Highlights of FDA Activities – 5/1/15 – 5/31/15

FDA Drug Safety Communications & Drug Information Updates:

FDA Safety Communication: Security Vulnerabilities Found with LifeCare PCA3 and PCA5 Infusion Pump Systems by Hospira 5/3/15

A security vulnerability in Hospira's LifeCare PCA3 and PCA5 Infusion Pump software was identified by an independent researcher. This vulnerability potentially allows unauthorized users to access the pump through an Ethernet or wireless connection, and remotely modify the dose delivered by the pump. No adverse events, unauthorized access, or malicious activity has currently been reported to the FDA related to this susceptibility.

FDA Drug Safety Communication: SGLT2 Inhibitors May Lead to Ketoacidosis 5/15/15

The FDA warns that SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis; this potential problem is still under investigation by the FDA and no labeling changes have occurred yet. No changes in prescribing practices are required at this time; however, patients should report if they are experiencing any signs of ketoacidosis including difficulty breathing, nausea, vomiting, abdominal pain, confusion or unusual fatigue or sleepiness. The FDA recommends that SGLT2 inhibitors be discontinued if ketoacidosis is confirmed.

FDA Drug Safety Communication: FDA cautions about dose confusion and medication errors for antibacterial drug Zerbaxa (ceftolozane and tazobactam) 5/20/15

Zerbaxa was approved as a strength of 1 g/0.5 g which indicates the strengths of ceftolozane and tazobactam respectively, however, it is dosed based on the sum of the two ingredients (1.5 g) causing dosing errors. Drug labeling will now reflect the sum of the ingredients (1.5 g) to prevent future dosing errors.

FDA Safety Communication: Unintentional Injection of Soft Tissue Filler into Blood Vessels in the Face 5/28/15

The FDA has reviewed information indicating that unintentional soft tissue filler injections into facial blood vessels can yield rare, but serious adverse effects. The filler material can cause embolization and blockage of vessels, leading to numerous possible adverse outcomes including impaired vision, blindness, skin/tissue necrosis, and stroke. Injection sites where this adverse effect has occurred most frequently include the skin between the eyebrows and nose, in and around the nose, forehead, and around the eyes.

Major Product Recalls Announced Through MedWatch:

Adrucil (fluorouracil injection, USP) 5 g/100 mL: Recall – Particulate Matter 5/5/15

Teva recalled 8 lots of fluorouracil pharmacy bulk packages (NDC 0703-3019-11 and 0703-3019-12) due to presence of particulate matter identified as an aggregate of silicone rubber pieces from a filler diaphragm and fluorouracil crystals. A complete list of recalled lots can be found on the FDA's MedWatch site (http://www.fda.gov/Safety/Recalls/ucm445584.htm).

Tiger Paw System II, Maquet Medical Systems: Recall – May Cause Tears and Bleeding in Heart Tissue 5/7/15

Surgical staple that is used to close tissue in the left atrial appendage of the heart is being recalled because incomplete closure of the staple may cause tissue tears and/or bleeding.

Avea Ventilator by CareFusion: Recall – Potential Malfunction of Pressure Transducer 5/27/15

AVEA ventilator-specific 5 psi pressure transducers may have a potential malfunction where a failure mode is developed over a period of time. If this occurs, this ventilator will stop and an alternative ventilator will be required. The recall encompasses all AVEA ventilators manufactured, serviced, and distributed globally between July 1, 2011 and March 15, 2015. A complete list of affected models and serial numbers can be obtained from the CareFusion website (http://www.carefusion.com/pdf/Alerts_and_Notices/AVEA/RC_AVEA-Affected-Serial-Numbers-Recall_SN_EN.pdf).

Dietary Supplement Recalls & Public Notifications

In May, the FDA issued notifications to the public regarding undeclared active ingredients in the following products. Patients are advised not to purchase or use these products.

Product	*Promoted Use*	*Hidden/Undeclared Drug Ingredient(s)*
Asihuri Plus Forte	Joint and nerve pain	Dexamethasone and phenylbutazone
Ginseng She Lian Wan	Joint pain, arthritis, and gout	Dexamethasone and chlorpheniramine
Jianbu Huqian Wan	Joint pain	Dexamethasone, chlorpheniramine, and furosemide
Saurean Fong Sep Lin	Backache	Dexamethasone and cyproheptadine

New Product Shortages Reported by the FDA:	*Date Initially Posted*
Calcium chloride injection, USP	5/11/15
Chloroquine phosphate tablets	5/14/15
Imipenem and cilastatin for injection, USP	5/22/15
Gemifloxacin mesylate (Factive) tablets	5/27/15

Product Discontinuations/Withdrawals

No product discontinuations/withdrawals were announced in May.

New Drug Approvals:	*Description*	*Date Approved*
Eluxadoline / Viberzi / Forest	See attached drug summary	5/27/15

New Indications:	*Description*	*Date Approved*
Moxifloxacin / Avelox / Bayer	Treatment of pneumonic plague and septicemic plague	5/8/15
Sumatriptan and naproxen sodium / Treximet / Pernix	Indication expanded to include acute treatment of migraine with or without aura in pediatric patients 12 years of age and older	5/14/15
Rifaximin / Xifaxan / Salix Pharms	Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults	5/27/15
Sirolimus / Rapamune / Wyeth	Treatment of lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects women of childbearing age	5/28/15

New Dosage Forms or Formulation:	*Description*	*Date Approved*
Glucagon for injection (synthetic) / Fresenius Kabi USA	For use as a diagnostic aid during radiologic examinations to temporarily inhibit movement of GI tract.	5/8/15
Hydrocodone bitartrate; pseudoephedrine hydrochloride; guaifenesin oral solution / Hycofenix / Mikart	A combination of hydrocodone, pseudoephedrine, and guaifenesin indicated for symptomatic relief of cough, nasal congestion, and loosening of mucus associated with the common cold.	5/14/15
Hydrocodone bitartrate; guaifenesin oral solution / Flowtuss / Mikart	A combination of hydrocodone and guaifenesin indicated for the symptomatic relief of cough and loosening of mucus associated with the common cold.	5/14/15
Paliperidone palmitate / Invega Trinza / Janssen Pharms	3-month injection indicated for treatment of schizophrenia after adequate treatment on the 1-month injectable suspension for at least 4 months	5/18/15

Tiotropium bromide; olodaterol / Stiolto Respimat / Boehringer Ingelheim	A combination of tiotropium and olodaterol, a long acting beta$_2$-adrenergic agonist indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic COPD.	5/21/15
Insulin Lispro / Humalog 200 / Eli Lilly & Co	A new 200 Units/mL concentration of insulin lispro for injection to improve glycemic control in adults and children with diabetes mellitus.	5/26/15

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Eluxadoline / Viberzi / Forest Pharmaceuticals, Inc.	
Generic Name / Brand Name / Company	Eluxadoline / Viberzi / Forest Pharmaceuticals, Inc.
Date of approval	5/27/15
Drug Class (Mechanism of Action if novel agent)	Mu-opioid receptor agonist (main); also delta-opioid receptor antagonist and kappa-opioid receptor agonist
Indication	Irritable bowel syndrome with diarrhea (IBS-D) in adults
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	75 mg and 100 mg tablets Recommended dosage: 100 mg twice daily with food; 75 mg twice daily with food in patients who do not have a gallbladder, are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors, or have mild to moderate hepatic impairment.
DEA Schedule	FDA recommended eluxadoline be classified as a controlled substance; DEA decision is pending
Date of market availability	Pending DEA scheduling, product launch anticipated in first quarter of 2016
Similar Medications (Look-Alike Sound-Alike)	Vibativ, Vibramycin
CLINICAL USE EVALUATION	
Common Adverse Effects	Adverse reactions reported in >5% of patients include: constipation, nausea, abdominal pain. Additional adverse reactions reported in >2% include upper respiratory tract infection, vomiting, nasopharyngitis, abdominal distention, bronchitis, dizziness, flatulence, rash, increased ALT, fatigue, and viral gastroenteritis.
Severe Adverse Effects	Sphincter of Oddi spasm; pancreatitis; severe constipation
Severe Drug-Drug Interactions	• Concomitant use of OATP1B1 inhibitors including but not limited to cyclosporine, gemfibrozil, rifampin, etc. may cause increased exposure to eluxadoline. Use lower dose and monitor closely. • Rosuvastatin should be lowered to the lowest effective dose due to potential OATP1B1 and BCRP substrate interactions that may increase risk for myopathy/rhabdomyolysis. • Drugs that cause constipation including alosetron, opioids, and anticholinergic drugs may increase risk for constipation-related side effects.

	• Additional CYP450 studies are being performed due to incomplete information on eluxadoline metabolism.
Severe Drug-Food Interactions	None
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	LFTs: eluxadoline is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C); dose should be adjusted if patient has mild to moderate (Child-Pugh Classes A and B, respectively) hepatic impairment Pancreatic enzymes: if elevated with acute biliary pain, consider discontinuing medication.
Used in Pediatric Areas	Safety and effectiveness has not been established in this population.
Renal or Hepatic Dosing	Discontinue/do not use in patients with severe hepatic impairment (Child-Pugh Class C); In patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment, reduce dose to 75 mg twice daily and monitor for impaired mental or physical abilities and other adverse reactions.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	• Monitor patients without gallbladder for new or worsening abdominal pain with or without nausea/vomiting. • Monitor patients for acute biliary pain with liver or pancreatic enzyme elevations • Contraindicated in patients with: o Known or suspected biliary duct obstruction or sphincter of Oddi disease/dysfunction; o Alcoholism, alcohol abuse, or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day o History of pancreatitis or structural diseases of the pancreas o Severe hepatic impairment (Child-Pugh Class C) o History of chronic or severe constipation or sequelae from constipation, or known suspected mechanical GI obstruction.
Special administration technique or considerations	• If a dose is missed, skip and take next dose at regular time; do not double up on doses to make up for a missed dose. • Take one tablet twice daily with food. • Do not take alosetron or *chronic* loperamide while taking eluxadoline due to potential for excessive constipation and related side effects. Avoid taking other medications that may cause constipation as well (anticholinergics, opioids, etc.) • Discontinue use if severe constipation for >4 days develops.
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