Summaries of Safety Labeling Changes Approved by the FDA: Boxed Warnings Highlights January – March 2017

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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. Search of Drug Safety Labeling Changes (SLC) database was conducted on 3/28/2017-4/19/2017 for date range 1/1/2017 to 3/31/2017 labeling section "Boxed Warning". These and other label changes are searchable in the Drug Safety Labeling Changes (SLC) database, where data are available to the public in downloadable and searchable formats. (Drug Safety Labeling Changes are available at: <http://www.accessdata.fda.gov/>

[scripts/cder/safetylabelingchanges/?source=govdelivery&utm_medium=email&utm_source=govdelivery](https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/?source=govdelivery&utm_medium=email&utm_source=govdelivery)) 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.

Bicnu (carmustine) for injection, for intravenous use (application number 017422)

Edited Boxed Warning (additions/revisions are underlined)

WARNING: MYELOSUPPRESSION and PULMONARY TOXICITY

Myelosuppression

- Bicnu causes suppression of marrow function (including thrombocytopenia and leukopenia), which may contribute to bleeding and overwhelming infections.
- Monitor blood counts weekly for at least 6 weeks after each dose. Adjust dosage based on nadir blood counts from the prior dose. Do not administer a repeat course of Bicnu until blood counts recover.

Pulmonary Toxicity

- Bicnu causes dose-related pulmonary toxicity...
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Cerebyx (fosphenytoin sodium) injection, for intravenous or intramuscular use (application number 020450)

Edited Boxed Warning (PLR conversion; additions and/or revisions underlined)

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION RATES

The rate of intravenous Cerebyx administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute in adults and 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous Cerebyx ...

Class of Direct-acting Antiviral (DAA) Medicines for Hepatitis C Virus

Daklinza (daclatasvir) tablets, for oral use (application number 206843); Epclusa (sofosbuvir and velpatasvir) tablets, for oral use (application number 208341); Harvoni (ledipasvir and sofosbuvir) tablets, for oral use (application number 205834); Olysio (simeprevir) capsules, for oral use (application number 205123); Sovaldi (sofosbuvir) tablets, for oral use (application number 204671); Technivie (ombitasvir, paritaprevir, and ritonavir) tablets, for oral use (application number 207931); Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use (application number 206619); Viekira XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, for oral use (application number 208624); Zepatier (elbasvir and grazoprevir) tablets, for oral use (application number 208261)

Added Section to Boxed Warning

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with {PRODUCT}. HBV reactivation has been reported in HCV/HBV coinfecting patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfecting patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Class of Prescription Opioid Pain and Prescription Opioid-Containing Cough Medicines, Benzodiazepines, and Other CNS Depressants

In an effort to decrease the use of opioids and benzodiazepines, or opioids and other CNS depressants, together, the FDA is requiring Boxed Warnings and patient-focused Medication Guides for prescription opioid analgesics, prescription opioid-containing cough products, benzodiazepines, and other CNS depressants with information about the serious risks associated with using these medications at the same time. A list of included products can be found in the FDA Drug Safety Communication (approximately 400 products labels in total). FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning, August 31, 2016.

<https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm>

Added Boxed Warning (example)
WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepine or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

Latuda (lurasidone hydrochloride) tablets, for oral use (application number 200603)

Edited Boxed Warning (additions and/or revisions are underlined)
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
Suicidal Thoughts and Behaviors

...Latuda is not approved for use in pediatric patients with depression.

Linzess (linaclotide) capsules, for oral use (application number 202811)

Edited Boxed Warning (additions and/or revisions are underlined)
WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- Linzess is contraindicated in patients less than 6 years of age; in nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration.
 - Avoid use of Linzess in patients 6 years to less than 18 years of age.
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Sporanox (itraconazole) Capsules (application number 020083); Sporanox (itraconazole) oral solution (application number 020657)

Edited Boxed Warning (additions and/or revisions are underlined)

Drug Interactions: Coadministration of the following drugs are contraindicated with Sporanox Capsules: ... nisoldipine, ivabradine, ranolazine,...

Trulicity (dulaglutide) injection, for subcutaneous use (application number 125469)

Edited Boxed Warning (additions/revisions underlined)
WARNING: RISK OF THYROID C-CELL TUMORS

- In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined.
 - Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Trulicity and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity.
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Unituxin (dinutuximab) injection, for intravenous use (application number 125516)

Edited Boxed Warning (Neurotoxicity replaces Neuropathy in all instances; additions and/or revisions underlined)

WARNING: SERIOUS INFUSION REACTIONS AND NEUROTOXICITY INFUSION REACTIONS

...Neurotoxicity

- Unituxin causes serious neurologic adverse reactions including severe neuropathic pain and peripheral neuropathy.

Severe neuropathic pain occurs in the majority of patients. Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion.

In clinical studies of patients with high-risk neuroblastoma, Grade 3 peripheral sensory neuropathy occurred in 2% to 9% of patients.

In clinical studies of Unituxin and related GD2-binding antibodies, severe motor neuropathy has occurred. Resolution of motor neuropathy did not occur in all cases. Discontinue Unituxin for severe unresponsive pain, severe sensory neuropathy, and moderate to severe peripheral motor neuropathy.

Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use (application number 205649)

Edited Boxed Warning (additions/revisions are underlined)

- 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.
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MedWatch-FDA's safety alerts for medical products and monthly Drug Safety Labeling Changes are available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm>

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