CLINICAL ALERT

MAGELLAN PHARMACY SOLUTIONS | iCORE HEALTHCARE

July 2013

Nationwide Doxycycline Shortage

The Centers for Disease Control and Prevention (CDC) has issued a health advisory regarding the continuing shortage of doxycycline and put forth recommendations for its use. In addition the nationwide shortage of oral tetracycline continues and it remains unavailable. Manufacturing issues and increased demand have resulted in drug shortages of some formulations of doxycycline, including doxycycline hyclate and doxycycline monohydrate, since January 2013. The drug is currently available from some manufacturers, but health care professionals may need to find new contacts to order supplies. The Intravenous formulation of doxycycline hyclate and the oral suspension doxycycline calcium are available. The recommendations are as follows: 1. Despite the shortage, doxycycline remains the treatment of choice for suspected rickettsial infections, including Rocky Mountain Spotted Fever (RMSF), ehrlichiosis, and anaplasmosis in patients of all ages; no alternatives can be recommended that have the same proven degree of efficacy in preventing severe morbidity and mortality. Because treatment delay can result in adverse or fatal outcome, planning for doxycycline availability is essential; 2. The efficacy of drugs other than doxycycline for Lyme disease prophylaxis following a tick bite has not been tested. Doxycycline is one of several possible antibiotics used in the treatment of Lyme disease. Common alternatives used for oral treatment of Lyme disease are amoxicillin and cefuroxime axetil. Providers should be judicious in its use following a tick bite; 3. Doxycycline should still be used for the prophylaxis and treatment of malaria according to the standard recommendations, noting other options as prophylaxis and treatment of the condition; 4. Alternatives exist for the treatment of sexually transmitted diseases (STDs). Providers should use clinical judgment in making treatment and prophylactic decisions. Updates on the availability of doxycycline and tetracycline are available on the American Society of Health-System Pharmacists (ASHP) and the Food and Drug Administration (FDA) websites.

American Thoracic Society Cystic Fibrosis (CF) Guidelines

The American Thoracic Society (ATS) has published updated Cystic Fibrosis Pulmonary Guidelines in the April 2013 issue of *American Journal of Respiratory and Critical Care Medicine*. An evidence review of chronic medications for CF lung disease was performed in 2007 to provide guidance to clinicians in evaluating and selecting appropriate treatment for individuals with this disease. The new guidelines have undertaken a new review of the literature to update the recommendations, including consideration of new medications and additional evidence on previously reviewed therapies. Inhaled aztreonam (Cayston®) now has the same recommendation as inhaled tobramycin for moderate to high disease (strength of recommendation A) as well as for mild disease (strength of recommendation B). Ivacaftor (Kalydeco™), a potentiator that activates defective CF transmembrane conductance regulator (CFTR) at the cell surface, has been added to the guidelines. For individuals with CF, six years of age and older, with at least one G551D CFTR mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life, and reduce exacerbations (strength of recommendation A). For individuals with CF, six years of age and older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations (strength of recommendation C).

Olanzapine Pamoate (Zyprexa® Relprevv™) Deaths

The FDA is investigating two unexplained deaths in patients who received an intramuscular injection of the atypical antipsychotic olanzapine pamoate (Zyprexa Relprevv). The patients died three-four days after receiving an appropriate dose of the drug, well after the three-hour post-injection monitoring period required under the Zyprexa Relprevv Risk Evaluation and Mitigation Strategy (REMS). Both patients were found to have very high olanzapine serum levels after death. Patients are required to receive the injection at a REMS–certified health care facility, to be continuously monitored at the facility for at least three hours following an injection, and to be accompanied home from the facility. The labeling contains warnings about the risk of post-injection delirium sedation syndrome. If therapy with olanzapine pamoate is started or continued in patients, health care providers should follow the REMS requirements and label recommendations. The FDA is continuing to evaluate these deaths and will provide an update as more information is available.

Angiotensin Receptor Blocker Safety

Recently, there have been concerns raised in the media about the safety of angiotensin receptor blockers (ARBs) and the increased risk of cancer, due to differing scientific opinions of FDA staff. As a result, the FDA has issued a communication aimed at patients advising them not to stop taking their ARB medication without first talking to their health care professional. Untreated hypertension can cause stroke, heart attack, heart failure, kidney damage, and other health problems. In 2010, the FDA conducted a safety review of ARBs after a published meta-analysis, reported a small but statistically significant increase of the risk of cancer in patients taking an ARB, compared to patients not taking an ARB. In July 2011, concluding evidence did not establish that treatment with ARBs increases a patient's risk of developing cancer. As part of its post-market drug safety review process, the FDA will continue to monitor ARB safety. A list of medications containing an ARB is available at: http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm#table.

FDA Advisory Panel Recommends Loosening Avandia Restrictions

On June 5–6, 2013, the FDA Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees met to review rosiglitazone (Avandia®). The focus of the 2-day hearing was the re-adjudication of the RECORD trial performed by the Duke Clinical Research Institute. In a combined meeting of separate FDA advisory committees, 20 of 26 panelists voted to recommend removing or modifying rosiglitazone's highly restrictive label and distribution channel. Five voted to keep the product's REMS as is. One panelist voted to remove the product from the market. Of the 20 panelists who voted to remove or modify the labeling and distribution system, 13 voted to modify it and 7 voted to remove the REMS entirely. The vote of the advisory panel comes 3 years after the FDA placed severe restrictions on the drug following concerns of increased cardiovascular risk. The final FDA decision is outstanding and it is unclear when the agency will make a ruling.

Drug Information Highlights

- Amedra and Lineage Pharmaceuticals have announced plans to launch epinephrine autoinjectors. Amedra plans to introduce brand Adrenaclick™, single-dose epinephrine autoinjector in June. Lineage (owned by Amedra) plans to launch single-dose generic epinephrine autoinjector, the authorized generic (AG) for Amedra Pharmaceutical's brand Adrenaclick. Brand Adrenaclick will be available as single and two-pack cartons. The AG will only be available in two-pack cartons. Both the brand and AG will be available in 0.15 mg and 0.3 mg strengths. Brand Adrenaclick and generic epinephrine autoinjectors were previously under different ownership (Shionogi and Greenstone, respectively) but manufacturing was discontinued a few years ago. They are now being re-introduced under new ownership. Adrenaclick and the AG epinephrine autoinjectors join EpiPen®, EpiPen® Jr. and Auvi-Q™ as self-injectable epinephrine products for the treatment of anaphylaxis.
- The FDA is requiring manufacturers to add information on the potential risk of thrombosis to the current Boxed Warning in the labels of all intravenous human immune globulin (IG) products and to add a Boxed Warning to the labels of all subcutaneous and intramuscular human IG products to highlight the risk of thrombosis and to add information on its mitigation. Labels for all human IG products already contain some information related to the risk of thrombosis in the current Warnings and Precautions sections.
- Teva Women's Health has received approval of Plan B One-Step®, levonorgestrel single-dose pill (1.5 mg tablet) as a nonprescription product for all women of child-bearing potential, without age or point-of-sale restrictions. In April 2013, the product was approved for nonprescription use for women as young as 15 years of age.

Sources:
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Editorial Staff:
Executive Editor:
Maryam Tabatabai, PharmD

Deputy Editors:
Donna Johnson, PharmD
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Raquel Holmes, RPh

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

FDA Approved New Molecular Entities (NMEs), Biologic Products (BLAs)/Orphan Drugs, and New Indications/New Formulations for Existing Products				
Generic Name	***Trade Name***	***Description***	***Applicant***	***FDA Status***
dabrafenib	Tafinlar®	Dabrafenib, a kinase inhibitor, is indicated for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. It is not indicated for the treatment of patients with wild-type BRAF melanoma. Confirmation of BRAF V600E mutation in tumor specimens must be obtained prior to initiation of treatment with dabrafenib. Due to the mechanism of action, dabrafenib can cause fetal harm and as such was assigned to pregnancy category D. Females of reproductive age should be advised to use highly effective contraception during treatment and for 4 weeks following discontinuation of treatment. Male patients should be advised of the risk for impaired spermatogenesis. The recommended dose of dabrafenib is 150 mg orally twice daily taken at least 1 hour before or at least 2 hours after a meal. It will be available as 50 mg and 75 mg capsules. An early third quarter 2013 launch is expected.	GlaxoSmith Kline	FDA NDA Approval 05/29/2013
trametinib dimethyl sulfoxide	Mekinist™	Trametinib, a kinase inhibitor, was approved by the FDA for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. It is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. Due to the mechanism of action, trametinib can cause fetal harm, and therefore, was assigned to pregnancy category D. Advise female patients of a reproductive age to use highly effective contraception during treatment and for 4 months after treatment, and to contact their health care provider if they suspect they are pregnant. Male patients should be advised of the risk for impaired spermatogenesis. The recommended dose of trametinib is 2 mg orally once daily taken at least 1 hour before or at least 2 hours after a meal. It will be available as 0.5 mg, 1 mg, and 2 mg tablets. An early third quarter 2013 launch is expected.	GlaxoSmith Kline	FDA NDA Approval 05/29/2013
neostigmine methylsulfate	Bloxiverz™	Bloxiverz, neostigmine methylsulfate, is the first FDA-approved form of neostigmine indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery in both adult and pediatric patients. It is administered intravenously to post-surgical patients by trained health care providers who will titrate the dosage based on twitches detected by a peripheral nerve stimulator. Administration of an anticholinergic agent, such as atropine or glycopyrrolate, is recommended prior to or concurrently with Bloxiverz. The dosage titration is the same for both adults and children. The maximum total dosage is 0.07 mg/kg or up to a total of 5 mg, whichever is less. Bloxiverz will be available in 0.5 mg/mL and 1 mg/mL in 10 mL multiple-dose vials. The manufacturer expects to launch the product in July 2013.	Eclat Pharm	FDA NDA Approval 05/31/2013
lenalidomide	Revlimid®	Celgene's lenalidomide, a thalidomide analogue, received an expanded indication for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. Lenalidomide is also approved for multiple myeloma (MM), in combination with dexamethasone, in patients who have received at least one prior therapy and for transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS), associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. Lenalidomide is only available through a restricted distribution program called the Revlimid REMS™ program.	Celgene	FDA sNDA Approval 06/05/2013
denosumab	Xgeva®	The FDA expanded the approved use of denosumab to include the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. Denosumab, a RANK ligand (RANKL) inhibitor, was initially approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors.	Amgen	FDA sBLA Approval 06/13/2013
telavancin	Vibativ®	The FDA expanded the approved indication for telavancin to include treatment of patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by *Staphylococcus aureus*. Telavancin should only be used for HABP/VABP when alternative treatments are not effective. Telavancin was originally approved for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria.	Theravance	FDA sNDA Approval 06/21/2013