Extended-release (ER) and Long-acting (LA) Opioid Analgesics Safety Labeling Updates
The U.S. Food and Drug Administration (FDA) has announced class-wide safety labeling changes and new post-market study requirements for all extended release (ER) and long-acting (LA) opioid analgesics to address the misuse, abuse, addiction, overdose, and death associated with these medications. These agents are used for both cancer-related pain and non-cancer related pain. This has been partly prompted in response to a citizen petition from the Physicians for Responsible Opioid Prescribing (PROP). Labeling changes will include important new language to help health care providers tailor their prescribing decisions based on a patient’s needs. The updated indication states that these drugs are for the management of severe pain requiring daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are inadequate. The updated indication further clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER and LA opioid analgesics are not indicated for as-needed pain relief. The new requirements also add a new boxed warning cautioning that chronic maternal use of ER and LA opioid analgesics during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management by neonatology experts. NOWS can occur in a newborn exposed to opioid drugs while in the mother’s womb. Symptoms include tachypnea, trembling, poor feeding, and excessive or high-pitched crying. The FDA is also requiring manufacturers to submit post-marketing studies with the goal of further assessing the risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. Once the safety changes are finalized, modifications will also be made to the Risk Evaluation and Mitigation Strategy (REMS) to reflect the updated information. Originally approved in 2012, the REMS requires that companies make educational programs available on how to safely prescribe ER and LA opioid analgesics, as well as Medication Guides and patient counseling documents. Immediate-release (IR) opioids are not affected by this change. However, changes for IR versions could be considered at a later time.

Import Alert
An import alert has been issued for Ranbaxy’s facility in Mohali, India. Ranbaxy will remain on the import alert until it complies with the U.S. current good manufacturing practices (CGMP), with a chance that U.S. officials may detain drugs manufactured at this facility. The FDA also ordered that the Mohali facility be subject to certain terms of the consent decree of permanent injunction entered against Ranbaxy in January 2012. The decree contains provisions to ensure CGMP compliance and data integrity at certain Ranbaxy facilities, including Paonta Sahib and Dewas, India. Ranbaxy’s Paonta Sahib and Dewas facilities have been on FDA import alert since 2008. Ranbaxy is required to hire a third-party expert to conduct a thorough inspection of the Mohali facility and certify to the FDA that the facilities, methods, processes, and controls are adequate to ensure continuous compliance with CGMP. Once the FDA is satisfied that Ranbaxy is in compliance with CGMP, the firm will be permitted to resume manufacturing and distribution of FDA-regulated drugs at the Mohali facility. The FDA does not anticipate that this new action will cause a supply disruption or shortage of drugs in the U.S.

Fentanyl Patch Safety Alert
The manufacturers of the brand Duragesic® and generic fentanyl transdermal patches are being required to include color changes in long-lasting ink to the writing on the patches so that the name and strength can be seen more easily. This is part of an effort to prevent accidental exposure to the patches, which can cause serious harm and death in humans and pets. The FDA continues to learn of deaths from accidental exposure to fentanyl patches, including two additional deaths in children, since the last public FDA communication in April 2012. As the FDA continues to learn of serious harm and deaths from accidental exposure to fentanyl patches, patients and health care providers are reminded that the patches are dangerous even after use as they still contain high amounts of strong narcotic pain drug. The change is intended to enable patients and caregivers to more easily find patches on patients’ bodies and locate patches that have fallen off. Health care professionals are advised to counsel patients and their caregivers on the appropriate use, storage, and disposal of fentanyl patches.

Tesamorelin (Egrifta®) Shortage
EMD Serono anticipates a shortage of tesamorelin (Egrifta) beginning in mid-October with a complete stock-out by mid-November 2013. To reduce the duration of the shortage, EMD Serono will implement a mitigation plan. Lots of tesamorelin were scheduled to be manufactured at the end of September to facilitate drug supply replenishment, which should start by mid-December 2013. As previously announced, production of tesamorelin was halted using the NDA-approved manufacturing process to rectify issues that were not linked to the product itself. Corrective measures were developed and implemented, and production resumed in May 2013. However, due to further quality issues, until process improvement measures are completed, production will be resumed using the current NDA-approved manufacturing process to produce drug product for the U.S. market. Tesamorelin is an injectable growth hormone-releasing factor to reduce the excess in abdominal fat in HIV-infected patients with lipodystrophy.

Sources:
www.cdc.gov
www.fda.gov
www.ashp.org
www.medscape.com
www.PTCommunity.com
www.pubmed.gov

Executive Editor:
Maryam Tabatabai, PharmD

Deputy Editors:
Barbara Dowd, RPh
Raquel Holmes, RPh
Donna Johnson, PharmD
Carole Kerzic, RPh

Contact Information:
Maryam Tabatabai, PharmD
(513) 794-5265
www.MagellanMedicaid.com

Drug Information Highlights
- Janssen Biotech’s ustekinumab (Stelara®) has received approval, alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults 18 years or older. Ustekinumab is already indicated for the treatment of plaque psoriasis in adults 18 years and older who are candidates for phototherapy or systemic therapy.
- UCB’s certolizumab pegol (Cimzia®) has received approval for the treatment of active psoriatic arthritis in adults. It is already approved for the treatment of moderately to severely active rheumatoid arthritis. In addition, it is approved for Crohn’s disease and for maintaining a clinical response in adult patients with a moderately to severely active disease who have had an inadequate response to conventional therapy.
- Watson’s Oxytrol® transdermal patch is now available over-the-counter (OTC) as Oxytrol® for Women for use in women with an overactive bladder (OAB). It is the first treatment for OAB to become available OTC. Oxybutynin remains available only by prescription for men. Oxytrol and Oxytrol for Women both deliver 3.9 mg of oxybutynin per 24 hours and are applied about every four days.
- Meda Pharmaceuticals’ azelastine hydrochloride (Astepro®) nasal spray has received an expanded indication for the treatment of seasonal and perennial allergic rhinitis in patients six years and older. Astepro is already approved for the treatment of perennial and seasonal rhinitis in patients 12 years and older.
- Merck has made a business decision to voluntarily discontinue the manufacture and distribution of all strengths of Juvisync™, a fixed-dose combination of sitagliptin and simvastatin, tablets in the U.S. All products currently distributed to the market will reach their expiration date by October 2014. There are no plans to recall the already distributed product. The individual components of this combination product, sitagliptin (Januvia®) for type 2 diabetes and the statin, simvastatin, will continue to remain available.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>lidocaine</td>
<td>no trade name</td>
<td>The first-time generic for Lidoderm® Patch 5%, lidocaine, received FDA approval in August 2012 and was launched in September 2013 pursuant to a patent settlement. Lidocaine patches are indicated for the relief of pain associated with postherpetic neuralgia in adults. Up to three patches may be applied to intact skin to cover the affected area, only once for up to 12 hours within a 24-hour period.</td>
<td>Actavis</td>
<td>FDA ANDA Approval</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>no trade name</td>
<td>The FDA approved, gatifloxacin 0.5% ophthalmic solution, first-time generic for Zymaxid®. Gatifloxacin is a topical fluoroquinolone indicated for the treatment of patients 1 year of age and older with bacterial conjunctivitis caused by susceptible organisms. The recommended dose is one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1, then one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7. The product launch is expected to be during the fourth quarter of 2013.</td>
<td>Lupin</td>
<td>FDA ANDA Approval</td>
</tr>
<tr>
<td>adefovir dipivoxil</td>
<td>no trade name</td>
<td>Adefovir dipivoxil, first-time generic for Hepsera®, was approved for the treatment of chronic hepatitis B in patients 12 years of age and older. The recommended dose is 10 mg once daily orally, with or without food. A dosage adjustment is required for adults with renal impairment. Adefovir dipivoxil is available as 10 mg oral tablets.</td>
<td>Sigmapharm</td>
<td>FDA ANDA Approval</td>
</tr>
<tr>
<td>lansoprazole/ amoxicillin/ clarithromycin</td>
<td>no trade name</td>
<td>The first-time generic version for Prevpac® received FDA approval. The components (lansoprazole, amoxicillin, and clarithromycin) are indicated for the treatment of adult patients with Helicobacter pylori (H. pylori) infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence. The recommended adult oral dose is 30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin, administered together twice daily (morning and evening) for 10 or 14 days. The components are supplied in boxes of 14 daily administration cards.</td>
<td>Teva</td>
<td>FDA ANDA Approval</td>
</tr>
<tr>
<td>paclitaxel protein-bound particles</td>
<td>Abraxane®</td>
<td>The FDA approved a new indication for Abraxane as the first-line treatment of patients with metastatic adenosquamous carcinoma of the pancreas, in combination with gemcitabine. It was already approved for use in metastatic breast cancer and Non-Small cell lung cancer. The recommended dosage of Abraxane for the treatment of metastatic pancreatic adenocarcinoma is 125 mg/m² intravenously over 30 to 40 minutes on Days 1, 8, and 15 of each 28-day cycle, administering gemcitabine on the same cycle immediately after Abraxane. It is available as 100 mg of paclitaxel in a single-use vial, individually packaged in a carton.</td>
<td>Celgene</td>
<td>FDA sNDA Approval</td>
</tr>
<tr>
<td>azacitidine</td>
<td>no trade name</td>
<td>Azacitidine, first-time generic for Vidaza®, was approved by the FDA for the treatment of patients with the following: French-American-British (FAB) myelodysplastic syndrome subtypes, refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia. The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m² subcutaneously or intravenously, daily for 7 days. Patients should be premedicated for nausea and vomiting. Azacitidine for injection is available in 100 mg single-use vials.</td>
<td>Dr. Reddy's Laboratories</td>
<td>FDA ANDA Approval</td>
</tr>
<tr>
<td>capecitabine</td>
<td>no trade name</td>
<td>The first-time generic for Xeloda®, capecitabine, was approved by the FDA. Capecitabine is an oral chemotherapy agent used to treat adults with metastatic colorectal cancer, adults with metastatic breast cancer, and adjuvant treatment in patients with Dukes' C colon cancer. The capecitabine dosage is calculated based on body surface area. The recommended total daily dose is 2,500 mg/m². The tablets are taken twice daily and should be swallowed whole with water within 30 minutes after a meal. Capecitabine is available as 150 mg and 500 mg tablets.</td>
<td>Teva</td>
<td>FDA ANDA Approval</td>
</tr>
<tr>
<td>vortioxetine</td>
<td>Brintellix™</td>
<td>Vortioxetine (Brintellix) received FDA approval for the treatment of adults with major depressive disorder (MDD). The mechanism of action is thought to be through a combination of pharmacodynamic activity by the inhibition of serotonin (5-HT), as well as acting as an agonist at 5-HT1A receptors, a partial agonist at 5-HT1B receptors, and an antagonist at 5-HT3, 5-HT1D, and 5-HT7 receptors. The recommended starting dose is 10 mg administered orally once daily without regard to meals. The dose may be titrated to 20 mg/day as tolerated. Brintellix will be available by the end of 2013 as 5 mg, 10 mg, and 20 mg tablets.</td>
<td>Takeda</td>
<td>FDA NDA Approval</td>
</tr>
</tbody>
</table>