FDA Updates

Recent FDA Boxed Warnings

The FDA's MedWatch program safety labeling changes for boxed warnings are compiled quarterly for drugs and therapeutic biologics where important changes have been made to the safety information. You can search these and other label changes in the Drug Safety Labeling Changes (SLC) database, where data are available to the public in downloadable and searchable formats. Boxed warnings are ordinarily used to highlight either adverse reactions so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug; or serious adverse reactions that can be prevented/reduced in frequency or severity by appropriate use of the drug; or FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.

QUINOLONE:

Edited and updated warning September 2016

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together including:

- Tendinitis and tendon rupture
- Peripheral neuropathy
- Central nervous system effects

Discontinue immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions. Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid quinolones in patients with known history of myasthenia gravis. Because fluoroquinolones have been associated with serious adverse reactions, reserve quinolones for use in patients who have no alternative treatment options for the following indications:

Avelox (moxifloxacin hydrochloride): Avelox in sodium chloride 0.8% in plastic container; moxifloxacin hydrochloride; Cipro in dextrose 5% in plastic container): Acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis.

Cipro (ciprofloxacin; ciprofloxacin hydrochloride): Acute exacerbation of chronic bronchitis, acute uncomplicated cystitis, and acute sinusitis.

Cipro XR; Noroxin (norfloxacin): Uncomplicated urinary tract infections.

Factive (gemifloxacin mesylate): Acute bacterial exacerbation of chronic bronchitis.

Levaquin (levofloxacin): Uncomplicated urinary tract infection, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis.

KRYSTEXXA (PEGLOTICASE):

Added section to warning September 2016

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA (Title Updated)

Addition of: Screen patients at risk for G6PD deficiency prior to starting Krystexxa. Hemolysis and methemoglobinemia have been reported with Krystexxa in patients with G6PD deficiency. Do not administer Krystexxa to patients with G6PD deficiency.

PLAVIX (CLOPIDOGREL BISULFATE):

Edited and updated warning September 2016

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

continued on page 49

continued from page 45

SYNJARDY (EMPAGLIFLOZIN; METFORMIN HYDROCHLORIDE):

Edited and updated warning September 2016

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally > 5 mcg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information.

If metformin-associated lactic acidosis is suspected, immediately discontinue Synjardy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

ZYDELIG (IDELALISIB):

Edited and updated warning September 2016

WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, INFECTIONS, AND INTESTINAL PERFORATION

- Fatal and/or serious hepatotoxicity occurred in 11 % to 18% of Zydelig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Zydelig as recommended.
- Fatal and/or serious and severe diarrhea or colitis occurred in 14% to 19% of Zydelig-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue Zydelig as recommended.
- Fatal and/or serious pneumonitis occurred in 4% of Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig as recommended.
- Fatal and/or serious infections occurred in 21% to 36% of Zydelig-treated patients. Monitor for signs and symptoms of infection. Interrupt Zydelig if infection is suspected.
- Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig for intestinal perforation.