Bone-Modifying Agents in Metastatic Breast Cancer

The American Society of Clinical Oncology (ASCO) has issued a 2011 update on the role of bone-modifying agents in the prevention and treatment of skeletal-related events in metastatic breast cancer with bone metastases. This update is based on systematic review and analysis of medical literature. A summary of the key recommendations include:

- Therapy with bone-modifying agents is only recommended for patients with metastatic breast cancer with evidence of bone metastases.
- Denosumab 120 mg subcutaneously every 4 weeks; intravenous pamidronate 90 mg over no less than 2 hours every 3 to 4 weeks; or intravenous zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended.
- One bone-modifying agent is not recommended over another, as there is insufficient evidence to demonstrate greater efficacy.
- In patients with creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval is required; serum creatinine levels should be monitored with each intravenous bisphosphonate dose.
- In patients with creatinine clearance < 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.
- Osteonecrosis of the jaw is an uncommon but potentially serious concern with the use of bone-modifying agents. Therefore all patients should have a dental examination and preventive dentistry before starting a bone-modifying agent.
- At onset of cancer bone pain, standard of care for pain management should be applied and bone-modifying agents initiated.
- Use of biochemical markers to monitor bone-modifying agent use is not recommended routinely. ASCO guidelines are typically updated every three years.

Prescription Cough, Cold, and Allergy Products

On March 2, 2011, as part of the Food and Drug Administration’s (FDA’s) Unapproved Drug Initiative, the FDA prompted removal of unapproved prescription cough, cold, and allergy products. The affected products cannot be legally marketed in the United States. Companies that have previously listed products subject to the recent action by the FDA are expected to stop manufacturing them within 90 days and stop shipping the products within 180 days. Companies that have not previously listed products subject to the FDA’s action are expected to stop manufacturing them within 90 days.

A variety of drug options remain available in the prescription cough, cold, and allergy products that are FDA-approved as well as those appropriately marketed as over-the-counter (OTC). For the list of unapproved prescription cough, cold, and allergy products please visit http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm245106.htm.

Drug Shortages and Recalls

Due to the shortage of both leucovorin and levoeleucovorin (Fusilev®) products, the FDA has utilized regulatory enforcement discretion for Spectrum Pharmaceuticals to temporarily import levoeleucovorin 100 mg powder for injection manufactured by Pfizer from Italy. No other entity except for Spectrum is authorized by the FDA to import or distribute Pfizer levoeleucovorin 100 mg powder for injection in the United States. It should be noted that there is potential for dosing errors when interchanging the reduced folates, leucovorin and levoeleucovorin (Fusilev®). The dose of levoeleucovorin (Fusilev®) is one-half the dose of racemic leucovorin injection.

King Pharmaceutical, a subsidiary of Pfizer, has announced a voluntary recall of all lots of morphine/naltrexone extended-release (Embeda®) capsules, a CII-controlled substance for moderate to severe pain management when a continuous, around-the-clock opioid is needed for an extended time period. The drug did not meet a pre-specified stability requirement during routine testing. Until the issue is resolved, the drug will not be available.

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<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
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<tbody>
<tr>
<td>azilsartan medoxomil</td>
<td>Edarbi™</td>
<td>Edarbi™ is a new angiotensin receptor blocker (ARB) indicated, either alone or with other antihypertensives, for the treatment of hypertension. The recommended dose of Edarbi™ is 80 mg once daily.</td>
<td>Takeda</td>
<td>FDA NDA Approval 02/25/2011</td>
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<tr>
<td>cinacalcet hydrochloride</td>
<td>Sensipar®</td>
<td>Sensipar® is now approved for severe hypercalcemia in patients with primary hyperparathyroidism (HPT) who are unable to undergo parathyroidectomy. Previously, Sensipar® was only approved for secondary HPT in patients with chronic kidney disease on dialysis or in patients with parathyroid carcinoma with hypercalcemia.</td>
<td>Amgen</td>
<td>FDA New Indication Approval 02/25/2011</td>
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<tr>
<td>roflumilast</td>
<td>Daliresp™</td>
<td>Daliresp™, a selective inhibitor of phosphodiesterase 4 (PDE4), is indicated for the treatment and to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with a history of exacerbations and chronic bronchitis. Daliresp™ is not a bronchodilator and should not be used to treat acute bronchospasms. Daliresp™ is given as one 500 mcg tablet daily.</td>
<td>Forest</td>
<td>FDA NDA Approval 02/28/2011</td>
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<td>antihemophilic Factor/von Willebrand Factor Complex [human]</td>
<td>Alphanate®</td>
<td>Labeling for Alphanate® now includes a statement indicating that certain manufacturing steps have been shown to reduce the infectivity of an experimental transmissible spongiform encephalopathy (TSE) agent that is a model for variant Creutzfeldt-Jakob disease (vCJD). Alphanate® may carry a risk of transmitting infectious agents (e.g., viruses) and theoretically, the CJD agent, because it is made from pooled human plasma. Alphanate® is indicated for the prevention and control of bleeding in patients with Factor VIII deficiency due to hemophilia A. Alphanate® is also indicated for surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease, except Type III undergoing major surgery, in whom desmopressin (DDAVP) is either ineffective or contraindicated.</td>
<td>Grifols</td>
<td>FDA Revised Labeling 03/07/2011</td>
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<tr>
<td>belimumab</td>
<td>Benlysta®</td>
<td>Benlysta®, a B-lymphocyte stimulator-specific inhibitor, is indicated for the treatment of adults with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The use of Benlysta® is not recommended in patients with severe active lupus nephritis, in patients with severe active central nervous system lupus, or in combination with biologics or intravenous cyclophosphamide, as Benlysta® has not been studies in these situations. Benlysta® is given as 10mg/kg intravenously every 2 weeks for the first 3 doses, then every 4 weeks thereafter.</td>
<td>Human Genome Sciences</td>
<td>FDA BLA Approval 03/10/2011</td>
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<tr>
<td>gadobutrol</td>
<td>Gadavist®</td>
<td>Gadavist®, a gadolinium-based contrast agent, is indicated for use in patients two years of age and above undergoing diagnostic MRI to detect and visualize areas with disrupted blood brain barrier and/or normal vascularity of the central nervous system.</td>
<td>Bayer Healthcare Pharm</td>
<td>FDA NDA Approval 03/14/2011</td>
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<td>imiquimod</td>
<td>Zyclara™</td>
<td>Zyclara™ 3.75% cream is now approved for the topical treatment of external genital and perianal warts in patients 12 years of age or older. Previously, Zyclara™ was only approved for the treatment of actinic keratoses of the face or balding scalp in immunocompetent patient. Zyclara™ should be applied topically once daily for up to eight weeks.</td>
<td>Graceway</td>
<td>FDA New Indication Approval 03/24/2011</td>
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<tr>
<td>ipilimumab</td>
<td>Yervoy™</td>
<td>Yervoy™, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, is indicated for the treatment of unresectable or metastatic melanoma. Yervoy™ has a black box warning discussing the potential for severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. Yervoy™ is given at a dose of 3 mg/kg intravenously over 90 minutes every 3 weeks for a total of 4 doses.</td>
<td>Bristol Myers Squibb</td>
<td>FDA NDA Approval 03/25/2011</td>
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