Summaries of safety labeling changes approved by FDA—boxed warnings highlights, July–September 2016

As part of FDA’s MedWatch program, changes to the boxed warnings in the labeling of drugs and therapeutic biologics are compiled quarterly. These and other labeling changes are searchable in the Drug Safety Labeling Changes (SLC) database,1 where data are available to the public in downloadable and searchable formats. Boxed warnings are ordinarily used to highlight (1) an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that the reaction be considered in assessing the risks and benefits of using the drug, (2) serious adverse reactions that can be prevented or reduced in frequency or severity by appropriate use of the drug, and (3) situations in which FDA approved a drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted. The following changes to boxed warnings were identified in an October 10 search of the Drug Safety Labeling Changes (SLC) database over the date range July 1, 2016, through September 30, 2016.

Class of Systemic Fluoroquinolone Antibacterial Drugs, includes Avelox (moxifloxacin hydrochloride), Avelox in 0.8% sodium chloride solution for i.v. use (moxifloxacin hydrochloride), Cipro (ciprofloxacin; ciprofloxacin hydrochloride), Cipro IV in 5% dextrose injection (ciprofloxacin), Cipro XR (ciprofloxacin), Factive (gemifloxacin mesylate), Levaquin (levofloxacin), moxifloxacin hydrochloride, and Noroxin (norfloxacin); refer to www.accessdata.fda.gov/scripts/cder/safetylabelingchanges for specific new drug application

Updated Quinolone Boxed Warning

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

• Fluoroquinolones, including (Product), 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 (Product) immediately and avoid the use of fluoroquinolones, including (Product), in patients who experience any of these serious adverse reactions. Fluoroquinolones, including (Product), may exacerbate muscle weakness in patients with myasthenia gravis. Avoid (Product) in patients with known history of myasthenia gravis.

• Because fluoroquinolones, including (Product), have been associated with serious adverse reactions, reserve (Product) for use in patients who have no alternative treatment options for the following indications:

  (for Avelox, Avelox in 0.8% sodium chloride solution for i.v. use, moxifloxacin hydrochloride, and Cipro IV)
  • Acute bacterial sinusitis
  • Acute bacterial exacerbation of chronic bronchitis

  (for Cipro)
  • Acute exacerbation of chronic bronchitis
  • Acute uncomplicated cystitis
  • Acute sinusitis

  (for Cipro XR and Noroxin)
  • Uncomplicated urinary tract infections

  (for Factive)
  • Acute bacterial exacerbation of chronic bronchitis

  (for Levaquin)
  • Uncomplicated urinary tract infection
  • Acute bacterial exacerbation of chronic bronchitis
  • Acute bacterial sinusitis

Updated Krystexxa Boxed Warning

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 Boxed Warning*

<table>
<thead>
<tr>
<th>Updated Plavix Boxed Warning</th>
<th>Plavix Previous Boxed Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE</strong></td>
<td><strong>WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS</strong></td>
</tr>
<tr>
<td>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.</td>
<td>The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient’s CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.</td>
</tr>
</tbody>
</table>

Synjardy (empagliflozin and metformin hydrochloride)  
*Edited Boxed Warning*

<table>
<thead>
<tr>
<th>Updated Synjardy Boxed Warning</th>
<th>Synjardy Previous Boxed Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARNING: LACTIC ACIDOSIS</strong></td>
<td><strong>WARNING: RISK OF LACTIC ACIDOSIS</strong></td>
</tr>
<tr>
<td>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 (&gt;5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally &gt;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 lactic acidosis is suspected, Synjardy should be discontinued and the patient hospitalized immediately.</td>
<td>Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, Synjardy should be discontinued and the patient hospitalized immediately.</td>
</tr>
</tbody>
</table>
Zydelig (idelalisib)

Edited Boxed Warning

<table>
<thead>
<tr>
<th>Updated Zydelig Boxed Warning</th>
<th>Zydelig Previous Boxed Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, INFECTIONS, and INTESTINAL PERFORATION</strong></td>
<td><strong>WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, and INTESTINAL PERFORATION</strong></td>
</tr>
<tr>
<td>- 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.</td>
<td>- Fatal and/or serious hepatotoxicity occurred in 14% of Zydelig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Zydelig as recommended.</td>
</tr>
<tr>
<td>- 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.</td>
<td>- Fatal and/or serious and severe diarrhea or colitis occurred in 14% of Zydelig-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue Zydelig as recommended.</td>
</tr>
<tr>
<td>- 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.</td>
<td>- Fatal and serious pneumonitis can occur in Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig as recommended.</td>
</tr>
<tr>
<td>- 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.</td>
<td>- Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig for intestinal perforation.</td>
</tr>
<tr>
<td>- Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials. Discontinue Zydelig for intestinal perforation.</td>
<td></td>
</tr>
</tbody>
</table>


Office of Health & Constituent Affairs
U.S. Food and Drug Administration
DOI 10.2146/news160072e