

The following is a message from the FDA's Office of Oncology Drug Products Director, Dr. Richard Pazdur:

On October 16, 2007, the U.S. Food and Drug Administration approved ixabepilone for injection (IXEMPRA™, Bristol-Myers Squibb) for the following two 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.
- 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.

A randomized, multinational, open-label trial of 752 patients with locally advanced or metastatic breast cancer evaluated the efficacy and safety of ixabepilone (40 mg/m² IV once every three weeks) plus capecitabine compared to therapy with capecitabine alone. Patients had previously received an anthracycline and a taxane, had evidence of disease progression or resistance, or, in the case of the anthracycline, received a minimum required cumulative dose.

Treatment arms were balanced with regards to prior therapies, disease sites, hormone receptor status and HER2 expression. Patients receiving combination therapy had a statistically significant improvement in progression-free survival (PFS), defined as radiologic progression or death from any cause (hazard ratio 0.69, p<0.0001). The median PFS was 5.7 months in the combination arm and 4.1 months in the capecitabine alone arm. Patients in the combination arm also had an increased objective tumor response rate. Survival data for this trial are not yet mature.

Ixabepilone monotherapy was evaluated in a single arm trial of 126 patients with metastatic or locally advanced breast cancer who had previously received an anthracycline, a taxane and capecitabine, and who had disease progression or, in the case of the anthracycline, received a minimum required cumulative dose. Ixabepilone was administered at the same dose and schedule as in the combination trial. The objective response rate based on independent radiologic review was 12.4% (95% CI: 6.9, 19.9). The objective response rate based on investigator assessments was 18.3% (95% CI: 11.9, 26.1). The median response duration was 6.0 months (95% CI: 5.0, 7.6).

Treatment with ixabepilone caused new or worsening peripheral neuropathy in approximately 65% of patients treated. Grade 3 or 4 peripheral neuropathy occurred in 23% of patients treated with ixabepilone and capecitabine, with no grade 3 or 4 peripheral neuropathy reported in the capecitabine arm. In the ixabepilone monotherapy trial, 14% experienced grade 3 or 4 peripheral neuropathy. Neuropathy was generally reversible to Grade 1 or better with cessation of therapy.

Ixabepilone in combination with capecitabine resulted in a 68% incidence of Grade 3 or 4 neutropenia compared to 11% with capecitabine alone. Twelve patients receiving ixabepilone in combination with capecitabine died from complications arising from neutropenia. The incidence of neutropenia related deaths was higher in patients with baseline moderate or severe hepatic impairment when treated with both ixabepilone and capecitabine.

This combination should not be used in patients with moderate or severe hepatic impairment. When used as monotherapy, 54% of patients treated with ixabepilone experienced Grade 3 or 4 neutropenia.

Other commonly observed toxicities (>20%) included anemia, leukopenia, thrombocytopenia, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional reactions occurred in 20% in the combination treatment arm: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications, is available at <http://www.fda.gov/cder/foi/label/2007/022065lbl.pdf>.