Nexium, esomeprazole magnesium, under the terms of a settlement agreement with AstraZeneca, on duration of tamoxifen treatment in patients with hormone receptor (HR) positive breast cancer, the most

Guideline Focus: Breast Cancer Updated Clinical Practice Guidelines

Although the potential for curing hepatitis C is promising, NAMD advises caution with sofosbuvir use in light of whether Ranbaxy will retain its 180-day market exclusivity for this product. It is not clear how long it will take the FDA to approve Ranbaxy’s ANDA. Ranbaxy continues to have import bans on four of its manufacturing facilities in India. Several other manufacturers have filed ANDAs for generic Nexium capsules. However, the FDA has not yet approved any of these ANDAs.

MED reviewed 10 published sofosbuvir (Sovaldi®) studies:
- Studies were found to have “poor” methodologic quality, risks of bias, and lacking comparison to current standards of treatment.
- Current evidence does not support routine use of sofosbuvir.

MED defines current standards of care as:
- Genotype 1 – peginterferon/ribavirin plus a protease inhibitor (boceprevir [Victrelis®] or telaprevir [Incivek®]).
- Genotypes 2 and 3 – peginterferon/ribavirin.

MED found the American Association of the Study of Liver Diseases/Infectious Disease Society of America (AASLD/IDSA) guidelines to be of:
- Poor methodological quality, findings based on poor quality evidence, authors and sponsors had multiple and significant conflicts of interest.

MED outlines several private payer policies in their report.

An outline of suggested MED criteria includes the following:
- Limit sofosbuvir use to only genotypes 2 and 3 until comparative trials are available for genotype 1.
- Do not use sofosbuvir as monotherapy.
- Limit sofosbuvir use to patients who failed or did not tolerate current standard of care regimens or in patients with contraindications to peginterferon.
- Confirm degree of liver fibrosis or cirrhosis before authorizing therapy.
- Treat only patients at greatest risk of progressing to cirrhosis, such as Metavir Fibrosis stage ≥ 2, and additional factors with potential to increase risk of progression to cirrhosis.
- Consider use for patients with HIV-1 or hepatitis B co-infection or in patients who are post-liver transplant carefully until comparative trials are available.
- Exclude sofosbuvir use in patients with drug or alcohol use within the past year. Exclude sofosbuvir use in patients with significant cardiac or pulmonary disease, uncontrolled hypertension, diabetes, seizure disorder, or renal disease.
- Monitor patients for adherence while on therapy and follow-up to avoid re-infection.

The National Association of Medicaid Directors (NAMD) issued a statement in response to OHSU’s report. Although the potential for curing hepatitis C is promising, NAMD advises caution with sofosbuvir use in light of the high cost, number of patients with hepatitis C, poor clinical evidence, and questionable practice guidelines.

Guideline Focus: Breast Cancer Updated Clinical Practice Guidelines

The American Society of Clinical Oncology (ASCO) has published a focused update to reflect emerging evidence on duration of tamoxifen treatment in patients with hormone receptor (HR) positive breast cancer, the most common type of breast cancer in women. The ASCO clinical practice guideline now recommends treatment with adjuvant tamoxifen for 10 years (previously it was five years) in women with stage I-II HR positive breast cancer, based on five clinical studies (including aTTom and ATLAS trials) of tamoxifen beyond five years of therapy. In the aTTom study, compared to women who stopped therapy at five years, women continuing tamoxifen for 10 years had a 25% lower recurrence rate and a 23% lower breast cancer mortality rate. In the ATLAS trial, there was a 2.8% reduction in mortality risk and a 25% reduction in the rate of recurrence for patients continuing tamoxifen for 10 years compared to five years. The 10-year duration of tamoxifen therapy is recommended for both premenopausal and postmenopausal women. However, postmenopausal women have the option of taking a sequence of tamoxifen and aromatase inhibitor (AI) therapy. AIs are not recommended for premenopausal women. The potential risks of adverse events and potential benefits of taking adjuvant tamoxifen for up to 10 years should be considered in individual patients. ASCO concluded that the benefits demonstrated by a longer duration of treatment with tamoxifen outweigh the possible risks.

Nexium® – Over-the-Counter (OTC) and Generic

As expected, on May 27th, Pfizer launched OTC Nexium® 24 Hour 20 mg delayed-release (DR) capsules for the treatment of frequent heartburn in adults ≥ 18 years old. Although Ranbaxy has permission to launch generic Nexium, esomeprazole magnesium, under the terms of a settlement agreement with AstraZeneca, it is still unclear if the FDA will grant effective approval of Ranbaxy’s abbreviated New Drug Application (ANDA) and whether Ranbaxy will retain its 180-day market exclusivity for this product. It is not clear how long it will take the FDA to approve Ranbaxy’s ANDA. Ranbaxy continues to have import bans on four of its manufacturing facilities in India. Several other manufacturers have filed ANDAs for generic Nexium capsules. However, the FDA has not yet approved any of these ANDAs.

Sources:
- Medscape.com
- PTCommunity.com
- NDA; Genzyme.
- June 7: Zerenex; ferric citrate iron-based oral compound for hyperphosphatemia in chronic kidney disease patients on dialysis; NDA; Keryx.
- June 10: Contrave; oral naltrexone/bupropion; weight loss; NDA; Orexigen/Takeda/GSK.
- June 11: Cerdelga; oral eliglustat; Gaucher’s Disease; NDA; Genzyme.
- June 20: Sivextro; intravenous and oral tedizolid; ABSSSI; NDA; Cubist.
- July 3: Hyjia; combination of human immunoglobulin/recombinant human hyaluronidase for treatment of adult primary immunodeficiency; subcutaneous injection every three to four weeks; Biologics License Application (BLA); Baxter/Halozyme. An earlier PDUFA date was extended to July 31, as FDA review of additional data is needed.
- 2nd Quarter 2014: Elcotate; injectable recombinant factor VIII Fc fusion protein; longer acting product for hemophilia A; BLA; Biogen.

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(513) 794-5265
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June 2014

Drug Information Highlights

- The recommended starting dose of eszopiclone (Lunesta®) has been decreased from 2 mg to 1 mg at bedtime in both men and women. This is due to the increased risk of next day impairment of driving and other activities that require full alertness. Dosing can be increased to 2 mg or 3 mg, if clinically appropriate. In 2013, the FDA issued a dose reduction for zolpidem.
- According to the FDA, in an observational cohort study of 134,000 Medicare patients, compared to warfarin, dabigatran (Pradaxa®) was associated with a reduced risk for ischemic stroke, intracranial hemorrhage, and death, with no difference in the risk of myocardial infarction. The risk for major gastrointestinal bleeding was increased with dabigatran.

Dalbavancin (Dalvance™) is an intravenous lipoglycopeptide approved to treat acute bacterial skin and skin structure infections (ABSSSI) caused by certain susceptible Gram positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). Durata Therapeutics’ product is the first drug designated as a Qualified Infectious Disease Product (QIDP); an antibacterial intended to treat serious or life-threatening infections. Two other antibiotics for ABSSSI are also in the FDA’s review process.

Pipeline News:

Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- June 7: Bunivavis; buprenorphine/naloxone buccal film; maintenance treatment of opioid dependence; New Drug Application (NDA); Biodelivery Sciences.
- June 7: Zerenex; ferric citrate iron-based oral compound for hyperphosphatemia in chronic kidney disease patients on dialysis; NDA; Keryx.
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### FDA Approved New Molecular Entities (NMEs), Biologic Products (BLAs)/Orphan Drugs, and New Indications/New Formulations for Existing Products

<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>siltuximab</td>
<td>Sylvant™</td>
<td>The FDA has approved siltuximab (Sylvant), an interleukin-6 (IL-6) antagonist, for the treatment of multicentric Castleman’s Disease (MCD) in patients who are HIV negative and human herpes virus-8 (HHV-8) negative. It is administered intravenously as 11 mg/kg over one hour every three weeks. Adverse effects include pruritus, weight gain, rash, and hyperuricemia. Sylvant is available as a lyophilized powder in 100 mg and 400 mg single-use vials.</td>
<td>Janssen</td>
<td>FDA BLA Approval</td>
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<td><strong>Priority Review</strong> 04/22/2014</td>
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<tr>
<td>mercaptopurine</td>
<td>Purixan™</td>
<td>Mercaptopurine, a component of maintenance treatment of acute lymphoblastic leukemia (ALL), was FDA approved as a 2,000 mg/100 mL oral suspension (Purixan). Purixan is the only liquid mercaptopurine preparation available and allows the desired weight-based dose to be more easily achieved, particularly in younger patients. Recommended starting dosage is 1.5 to 2.5 mg/kg once daily.</td>
<td>Nova</td>
<td>FDA NDA Approval</td>
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<td><strong>Priority Review</strong> 04/28/2014</td>
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<tr>
<td>ceritinib</td>
<td>Zykadia™</td>
<td>Ceritinib (Zykadia) is a kinase inhibitor approved for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib (Xalkori®). Among previously-treated patients, ceritinib achieved an overall response rate of 54.6 percent and a median duration of response of 7.4 months. The majority of patients in clinical trials experienced gastrointestinal side effects which may necessitate a dose reduction. Recommended dosage is 750 mg once daily on an empty stomach, until disease progression or unacceptable toxicity. Discontinue in patients unable to tolerate 300 mg daily. Zykadia is available as 150 mg capsules.</td>
<td>Novartis</td>
<td>FDA NDA Approval</td>
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<td><strong>Priority Review</strong> 04/29/2014</td>
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<tr>
<td>umeclidinium</td>
<td>Incruse™ Ellipta®</td>
<td>The FDA has approved the anticholinergic, umeclidinium (Incruse Ellipta) for the maintenance treatment of chronic obstructive pulmonary disease (COPD). It should not be used to relieve acute symptoms of COPD or in patients with severe hypersensitivity to milk proteins. The recommended dosing is one oral inhalation once daily, delivering umeclidinium 62.5 mcg per dose. Availability is expected in fourth quarter of 2014.</td>
<td>GSK</td>
<td>FDA NDA Approval</td>
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<td><strong>Priority Review</strong> 04/30/2014</td>
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<td>omega-3-carboxylic acids</td>
<td>Epanova™</td>
<td>Omega-3-carboxylic acids (Epanova) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. Epanova contains omega-3 in free fatty acid form as 50-60 percent EPA and 15-20 percent DHA. In clinical trials, treatment with Epanova led to significant reductions in fasting TG and non-HDL-C levels, but the effect of Epanova on cardiovascular (CV) mortality and morbidity has not been determined. The recommended dosage is 2 or 4 g once daily. It is available as 1 gm capsules.</td>
<td>AstraZeneca</td>
<td>FDA NDA Approval</td>
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<td><strong>Priority Review</strong> 05/05/2014</td>
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<td>vorapazar</td>
<td>Zontivity™</td>
<td>The FDA has approved vorapazar (Zontivity), the first protease-activated receptor-1 (PAR-1) antagonist for the reduction of thrombotic CV events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). Vorapazar has been shown to reduce the rate of a combined endpoint of CV death, MI, stroke, and urgent coronary revascularization when given in addition to aspirin and/or clopidogrel. It has not been studied as monotherapy. A boxed warning regarding bleeding risk advises that vorapazar should not be used in patients with a history of stroke, transient ischemic attack (TIA) or intracranial hemorrhage (ICH), or active pathological bleeding. The recommended dosage is one 2.08 mg tablet once daily. Launch is expected in July 2014.</td>
<td>Merck</td>
<td>FDA NDA Approval</td>
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<td><strong>Priority Review</strong> 05/08/2014</td>
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<td>travoprost</td>
<td>Izba™</td>
<td>The FDA approved travoprost 0.003% ophthalmic solution, Izba, for the treatment of open-angle glaucoma or ocular hypertension. The recommended dosage is one drop in the affected eye(s) once daily in the evening.</td>
<td>Alcon</td>
<td>FDA NDA Approval</td>
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<td><strong>Priority Review</strong> 05/15/2014</td>
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<td>vedolizumab</td>
<td>Entyvio™</td>
<td>Vedolizumab (Entyvio) is an integrin receptor antagonist approved for the treatment of adults with moderately to severely active ulcerative colitis (UC) or Crohn’s disease (CD) who have not had an adequate response to standard therapy. Progressive multifocal leukoencephalopathy (PML) and death have been associated with integrin receptor antagonist therapy; therefore, patients should be monitored for neurological signs or symptoms. Administer 300 mg intravenously over 30 minutes at zero, two, and six weeks, then every eight weeks thereafter.</td>
<td>Takeda</td>
<td>FDA BLA Approval</td>
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<td><strong>Priority Review</strong> 05/19/2014</td>
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