PHARMACY CORNER

Denosumab Injection Approved for Skeletal Injury Prevention

The U.S. Food and Drug Administration (FDA) has approved denosumab (Xgeva™, Amgen) to help prevent skeletal injuries in patients with solid tumors that have metastasized and caused bone damage. Previous agents approved for this setting include the bisphosphonates zoledronic acid (Zometa®, Novartis Pharmaceuticals) and pamidronate disodium (Aredia®, Novartis Pharmaceuticals). Denosumab is a fully humanized monoclonal antibody that targets receptor activator of nuclear factor k B ligand—a protein involved in the process of bone destruction by osteoclasts.

In a phase III clinical trial reported by Stopeck et al. (2010), denosumab (n = 1,026) demonstrated superiority compared to zoledronic acid (n = 1,020) in increasing time to first skeletal-related events (pathologic fracture, spinal cord compression, or the need for radiation therapy or surgery to the bones) by 18% (hazard ratio [HR] = 0.82, confidence interval [CI] = 0.71–0.95, p = 0.01) in patients with breast cancer and bone metastases.

A suggested benefit of using denosumab versus zoledronic acid is a decreased risk of renal failure associated with therapy. In the clinical trial comparing the two, zoledronic acid was associated with a 2.5% incidence of renal failure versus 0.2% with denosumab.

Hypocalcemia was observed more frequently following denosumab (5%) than zoledronic acid (3.4%). Patients should be treated as indicated with calcium, magnesium, and vitamin D. Of note, patients with decreased creatinine clearance are at increased risk for experiencing hypocalcemia and should be monitored accordingly.

Compared with zoledronic acid, the incidence of osteonecrosis of the jaw was not significantly different between study arms (2% denosumab, 1.4% zoledronic acid, p = 0.39). Precautionary measures should include a dental evaluation and completion of necessary dental work prior to initiating therapy.

Denosumab is given as a monthly 120 mg subcutaneous injection.

For more information, visit www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234346.htm.

Stopeck, A.T., Lipton, A., Body, J.J., Steger, G.G., Tonkin, K., de Boer, R.H., . . . Braun, A. (2010). Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *Journal of Clinical Oncology, 28*, 5132–5139. doi: 10.1200/JCO.2010.29.7101

New Option Available for Metastatic Breast Cancer

The FDA has granted approval for eribulin mesylate (Halaven™ Injection, Eisai Inc.) for treatment of patients with metastatic breast cancer previously treated with at least two other chemotherapy regimens—including an anthracycline and a taxane. Eribulin mesylate is a microtubule inhibitor drug that is an analog of a molecule found in the marine sponge *Halichondria okadai*.

Approval was granted based on the E7389-G000-305 study in which patients were randomized 2:1 to receive eribulin mesylate (n = 508) or another single agent chosen by their physician (n = 254). The majority of the control arm received cytotoxic chemotherapy, and the most common agents chosen were vinorelbine, gemcitabine, capecitabine, a taxane, or an anthracycline. A hormonal agent was chosen as the treatment for 2% of the patients in the control arm. The eribulin mesylate arm demonstrated a statistically improved median overall survival of 13.1 months versus 10.6 months in the control group (p = 0.041).

The drug is dosed at 1.4 mg/m^2 IV over 2–5 minutes on days 1 and 8 of 21-day cycles. The dose should be reduced in patients with renal or hepatic impairment. Common adverse reactions include neutropenia, anemia, asthenia or fatigue, alopecia, peripheral neuropathy, nausea, and constipation. For patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, QT prolongation also may occur, and patients should be monitored appropriately. The most common serious adverse reactions during clinical trials included febrile neutropenia (4%) and neutropenia (2%).

Doses should not be given if the patient has an absolute neutrophil count less than 1,000/mm^3, has a platelet count less than 75,000/mm^3, or is experiencing grade 3 or 4 nonhematologic toxicities. The package insert includes directions regarding when to resume therapy following resolution of toxicities, along with reduced dosage guidelines. Doses should not be escalated once they have been reduced.

For more information, visit www.fda.gov/AboutFDA/CentersOffices/CDER/ucm234527.htm.

Accelerated Approval Granted for Astrocytoma Drug

The FDA has given accelerated approval to everolimus (Afinitor®, Novartis Pharmaceuticals) for treating inoperable subependymal giant cell astrocytoma (SEGA) associated with the rare genetic disorder tuberous sclerosis. Everolimus, an oral drug, is a kinase inhibitor that was previously approved for advanced renal cell carcinoma following treatment failure with sorafenib or sunitinib.

The medication may be given without regard to meals, but it should be given at the same time each day. Dosing for SEGA initially is based on body surface area (BSA) and subsequently adjusted, if needed, based on serum drug concentration troughs and other factors.

Starting everolimus dose should follow these guidelines:

- BSA: 0.5–1.2 m^2; dose: 2.5 mg
- BSA: 1.3–2.1 m^2; dose: 5 mg
- BSA: 2.2 m^2 or higher; dose: 7.5 mg

For more information, visit www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm231793.htm.

SAFETY CONCERNS

Cardiac Risks Associated With Antiemetic Drug

The IV form of dolasetron mesylate (Anzemet®, sanofi-aventis) should no longer be used for the prevention of chemotherapy-induced nausea and