Ixempra™ (Ixabepilone)

Generic name: Ixabepilone

Brand Name: Ixempra™

Manufacturer: Bristol-Myers squibb

Chemical Name:

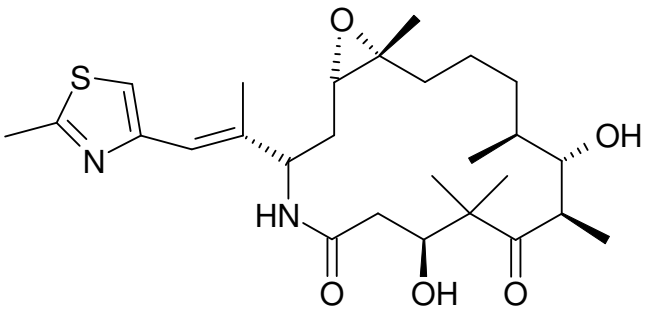
1S,3S,7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(iE)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0] heptadecane-5,9-dione

CAS number: 219989-84-1[1])

FDA classification: Treatment for metastatic or locally advanced breast cancer [2].

Molecular Weight: 506.7 [3]

Structure:



Mechanism of Action

Ixabepilone (aza-epothilone B) is a semi-synthetic and water-soluble epothilone analog, which is a group of cytotoxic macrolide isolated from the myxobacterium Sorangium cellulosum [4]. This agent is classified as a novel class of drugs targeting microtubules in a mechanism of action similar to taxanes (e.g. paclitaxel), and is particularly designed to provide enhanced antineoplastic activity [5] by overcoming problems associated with taxane-based therapy (difficulties in formulation, administration, etc). Similar to paclitaxel, Ixabepilone exerts its cytotoxic action by binding to the β-tubulin subunit in human cells, thereby preventing the polymerization of these heterodimeric subunits and suppressing the dynamics of microtubules [4]. As a result, the formation of functional mitotic spindles during cell division is prohibited, the cell cycle arrests at the G2/M checkpoint and subsequently apoptosis is induced leading to cytotoxicity [4]. Ixabepilone is also found to be less susceptible to drug resistance mechanisms on certain cancer cells, including the overexpression of p-glycoprotein and MRP-1 efflux transporters and βIII-tubulin isoforms [4]. In addition, the drug demonstrated high activity against various paclitaxel-sensitive and paclitaxel-resistant models including ovarian and breast cancer xenografts [4].

Indication

Ixabepilone is currently approved by the FDA for the treatment of metastatic or locally advanced breast cancer [6]. In combination with capecitabine, this drug demonstrated superior activity over capecitabine alone [5], and this regimen is indicated for patients who fail to respond to taxanes and anthracyclines [6]. Ixabepilone can also be used as a monotherapy in patients who did not benefit from capecitabine, taxanes and anthracyclines [6].

DOSAGE AND ADMINISTRATION [3]

Recommended dosage

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

Dose Adjustments in Patients with Hepatic Impairment

Hepatic impaired patients should have Ixempra dose reduced according to the severity of impairment. The following table summarizes the judging criteria.

	Transaminase		Bilirubin	Ixempra (mg/m2)
Mild	AST and ALT ≤2.5 x ULN	and	≤1 x ULN	40
	AST or ALT ≤10 x ULN	and	≤1.5 x ULN	32
Moderate	AST and ALT ≤10 x ULN	and	>1.5 x ULN - ≤3 x ULN	20 - 30

Dose adjustments in patients experiencing toxicity

The dose of Ixempra should be reduced by 20% for patients having the following toxicity:

- Grade 2 neuropathy (moderate) lasting ≥7 days
- Grade 3 neuropathy (severe) lasting <7 days
- Any grade 3 toxicity (severe) other than neuropathy
- Neutrophil <500 cells/mm3 for ≥7 days
- Febrile neutropenia
- Platelets <25,000/mm^3 or platelets <50,000/mm^3 with bleeding

Ixempra should be discontinued in patients having the following toxicity:

- Grade 3 neuropathy (severe) lasting ≥7 days or disabling neuropathy
- Any grade 4 toxicity (disabling)

Monitoring Parameters [3]

- CBC with differential
- LFTs
- platelet count
- serum bilirubin
- WBC

Adverse Drug Reactions

Common ADR (≥ 20%)

Peripheral neuropathy [3]

According to Study 081, Ixabepilone monotherapy caused peripheral sensory neuropathy in 62% of patients. It is the most common adverse effect requiring treatment discontinuation. 6% of patients in Study 081 had the Ixabepilone monotherapy discontinued due to the development of neuropathy. Patients usually

experience symptoms of this adverse effect, including numbness, tingling and burning sensation in extremities, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain, early in the treatment course. About 75% of those patients have new-onset or worsening neuropathy in the first 3 cycles of treatment. The neuropathy caused is generally reversible and could be managed by dose reduction, delay and discontinuation. In Study 081, 87% of patients who had the dose reduced showed no worsening or even improvement in their neuropathic condition. In a prospective study on Ixabepilone-induced neuropathy in 47 patients, the median time of onset of this adverse effect was 144 days in 11 patients. 8 of them had the problem resolved in a median of 15 days but not for 3 of them even after 746 days after symptoms onset. [7] According to a pooled analysis, diabetic patients may experience more severe neuropathy, but it is not shown that patients with grade 1 neuropathy or those who had received prior neurotoxic chemotherapy are at increased risk of this adverse effect.

Myelosuppression [3]

Suppression of bone marrow can be manifested as leukopenia, thrombocytopenia and anemia, but it is primarily expressed as neutropenia. In a monotherapy study, 54% of patients developed grade ¾ neutropenia while 49% of patients developed grade ¾ leukopenia. 3% and 5% of patients developed febrile neutropenia and infection with neutropenia respectively. Patients may suffer from serious infections during neutropenia which may even lead to deaths in 0.4% of patients. This risk is higher in patients with impaired liver function and in patients receiving capecitabine at the same time. Since myelosuppression is dose-related, management of this adverse effect involves dose reduction.

Others [3]

Other common adverse effects related to Ixabepilone include fatigue/asthenia 56% (Grade ¾: 13%), myalgia/arthralgia 49% (Grade ¾: 8%), alopecia 48% (Grade ¾: 0%), nausea 42% (Grade ¾: 2%), stomatitis/mucositis 29% (Grade ¾: 6%), vomiting 29% (Grade ¾: 1%), diarrhea 22% (Grade ¾: 1%), and musculoskeletal pain 20% (Grade ¾: 3%).

LESS COMMON ADR (< 20%)

Hypersensitivity Reactions [3]

Some patienes on Ixabepilone may develop hypersensitivity reactions like flushing, dyspnea, bronchospasm and rash, and 1% of patients even experience severe hypersensitivity reactions like anaphylaxis. Therefore, all patients should receive an H_1 and an H_2 antagonist approximately one hour before Ixabepilone infusion and the patients should be monitored for any hypersensitivity reactions. If the patient develops hypersensitivity reactions, the treatment should be stopped and supportive therapy including corticosteroids and adrenaline should be given. If a patient who developed this adverse effect is to be treated with Ixabepilone again, the infusion time should be prolonged and the patient should be premedicated with a corticosteroid in addition to the H_1 and H_2 antagonist. Patients should not take Ixabepilone in case of history of severe hypersensitivity reaction to Cremophor® EL or its derivatives.

Cardiac Adverse Effects [3]

There are reports of myocardial ischemia, supraventricular arrhythmia and ventricular dysfunction in patients receiving Ixabepilone. These adverse effects are more common in combination therapy of

Ixabepilone and capecitabine (1.9%) than in capecitabine monotherapy (0.3%). Ixabepilone should be used in caution in patients with heart disease. If a patient developed these adverse effects, the drug should be discontinued.

Warning and Precautions [3]

Pregnancy and Nursing

Ixempra belongs to pregnancy category D and may cause harmful effects on fetus if given to pregnant women. Therefore, patients should be advised not to become pregnant if they are under Ixempra therapy and they should use appropriate contraceptive method. However, if Ixempra is used in pregnancy or if patients become pregnant when they take this medication, they should be warned with the potential hazards to the fetus. Up till now, there is scientific evidence concerning the use of Ixempra in pregnancy.
It is not known if Ixempra is secreted into breast milk or not. However, in view of potential harmful effects of to the infants, nursing mother should either stop breast feeding or discontinue Ixempra therapy.

Liver function Impairment

Compared to patients with normal liver function, patients with impaired liver function have increased exposure (measured by area under the curve) to Ixempra after an equivalent dose. The increase in drug exposure ranges from 22% to 81% depending on the severity of liver damage.
Dose reduction is therefore recommended when giving Ixempra as monotherapy in patients with liver impairment. Because of this, a liver function test is recommended before starting Ixempra therapy.

Kidney function Impairment

Pharmacokinetically, Ixempra is minimally excreted through kidneys. In a population pharmacokinetic analysis of Ixempra as monotherapy, mild to moderate renal insufficiency (CrCL >30 mL/min) has no clinically significant effects on the pharmacokinetics of Ixempra. The effect of renal impairment on combination therapy (with capecitabine) has not been evaluated in patient with CrCL <50 mL/min.

Monitoring Parameters

The following parameters should be monitored for adverse reactions of Ixempra:

- numbness and tingling of limbs (for neuropathy)
- any infections/blood count (for myelosuppression)
- skin reactions e.g. utricaria and rash (for hypersensitivity reactions)

Contraindications [3]

Ixempra is contraindicated in the following conditions:

- patients with history of severe hypersensitivity reaction to agents containing Cremophor® EL or its derivatives (eg, polyoxyethylated castor oil)
- patients with decreased neutrophil count (< 1500 cells/mm^3) or a platelet count (< 100,000 cells/mm^3)
- patients with impaired liver function (AST or ALT level higher than 2.5 times of upper normal limit or bilirubin level higher than upper normal limit) and use in combination with capecitabine

Drug interactions

DRUG-DRUG INTERACTIONS

Ixabepilone is a substrate of cytochrome P450 isoenzyme CYP3A4. Its *in vivo* oxidative metabolism depends on the enzyme and thus inhibitors or inducers of the P450 3A4 enzyme are going to have drug pharmacokinetic interactions with Ixabepilone. The most significant and documented interaction is its interaction with ketoconazole. A study by S. Goel *et al*. demonstrated that injection of Ixabepilone with oral ketoconazole produces a drug-drug interaction that increased the mean geometric AUC of Ixabepilone by 77.6% (2892 vs 1628ng/mL); and the maximum tolerated dose of Ixabepilone halved after co-administration of ketoconazole to 20mg/m^2. [8] This result is similar with the manufacturer's note about 79% AUC increase with ketoconazole. The manufacturer recommends co-administration with potent CYP3A4 inhibitors should be avoided, and dosage adjustment to 20mg/m^2 should be done if there is no alternative. [3] Increased plasma concentration of the drug leads to higher risk of toxicity and adverse drug reactions. Frequent monitoring of peripheral blood counts is necessary if there are possible drug interactions. [3] Conversely, inducers of CYP3A4 can lead to increased clearance of Ixabepilone and subtherapeutic level of the drug.

Inhibitors of CYP3A4 which can potentially increase plasma level of Ixabepilone: [9, 10]

- **Ciprofloxacin**
- **Itraconazole**
- **Ketoconazole**
- **Nefazodone**
- **Clarithromycin**
- **Erythromycin**
- **Delavirdine**
- **Indinavir**
- **Ritonavir**
- **Diltiazem**
- **Norfluoxetine**
- Aprepitant
- Fluoxetine
- Sertraline
- Fluconazole
- Nelfinavir
- Haloperidol
- Pimozide
- Cimetidine
- Tamoxifen
- Verapamil

Drugs in **Bold** are potent inhibitors of CYP3A4 and should be avoided to be used with Ixabepilone.

Inducers of CYP3A4 which can potentially decrease plasma level of Ixabepilone: [9, 10]

- **Phenytoin**
- **Phenobarbitone**
- **Carbamazepine**
- **Rifampin**
- Cyclophosphamide
- Pioglitazone
- Efavirenz
- Nevirapine
- Dexamethasone

Drugs in **Bold** are potent inducers of CYP3A4. Manufacturer suggests considering alternatives with less enzyme induction.

DRUG-FOOD INTERACTIONS

The disturbance of CYP3A4 is the only mechanism known to cause interactions with Ixabepilone by now. Ixabepilone is only available in IV formulation, therefore it would only interact with food that interfere with systemic level of CYP3A4.

Grapefruit juice is widely regarded as an agent to cause inhibition of CYP3A4 and is prone to drug-food interactions. Although some literatures stated that grapefruit juice mainly inhibit intestinal CYP3A4 and has little inhibition on hepatic CYP3A4 [10], the manufacturer regards it as a potent inhibitor and recommends to avoid grapefruit juice to prevent ***increases*** in Ixabepilone level. [3]

Drug-herb interactions

St. John's wort, which is used for anti-depression, is a renowned herb to cause drug-herb interaction as it is an inducer of CYP3A4. [10] It may ***decrease*** Ixabepilone level unpredictably as noted by the manufacturer. St. John's wort should be avoided during Ixabepilone therapy. [3]

Pharmacokinetics [3]

Absorption

Intravenous administration of single dose 40 mg/m^2 of to patients, the mean Cmax was 252 ng/mL, Tmax was 3 hours and mean AUC was 2143 ng hr/mL (CV 48%). In cancer patients, the pharmacokinetics of ixebepilone was linear at doses of 15 to 57 mg/m^2.

Distribution

The mean volume of distribution of 40 mg/m^2 Ixabepilone was greater than 1000 L. Binding of ixebepilone to human serum proteins ranged from 67 to 77%, and the blood-to-plasma concentration ratios in human blood ranged from 0.65 to 0.85 over a concentration range of 50 to 5000 ng/mL.

Metabolism

Ixebepilone is extensively metabolized in the liver by CYP3A4 enzyme. The metabolites of ixebepilone were not active against human tumor cells. *In vitro* studies shows that the clinically relevant concentrations of ixebepilone neither inhibit nor induce the activity of CYP1A2, CYP2B6, CYP2C9, or CYP3A4 in cultured human hepatocytes. Hence, ixebepilone will not affect the plasma levels of drugs which are substrates of CYP enzymes.

Elimination

Ixebepilone has a half life of about 52 hours. It is eliminated mainly as charged form. After intravenous administration of ixebepilone, approximately 86% and 7.2% of the dose are charged and uncharged ixebepilone respectively.

Pharmacodynamics [3]

In cancer patients, Ixabepilone give a plasma concentration-dependent effect on tubulin dynamics in peripheral blood mononuclear cells. Ixabepilone has antitumor activity against multiple human tumor xenografts, including drug-resistant types that overexpress P-gp, MRP-1, and βIII 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. Apart from direct antitumor activity, Ixabepilone has antiangiogenic activity.

DOSAGE FORMS AND STRENGTHS [3]

Injectable solution: IXEMPRA™ 15 mg with 8 mL of diluent
IXEMPRA™ 45 mg with 23.5 mL of diluent

Diluent of IXEMPRA™ is sterile, non-pyrogenic solution of 52.8% (w/v) purified polyoxyethylated castor oil and 39.8% (w/v) of dehydrated alcohol, USP. [11]

PATIENT COUNSELING INFORMATION [3]

WHAT IS IXEMPRA™? [3]

IXEMPRA™ (pronounced as ik SEM pra) is a medicine used to treat breast cancer, especially when other medications do not work or are not working anymore. It could be used alone or with other drug called capecitabine.

IXEMPRA is given by intravenous injection, usually every three weeks. Each injection will take about 3 hours.

IS IXEMPRA™ SUITABLE FOR ME? [3]

IXEMPRA™ is not suitable for you if:

- ✧ You are allergic to any ingredients in IXEMPRA™, TAXOL®, which contains Cremophor® EL or polyoxyethylated castor oil
- ✧ You have low white blood cell count or platelet level
- ✧ You are taking capecitabine (another cancer drug) and having high liver enzyme levels
- ✧ You are taking cephalosporins (eg. Cefotetan), disulfiram or metronidazole

WHAT SHOULD I KNOW BEFORE USING IXEMPRA™? [3]

Before using IXEMPRA™, inform your physician about your medical history which may affect the choice of drug, especially:

- ➢ Liver problems (including elevation of liver enzymes, hepatitis, cirrhosis, etc.)
- ➢ Heart diseases (including angina, chest pain, etc.)
- ➢ Drug allergy history
- ➢ Pregnancy, breast-feeding or planning to be pregnant
- ➢ Current medications, including prescription, non-prescription drugs, herbal or dietary supplements. They may affect performance of each other.
  - ✧ Cephalosporins (eg. Cefotetan), disulfiram, furazolidone, metronidazole, or sulfonylureas
  - ✧ Azoles (eg. Ketoconazole), delavirdine, fluconazole, clarithromycin, nefazodone, trazodone,
  - ✧ Carbamazepine, barbiturates, dexamethasone, phenytoin, verapamil, rifampin or St. John's wort

WHAT SHOULD I KNOW DURING USING IXEMPRA™? [3]

If you experience any allergic reaction to IXEMPRA™, you may need steroid prior future injections of IXEMPRA™. More slowly administration may be also required.

As IXEMPRA™ contains alcohol, you may be dizzy or drowsy. Avoid operating machinery or driving.

Avoid drinking grapefruit juice while receiving IXEMPRA™ as it may increase the level of IXEMPRA™ and causes side effects more easily.
Your physician should monitor your liver function regularly while you are receiving IXEMPRA™.
Effective contraceptive measures should be employed to prevent pregnancy as IXEMPRA™ may be harmful to foetus.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF IXEMPRA™? [3, 12, 13]

IXEMPRA™ may cause some serious side effects in individuals. Patients who experience these symptoms should report to their physicians:

- Numbness and tingling of hands or feet may suggest peripheral neuropathy
- Fever of 100.5° F or higher or any signs of suspected infection, for example chills, cough, or burning or pain on urination may suggest neutropenia, which means the fall in white blood cell count.
- Uriicaria, pruritus, rash, flushing, swelling, dyspnea or congested chest may suggest hypersensitivity reactions against IXEMPRA™.
- Suspected or confirmed pregnancy as IXEMPRA™ may be harmful to foetus.
- Chest pain, difficulty in breathing, shortness of breathe, palpitations or unusual weight gain may suggest side effects affecting cardiovascular system.

IXEMPRA™ may also cause milder side effects that may not require special attention:

- Patients may experience tiredness, loss of appetite, mild fever, headache, muscle and joint pain, nausea and vomiting, diarrhea, constipation and abdominal pain
- Decrease in red blood cell count (anemia) or platelets (thrombocytopenia)
- Changes in toenails and fingernails, hair loss, sores on lip, in the mouth and esophagus
- Red palms and soles of feet (hand-foot syndrome) that similar to sunburn, dry and peeling skin

If you find these side effects bothersome or persist for long time, you may inform you physician and seek for advices. If you experience any other strange side effects, you may also inform your physician.

Cost[4]

IXEMPRA™ 15 mg US $921.96
IXEMPRA™ 45 mg US $2,765.89

References

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