with IXEMPRA)	
Capecitabine dose modification	
Nonhematologic	
Follow capecitabine label	
Hematologic	
Platelets <25,000 cells/mm ³ or platelets <50,000 cells/mm ³ with bleeding	Hold for concurrent diarrhea or stomatitis until platelet count is >50,000 cells/mm ³ , then continue at the same dose
Neutrophils <500 cells/mm ³ for ≥7 days or febrile neutropenia	Hold for concurrent diarrhea or stomatitis until neutrophil count is >1,000 cells/mm ³ , then continue at the same dose

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

Re-treatment criteria¹

- 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 table above
- Patients should not begin a new cycle of treatment unless the neutrophil count is ≥1,500 cells/mm³, the platelet count is ≥100,000 cells/mm³, and nonhematologic toxicities have improved to grade 1 (mild) or resolved

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Dose modification for patients with hepatic impairment¹

- Assessment of hepatic function is recommended before initiation of IXEMPRA® (ixabepilone) and periodically thereafter
- Patients with baseline AST or ALT $>2.5 \times \text{ULN}$ or bilirubin $>1.5 \times \text{ULN}$ experienced greater toxicity than patients with baseline AST or ALT $\leq 2.5 \times \text{ULN}$ or bilirubin $\leq 1.5 \times \text{ULN}$ when treated with IXEMPRA at 40 mg/m² 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 $>2.5 \times \text{ULN}$ or bilirubin $>1 \times \text{ULN}$**
- Patients receiving combination treatment who have AST and ALT $\leq 2.5 \times \text{ULN}$ and bilirubin $\leq 1 \times \text{ULN}$ may receive the standard dose of IXEMPRA (40 mg/m²)

Dose adjustments for IXEMPRA in combination with capecitabine in patients with hepatic impairment

Transaminase levels		Bilirubin levels	IXEMPRA (mg/m ²)
AST or ALT $>2.5 \times \text{ULN}$	or	Bilirubin $>1 \times \text{ULN}$	Do not administer
AST and ALT $\leq 2.5 \times \text{ULN}$	and	Bilirubin $\leq 1 \times \text{ULN}$	40

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

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/m²; the dosage in subsequent cycles may be escalated up to, but should not exceed, 30 mg/m² if tolerated
- Use in patients with AST or ALT $>10 \times \text{ULN}$ or bilirubin $>3 \times \text{ULN}$ is not recommended
- Limited data are available for patients with AST or ALT $>5 \times \text{ULN}$; 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 ²) [†]
Mild	AST and ALT $\leq 2.5 \times \text{ULN}$	and	Bilirubin $\leq 1 \times \text{ULN}$	40
	AST and ALT $\leq 10 \times \text{ULN}$	and	Bilirubin $\leq 1.5 \times \text{ULN}$	32
Moderate	AST and ALT $\leq 10 \times \text{ULN}$	and	Bilirubin $>1.5 \times \text{ULN}$ to $\leq 3 \times \text{ULN}$	20-30

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

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

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Dose modification: inhibitors and inducers of CYP3A4¹

CYP3A4 inhibitors

- Avoid the use of concomitant strong CYP3A4 inhibitors, including:
 - Ketoconazole
 - Itraconazole
 - Clarithromycin
 - Atazanavir
 - Nefazodone
 - Saquinavir
 - Telithromycin
 - Ritonavir
 - Amprenavir
 - Indinavir
 - Nelfinavir
 - Delavirdine
 - Voriconazole

Grapefruit juice may also increase plasma concentrations of IXEMPRA® (ixabepilone) and should be avoided

- Based on pharmacokinetic studies, if a strong CYP3A4 inhibitor must be coadministered, a dose reduction to 20 mg/m² 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, including:
 - Phenytoin
 - Carbamazepine
 - Rifampin
 - Rifabutin
 - Dexamethasone
 - 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/m² to 60 mg/m², 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/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

St. John's wort may decrease ixabepilone plasma concentrations unpredictably and should be avoided

AUC, area under the curve.

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Premedication¹

- To minimize the chance of occurrence of a hypersensitivity reaction, all patients must be premedicated approximately 1 hour before the infusion of IXEMPRA[®] (ixabepilone) 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 have 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

Overdosage¹

- 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/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

Use in specific populations¹

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 dose adjustment based on 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 patients with breast cancer 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.

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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 × 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

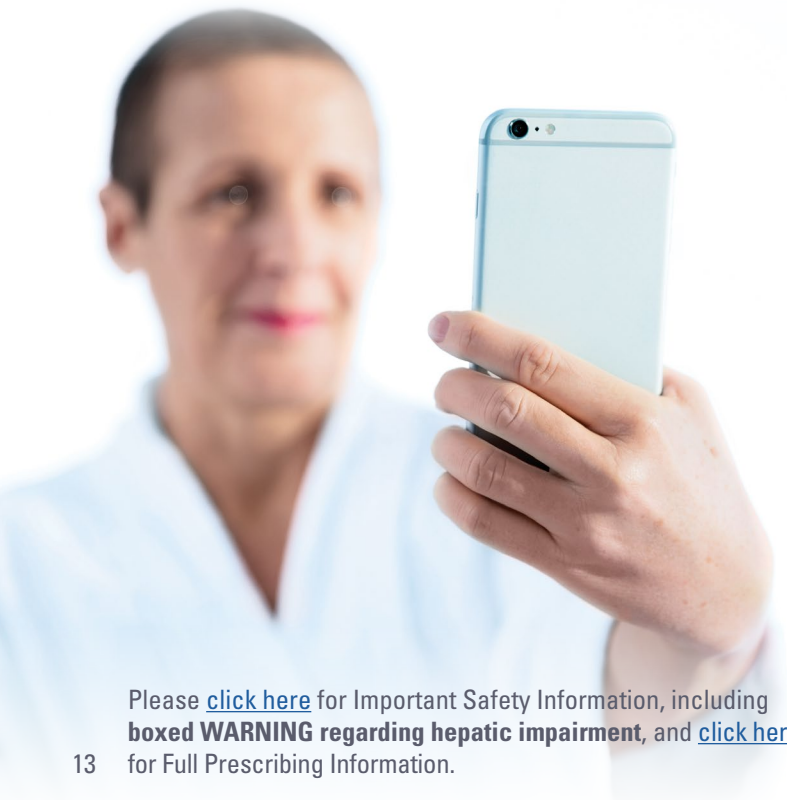
Pregnant women and breastfeeding mothers

- 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 into human milk and because of the potential for serious adverse reactions in breastfeeding infants from IXEMPRA, a decision must be made whether to discontinue breastfeeding 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.



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How supplied

A 2-vial kit, IXEMPRA® (ixabepilone) for injection and diluent, which must be refrigerated¹

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^{1,3}

Required materials for dose preparation and administration	
For preparation	<ul style="list-style-type: none">• Qualified infusion fluid (DEHP-free)*<ul style="list-style-type: none">– Lactated Ringer’s Injection, USP– 0.9% Sodium Chloride Injection, USP– PLASMA-LYTE® A Injection pH 7.4• Sterile, disposable syringes/needles• Impervious gloves, gown• Other safety precautions required by your institution
For administration	<ul style="list-style-type: none">• One IV administration set (DEHP-free)• One IV catheter• Alcohol pads• In-line filter (0.2 to 1.2 microns)

DEHP, di-(2-ethylhexyl) phthalate.

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

*See page 16 for the qualified infusion fluids.



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Handling guidelines

As with all antineoplastic agents, care should be taken when preparing and handling IXEMPRA® (ixabepilone).

- 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 administration¹
- If IXEMPRA comes into contact with skin or mucosa, immediately and thoroughly wash with soap and water, as appropriate²
- IXEMPRA should be prepared in a class II vertical laminar airflow safety cabinet using standard precautions for the safe handling of antineoplastic agents²
- The preparation area should be isolated and equipped with a hand-wash sink and an eye-wash station²
- Institution-specific guidelines for handling antineoplastic agents should also be followed

Other important considerations when preparing IXEMPRA

- Only personnel trained in the handling of antineoplastic agents should be involved in preparing IXEMPRA¹

Please follow procedures for proper handling, preparation, and administration of antineoplastic agents

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 March 3, 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. Accessed March 3, 2016.

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

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Constitution of IXEMPRA® (ixabepilone)¹

- 1 Remove the IXEMPRA Kit from the refrigerator and allow 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.
- 2 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
- 3 Gently swirl and invert the vial until the powder in IXEMPRA is completely dissolved; **do not shake**.
- 4 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 IXEMPRA¹

- 1 Before IV administration, the constituted solution must be further diluted with one of the 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**

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.

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.

- 2 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)

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

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16 for Full Prescribing Information.

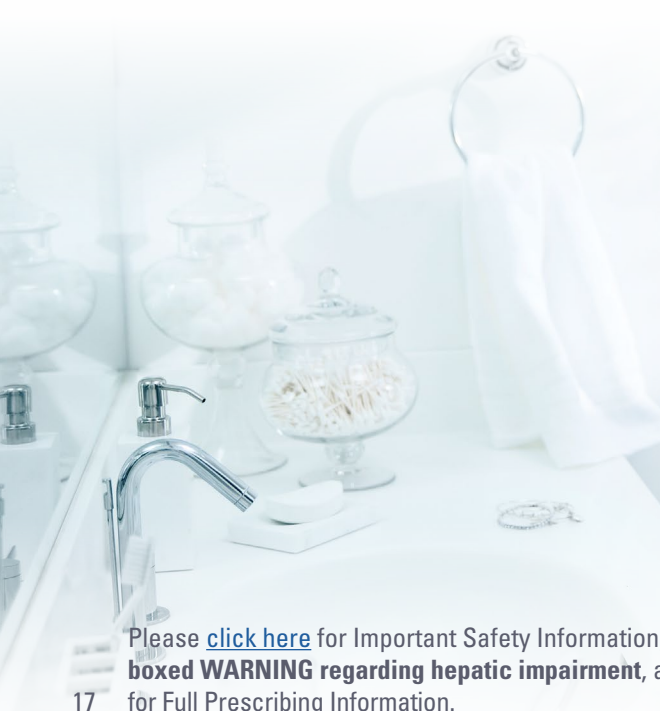
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- 3 Aseptically withdraw the appropriate volume of constituted solution (2 mg of IXEMPRA® [ixabepilone] per mL) to achieve the required dose based on patient's body surface area.
- 4 Aseptically transfer to an IV bag containing the appropriate volume of infusion fluid to achieve the desired final concentration of IXEMPRA.
- 5 Thoroughly mix the infusion by manual rotation; **do not shake**.
- 6 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 used¹
- 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 leakage²
- Syringes, IV containers, and pumps should be wiped clean of any drug contamination with an alcohol gauze pad²
- **Infusion should be given over 3 hours while patient is closely monitored for adverse reactions¹**
- 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 period¹
- Institution-specific guidelines for IV administration should also be followed
- Any remaining solution should be discarded according to institutional procedures for antineoplastic agents¹

DEHP, di-(2-ethylhexyl) phthalate.



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Common adverse reactions

Safety information: adverse reactions¹

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

Neuropathy¹

Peripheral neuropathy is a common side effect associated with IXEMPRA. Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy.

Neuropathy usually occurred early during treatment (approximately 75% of new-onset or worsening neuropathy occurred during the first 3 cycles). Patients experiencing new or worsening peripheral neuropathy may require dose delays, 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.

Neuropathy is common, cumulative, and generally reversible and should be managed by dose adjustment, delays, or discontinuation of treatment¹

Treatment-related peripheral neuropathy		
	IXEMPRA as monotherapy (Study 081; N=126)	IXEMPRA with capecitabine (Study 046; n=369)
Preexisting neuropathy (grade 1)	27%	24%
Peripheral neuropathy (all grades)*	63%	67%
Peripheral neuropathy (grades 3/4)*	14%	23%
Discontinuation due to neuropathy	6%	21%
Median number of cycles to onset of grades 3/4 neuropathy	4	4
Median time to improvement [†] of grades 3/4 neuropathy	4.6 weeks	6.0 weeks

*Sensory and motor neuropathy combined.

[†] Improvement was defined as a decrease in symptoms to baseline or grade 1.

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 grades 3/4 neuropathy in Studies 046 and 081, 76% and 79%, respectively, had documented improvement to baseline or grade 1 twelve weeks after onset.

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Grading⁴

Grading sensory neuropathy

A disorder characterized by inflammation or damage to the sensory nerves

NCI CTCAE grading scale v4.03	Sensory neuropathy
1	Asymptomatic; loss of deep tendon reflexes or paresthesia
2	Moderate symptoms; limiting instrumental activities of daily living (ADLs)*
3	Severe symptoms; limiting self-care ADLs*
4	Life-threatening consequences; urgent intervention indicated
5	Death

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

*ADLs include preparing meals, using the telephone, bathing, dressing, and using the toilet.

Grading motor neuropathy

A disorder characterized by inflammation or damage to the motor nerves

NCI CTCAE grading scale v4.03	Motor neuropathy
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Moderate symptoms; limiting instrumental ADLs*
3	Severe symptoms; limiting self-care ADLs*; assistive device indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

*ADLs include preparing meals, using the telephone, bathing, dressing, and using the toilet.

Signs and symptoms⁵

- Sensation of tingling, numbness, or burning in the hands and/or feet
- Pain when walking
- Motor weakness may result in loss of fine motor skills, such as buttoning clothes or picking up objects

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Common adverse reactions (cont'd)



Patient counseling information: neuropathy

Assessment tips

You may want to observe your patient and assess the following signs of neuropathy regularly, preferably at each visit, so that treatment can be individualized:

- Common risk factors for neuropathy, such as diabetes or alcoholism^{6,7}
- Walking (eg, imbalance, staggering, or abnormal gait)⁸
- Clothing (eg, if patient is avoiding wearing buttons, zippers, and/or shoes with laces)⁸
- Writing with difficulty⁸
- Baseline neuropathy, if existing; use this guide to address peripheral neuropathy related to IXEMPRA® (ixabepilone)⁸

Questions to ask patients

Being alert to signs of neuropathy includes observing and asking questions of your patients, including:

- Do you feel pain, numbness, tingling, or a burning sensation in your hands or feet?⁵
- How would you describe the pain (for example, burning, shooting, shocking, tingling, difficult to describe)?^{5,8}
- Do you have weakness in any part of your body?⁵
- Do you have pain when walking, gripping objects, and/or getting dressed (for example, buttoning or unbuttoning, tying shoes)?^{5,8}
- Have you felt clumsy or have you fallen down, stumbled, or staggered recently?⁸

Counseling tips

Share these tips with your patients experiencing neuropathy:

- Check the water temperature with a thermometer before bathing to avoid burns⁵
- Wear gloves and footwear with rubber soles when performing daily activities to avoid accidents⁵
- Remove throw rugs, use shower mats, and walk slowly to avoid falling⁵
- Be cautious when handling sharp objects, such as scissors and knives⁵
- Use a walker or cane for balance⁵
- Use caution when driving (for example, make sure your hands and feet can control the gas and brake pedals and the steering wheel)⁹

If you think a patient may be experiencing neuropathy, discuss your observations with the doctor.

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Fatigue

Fatigue is a common side effect of IXEMPRA® (ixabepilone).¹ Clinical practice guidelines recommend screening patients for fatigue at the initial visit, regularly during and after treatment, and as clinically indicated.¹⁰



Patient counseling information: fatigue

Assessment tips

You may want to observe your patient and assess if he or she¹⁰:

- Looks tired
- Is having trouble sleeping

Questions to ask patients

Being alert to signs of fatigue includes observing and asking questions of your patients, including¹⁰:

- On a scale of 1 to 10, how was your level of fatigue before you started IXEMPRA?
- On a scale of 1 to 10, how would you rate your level of fatigue right now?
- What makes your fatigue worse? What makes it better?
- Are you having problems sleeping?
- What activities that you used to do are you no longer able to do because you are too tired?
For example:
 - Has fatigue affected your ability to work?
 - Are you too tired to do house chores or other work around the home?
 - Are you having trouble starting or finishing things because you are too tired?
 - Have you stopped attending social gatherings or visiting people because you are too tired?

Counseling tips

Share these tips with your patients experiencing fatigue:

- Fatigue is often caused by more than one problem; a variety of things may help manage fatigue, such as exercise, stress management, treating sleep problems, and improving diet¹¹
- Save your energy to do the things that are most important; let others help with shopping, cooking, and driving^{5,11}
- Use activities such as listening to music, reading a book, or visiting with friends to avoid fatigue¹¹
- Take short walks—research shows that the right amount, type, and time of exercise may help lessen fatigue and improve quality of sleep; check with your doctor for appropriate exercise recommendations^{5,11}
- Sleep at least 8 hours per night—you may need more sleep than you did before starting chemotherapy⁵
- Keep track of how you feel; this may help you plan your activities for the day⁵

If you think a patient may be experiencing fatigue, discuss your observations with the doctor.

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Talking with your patients about IXEMPRA® (ixabepilone)



Patient counseling information: general considerations

- Advise patients about side effects and what to expect from IXEMPRA treatment
- Remind patients about the importance of reporting side effects promptly
- Educate patients on the benefits of maintaining good nutrition and hydration
- Remind patients to promptly report to your office any new medications
- Remember to educate caregivers as well
- Talk to patients about scheduling and keeping appointments as recommended

IXEMPRA patient brochure: *Understanding your treatment with IXEMPRA® (ixabepilone)*



This brochure contains important information about IXEMPRA treatment for the patient audience and includes core content such as:

- Patient Information
- Serious side effects
- Common side effects
- Important Safety Information
- A side effects tracker
- Patient support
- Resources

See your representative for copies of this brochure

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Resources

American Medical Association (AMA). Improving the health of the nation is at the core of the AMA's work to enhance the delivery of care and enable physicians and health teams to partner with patients to achieve better health for all. ama-assn.org

American Society of Clinical Oncology (ASCO). The ASCO mission is conquering cancer through research, education, and promotion of the highest quality patient care. asco.org

National Comprehensive Cancer Network® (NCCN®). The NCCN, a not-for-profit alliance of 27 of the world's leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives. nccn.org

Oncology Nursing Society (ONS). The ONS is a professional association of more than 39,000 members committed to promoting excellence in oncology nursing and the transformation of cancer care. ons.org

San Antonio Breast Cancer Symposium (SABCS). Since 1977, the Symposium's mission has been to provide state-of-the-art information on breast cancer research. From a one-day regional conference, the Symposium has grown to a five-day program attended by a broad international audience of academic and private researchers and physicians from over 90 countries. sabcs.org

MEDLINE/PubMed. A service of the National Library of Medicine, PubMed comprises more than 25 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites. ncbi.nlm.nih.gov/pubmed

Medscape. Medscape offers specialists, primary care physicians, and other health professionals the Web's most robust and integrated medical information and educational tools. medscape.com

National Cancer Institute (NCI). The NCI is the federal government's principal agency for cancer research and training. Part of the National Institutes of Health, which is one of 11 agencies that comprise the Department of Health and Human Services, the NCI is a team of almost 4,000 people. cancer.gov

OncoLink. OncoLink was the first cancer information website on the Internet, started in 1994, and remains one of the largest. This award-winning site is maintained by a group of oncology healthcare professionals who understand the needs of patients, caregivers, and healthcare professionals. oncolink.com

ClinicalTrials.gov. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. clinicaltrials.gov

IMPORTANT SAFETY INFORMATION

WARNING: Toxicity in hepatic impairment

- **IXEMPRA® (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 × ULN or bilirubin >1 × 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 × ULN. Use of IXEMPRA in patients with AST or ALT >10 × ULN or bilirubin >3 × 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/mm³ or a platelet count <100,000 cells/mm³

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 H₁ and an H₂ 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 H₁ and H₂ 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

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%

Cremophor is a registered trademark of BASF AG.

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

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QUICK REFERENCE: Preparing and dosing IXEMPRA® (ixabepilone)¹

Preparing IXEMPRA for infusion

The IXEMPRA infusion dose is calculated by following these 3 steps:

Dosing calculations	
1	Calculate the total IXEMPRA dose required: Prescribed IXEMPRA dose × patient body surface area (max, 2.2 m ²) = total IXEMPRA dose
2	Calculate the total infusion volume required: mL of constituted solution + mL of infusion fluid = total infusion volume
3	Calculate the final infusion concentration required: Total dose of IXEMPRA in mg / total infusion volume in mL = final infusion concentration
Final infusion concentration must be between 0.2 mg/mL and 0.6 mg/mL	

Recommended dosing for IXEMPRA

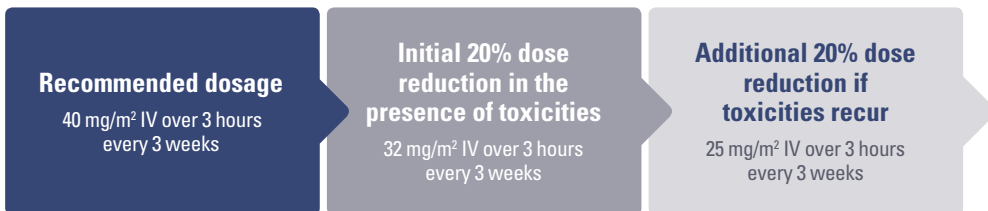


The dose of IXEMPRA is the same for **monotherapy** and **combination** therapy with capecitabine.

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

Rules regarding nurse participation in, and responsibility for, dosing and administration practices can vary by state and institution. This reference guide is not intended to replace those rules.

IXEMPRA dose modification



Please see full dosing instructions on pages 8-13 and dose modification instructions on pages 9-11.

Safety information

WARNING: toxicity in hepatic impairment

See Full Prescribing Information for complete boxed WARNING. IXEMPRA in combination with capecitabine must not be given to patients with AST or ALT >2.5 × ULN or bilirubin >1 × ULN due to increased risk of toxicity and neutropenia-related death.

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

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