Highlights of FDA Activities – 2/1/15 – 2/28/15

FDA Drug Safety Communications & Drug Information Updates:

Safety Communication: Endoscopic Retrograde Cholangiopancreatography (ERCP) Duodenoscopes – Design May Impeded Effective Cleaning 2/19/2015

FDA advised health care providers that the complex design of ERCP endoscopes may impede effective cleaning. The FDA is reviewing information regarding 135 patients in the US with possible microbial transmission associated with these devices. Cleaning instructions should be closely followed to minimize risk of disease transmission. Patients should be informed of the potential benefits and risks associated with the procedure.

Safety Communication: FDA Requires Label Warnings to Prohibit Sharing of Multi-dose Diabetes Pen Devices Among Patients 2/25/2015

The FDA is now requiring that multi-dose diabetes pen devices include additional label warnings in an attempt to reduce sharing of these pens and the spread of infection. The new warning label reads "For single patient use only" and it is to be displayed on the pens and the packaging containing multiple doses of insulin and other injectable diabetes medicines.

Major Product Recalls Announced Through MedWatch:

Covidien Trellis 6 and Trellis 8 Peripheral Infusion Systems: Recall – Mislabeled Balloon Inflation Ports 2/11/2015

An error in manufacturing resulted in the mislabeling of Balloon Inflation Ports which may cause the device operator to deflate the balloons in the incorrect order, which may allow a blood clot to break-free and travel into the lungs. A total of 1126 devices were distributed in the U.S. between 6/6/14 and 11/13/14. A complete list of recalled products, models, and lot numbers can be found at FDA.gov/medicaldevices/safety/listofrecalls.

Ketorolac Tromethamine Injection by Hospira: Recall – Particulate in Glass Vials 2/11/2015

Calcium-ketorolac crystal particulate was confirmed to be found in glass fliptop vials containing ketorolac tromethamine injection solution. The vials that may contain these particulates were distributed from February 2013 to December 2014. A list of the lots being recalled can be found at fda.gov/Safety/Recalls/ucm433857.htm.

Atracurium Besylate Injection by Sagent Pharmaceuticals: Recall – Product Sterility 2/24/2015

Practices at the manufacturer's site potentially compromised product sterility of two lots of Atracurium Besylate, USP, 50 mg/5 mL single-dose vials (Lots VATA012 and VATA015) and four lots of Atracurium Besylate, USP, 100 mg/10 mL multi-dose vials (VATB012, VATB013, VATB014, and VATB017) manufactured by . Emcure Pharmaceuticals Ltd. and distributed by Sagent Pharmaceuticals from February 2014 through February 2015.

GE Healthcare Magnetic Resonance Imaging (MRI) Systems with Magnet Rundown Unit: Recall— Potential Disabling of the Magnet Rundown Unit 2/25/2015

Magnetic rundown units are designed to shut off the magnetic field of an MRI in the case of an emergency; however, there are reports that some MRI units have undergone modifications that have disabled the rundown unit. The manufacturer has issued instructions for a test to confirm that the rundown unit is connected.

Colistimethate and Rifampin Injection by Heritage Pharmaceuticals: Recall – Product Sterility 2/25/2015

Practices at the manufacturer's site potentially compromised product sterility of ten lots of Colistimethate for Injection, USP, 150 mg single-dose vial (NDC 23155-193-31) and three lots of Rifampin for Injection, USP, 600 mg single-dose vial (NDC 23155-340-31) manufactured by Emcure Pharmaceuticals Ltd. and distributed by Heritage Pharmaceuticals. These products were distributed nationwide from December 2012 through January 2015 (Colistimethate) and from October 2014 through January 2015 (Rifampin). A list of the lots being recalled can be found at http://www.fda.gov/Safety/Recalls/ucm435560.htm.

Teleflex Medical, MAQUET Servo Humidifier 163: Recall - Cracks in Connector and Connector Tubes 2/25/2015

MAQUET Servo Humidifier 163 distributed between June 2013 and November 2014 are affected by this recall. Cracks were found in the connecter when patients were being prepared for support with a ventilator. Connecter tube cracks were also found during the manufacturing process. A list of the lots being recalled can be found at http://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm435607.htm

HeartWare Ventricular Assist System Controllers by HeartWare International: Recall – Trial Controllers Susceptible to Electrostatic Discharge 2/27/2015

HeartWare Ventricular Assist System Controllers distributed during the clinical trial period prior to approval in 2012 are affected. These controllers exhibit a higher susceptibility to electrostatic discharge compared to newer controllers. An electrostatic event may cause the pump to stop which could ultimately lead to serious injury or death of a patient. The recalled units have product codes 1400 and 1401XX. It is recommended that clinicians review the risks with the patient and if medically advisable, exchange the recalled controllers with a new controller.

Dietary Supplement Recalls & Public Notifications

In February, 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)***
Yanhee Slim	Weight Loss	Lorcaserin
Nine Slim	Weight loss	Phenolphthalein
Seven Slim	Weight loss	Phenolphthalein
iNDiGO*	Weight loss	Phenolphthalein
BtRim Max*	Weight loss	Phenolphthalein
EDGE Amplified Weight Release*	Weight loss	Phenolphthalein and fluoxetine
INSANE Bee Pollen*	Weight loss	Phenolphthalein and fluoxetine
Botanical Slimming	Weight loss	Fluoxetine
Oxy ELITE Pro Super Thermogenic	Weight loss	Fluoxetine
AMPD Gold Bee Pollen*	Weight loss	Sildenafil
Tibet Babao	Sexual enhancement	Sildenafil
72HP	Sexual enhancement	Sildenafil
Black King Kong	Sexual enhancement	Sildenafil
Germany Niubian	Sexual enhancement	Sildenafil
Night Man	Sexual enhancement	Sildenafil
Libigrow XXX Treme	Sexual enhancement	Sildenafil
Wyked Labs MI-Alpha*	Prohormone – body building	Prohormones resembling anabolic steroids
Wyked Labs M14-Ment*	Prohormone – body building	
Wyked Labs Halo-70*	Prohormone—body building	
Wyked Labs 7-Ment Alpha*	Prohormone—body building	
Wyked Labs Estrastain*	Prohormone—body building	
Wyked Labs Swoll-250*	Prohormone—body building	
Formexx Black*	Anabolic/estrogen blocker—body building	
Slim X Lean*	Weight loss	

*Recalled

New Product Shortages Reported by the FDA:	***Date Initially Posted***
Ketorolac Tromethamine Injection	2/5/2015
Cefotaxime Sodium (Claforan) Injection	2/17/2015

Product Discontinuations/Withdrawals	***Date Posted***
Gentamicin Sulfate Injection, USP (Hospira) 1.2 mg/mL premix, 50 mL	2/5/15
Nitroglycerin in 5% Dextrose Injection (Hospira) 250 mL and 500 mL bottles	2/5/15
Ticarcillin disodium and clavulanate potassium for injection (Timentin, GlaxoSmithKline)	2/9/15

New Drug Approvals:	***Description***	***Date Approved***
Palbociclib / Ibrance / Pfizer	See attached drug summary	2/3/2015
Lenvatinib / Lenvima / Eisai	See attached drug summary	2/13/2015
Panobinostat / Farydak / Novartis	See attached drug summary	2/23/2015
Ceftazidime-avibactam / Avycaz / Actavis	See attached drug summary	2/25/2015
Insulin Glargine / Toujeo / Sanofi Aventis	New strength of 300 units/mL	2/25/2015

New Indications:	***Description***	***Date Approved***
Ciprofloxacin / Cipro / Bayer	Treatment and prophylaxis of plague due to *Yersinia pestis* in adults and children from birth to 17 years of age	2/2/15
Ranibizumab injection / Lucentis / Genentech	Treatment of diabetic retinopathy in patients with diabetic macular edema	2/6/15
Ruflinamide / Banzel / Eisai	Treatment of seizures associated with Lennox-Gastaut Syndrome in pediatric patients	2/17/15
Lenalidomide / Revlimid / Celgene	In combination with dexamethasone in newly diagnosed multiple myeloma	2/18/15
Azelastine nasal spray / Astepro / Meda	Relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older	2/20/15
Azelastine HCl and fluticasone propionate nasal spray / Dymista / Meda	Relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older	2/20/15

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Olopatadine 0.7% ophthalmic solution / Pazeo / Alcon	Treatment of allergic conjunctivitis	1/30/15
Lamivudine and raltegravir / Dutrebis / Merck	New tablet combination for use with other antiretroviral agents for the treatment of HIV-1 infection	2/6/15

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Palbociclib / Ibrance / Pfizer	
Generic Name / Brand Name / Company	Palbociclib / Ibrance / Pfizer
Date of approval	February 3, 2015
Drug Class (Mechanism of Action if novel agent)	Cyclin-Dependent Kinase Inhibitor
Indication	Metastatic breast cancer, HER2-negative, estrogen receptor-positive, postmenopausal women, first-line, in combination with letrozole
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	Oral capsules: 75 mg, 100 mg, 125 mg Dose: 125 mg orally once daily with food at the same time each day for 21 consecutive days, followed by 7 days off treatment of a 28-day cycle; given with letrozole 2.5 mg orally once daily continuously through the 28-day cycle
DEA Schedule	Not Applicable
Date of market availability	Early 2015
Similar Medications (Look-Alike Sound-Alike)	None
CLINICAL USE EVALUATION	
Common Adverse Effects	Decreased WBC count (95%), decreased hemoglobin (83%), lymphocytopenia (81%), neutropenia (75%), decreased platelet count (61%), leukopenia (43%), fatigue (41%), anemia (35%), upper respiratory tract infection (31%), nausea (25%), stomatitis (25%), alopecia (22%), diarrhea (21%)
Severe Adverse Effects	Pulmonary embolism, diarrhea, anemia, leukopenia, neutropenia
Severe Drug-Drug Interactions	Avoid concomitant use of strong CYP3A inhibitors and strong or moderate CYP3A inducers. Caution with CYP3A substrates
Severe Drug-Food Interactions	Grapefruit may increase palbociclib concentrations; avoid grapefruit and grapefruit juice
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	CBC prior to starting therapy, at the beginning of each cycle, on day 14 of the first 2 cycles, and as clinically indicated
Used in Pediatric Areas	Safety and efficacy have not been studied.
Renal or Hepatic Dosing	No dosage adjustments necessary in renal or hepatic impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	• There are currently no contraindications to the use of palbociclib. • Neutropenia may occur. Monitor CBC prior to initiation and at the beginning of each cycle, as well as on Day 14 of the first two cycles. • Higher infection rates have been reported. Monitor for signs and symptoms of infection. • Pulmonary embolism has been reported at a higher rate. Monitor for signs and symptoms of pulmonary embolism.
Special administration technique or considerations	• Take with food. • Capsule should not be ingested if it is broken, cracked or otherwise not intact.
Prepared by	Isaac Wong, Pharm.D. Candidate 2015

Lenvatinib / Lenvima / Eisai	
Generic Name / Brand Name / Company	Lenvatinib / Lenvima / Eisai
Date of approval	February 13, 2015
Drug Class (Mechanism of Action if novel agent)	Receptor tyrosine kinase inhibitor
Indication	Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
Comparative agent – Therapeutic interchange?	None

Dosage forms/strengths. Common Dose/sig	Oral capsules: 4 mg and 10 mg Dose: 24 mg orally once daily with or without food
DEA Schedule	Not Applicable
Date of market availability	April 2015
Similar Medications (Look-Alike Sound-Alike)	None
CLINICAL USE EVALUATION	
Common Adverse Effects	Hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia (32%), abdominal pain (31%), dysphonia (31%), constipation (29%), oral pain (25%), cough (24%), peripheral edema (21%), rash (21%)
Severe Adverse Effects	Pneumonia, hypertension, dehydration, cardiac failure, blood clot formation, liver damage, kidney damage, gastrointestinal perforation, fistula formation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhage, embryofetal toxicity, impaired TSH suppression
Severe Drug-Drug Interactions	No known drug interactions
Severe Drug-Food Interactions	No known drug interaction
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Monitor liver function tests before initiation, every 2 weeks for the first 2 months, and then at least monthly. Monitor for proteinura before initiation and periodically throughout treatment. Monitor TSH monthly. Monitor electrolytes at least monthly.
Used in Pediatric Areas	Safety and effectiveness have not been established.
Renal or Hepatic Dosing	Severe renal or hepatic impairment: 14 mg orally once daily
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	There are currently no contraindications for the use of lenvatinib. Warnings: • Increased incidence of hypertension • Increased risk of cardiac dysfunction • Risk of arterial thromboembolic events • May increase ALT and AST • Proteinuria may occur • Renal impairment has been reported • May cause QTc interval prolongation • GI perforation or fistula have been reported • Hypocalcemia • Increased risk for bleeding events • Impairs exogenous thyroid suppression • May cause fetal harm
Special administration technique or considerations	• May be taken with or without food • Take at the same time each day
Prepared by	Isaac Wong, Pharm.D. Candidate 2015

Panobinostat / Farydak / Novartis	
Generic Name / Brand Name / Company	Panobinostat / Farydak / Novartis
Date of approval	February 23, 2015
Drug Class (Mechanism of Action if novel agent)	Antineoplastic agent; Histone deacetylase (HDAC) inhibitor
Indication	Treatment for refractory multiple myeloma (in combination with bortezomib and dexamethasone) in patients having received at least two prior regimens, including bortezomib and an immunomodulatory agent
Comparative agent – Therapeutic interchange?	Carfilzomib (same indication; different mechanism)

Dosage forms/strengths. Common Dose/sig	Capsules: 10 mg, 15 mg, and 20 mg Dose: 20 mg, taken orally once every other day for 3 doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles. Treatment for an additional 8 cycles may be considered for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity
DEA Schedule	Not applicable
Date of market availability	March 2015
Similar Medications (Look-Alike Sound-Alike)	Farxiga
CLINICAL USE EVALUATION	
Common Adverse Effects	Common ADRs (Incidence > 20%): diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting Common non-hematologic ADRs (Incidence ≥ 40%): hypophosphatemia, hypokalemia, hyponatremia, and increased creatinine. Common hematologic ADRs (incidence ≥60%) thrombocytopenia, lymphopenia, leukopenia, neutropenia, and anemia
Severe Adverse Effects	
Severe Drug-Drug Interactions	• Strong CYP3A4 inhibitors (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole): Reduce panobinostat dose. • Strong CYP3A4 inducers: Avoid concomitant use with panobinostat. • Sensitive CYP2D6 substrates (atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, and venlafaxine): Avoid concomitant use with panobinostat. • Anti-arrhythmic drugs/QT-prolonging drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol): Avoid concomitant use.
Severe Drug-Food Interactions	Star fruit, pomegranate or pomegranate juice, and grapefruit or grapefruit juice are known to inhibit CYP3A enzymes. Avoid these foods when taking panobinostat.
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Complete blood count before initiating and weekly. Electrolytes and liver function tests at baseline and periodically during therapy.
Used in Pediatric Areas	Safety and efficacy have not been established.
Renal or Hepatic Dosing	**Hepatic:** Reduce the starting dose to 15 mg in patients with mild hepatic impairment and 10 mg in patients with moderate hepatic impairment. Avoid use in patients with severe hepatic impairment. **Renal:** Mild [creatinine clearance (CrCl) ≥50 to <80 mL/min] to severe renal impairment (CrCl <30 mL/min) did not impact the plasma exposure of panobinostat. Panobinostat has not been studied in patients with end stage renal disease (ESRD) or patients on dialysis. The dialyzability of panobinostat is unknown.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	There are no contraindications listed in the manufacturer's labeling. Warnings: • Severe diarrhea occurred in 25% of patients. Monitor for symptoms, treat, and interrupt therapy as recommended in labeling. • Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred. Monitor ECG and electrolytes. • Hemorrhage: Fatal and serious cases of gastrointestinal and pulmonary hemorrhage. Monitor platelet counts and transfuse as needed.

	• Hepatotoxicity: Monitor hepatic enzymes and adjust dosage if abnormal liver function tests are observed during FARYDAK therapy. • Embryo-Fetal Toxicity: can cause fetal harm. Advise women of the potential hazard to the fetus and to avoid pregnancy while taking panobinostat and for 1 month after the last dose. Sexually active men taking panobinostat should use condoms while receiving panobinostat and for at least 3 months after the last dose.
Special administration technique or considerations	• Dose should be taken at about the same time each day. • Take with or without food. • Capsules should be swallowed whole with a cup of water. Do not open, crush, or chew the capsules. • Avoid contact with the powder in the capsules. If you accidentally get powder from the capsule on your skin, wash the area with soap and water. If you accidentally get powder from the capsule in your eyes, flush your eyes with water.
Prepared by	Jessica Wu, Pharm.D. Candidate 2015

Ceftazidime-Avibactam Injection / Avycaz / Actavis	
Generic Name / Brand Name / Company	Ceftazidime-avibactam / Avycaz / Actavis
Date of approval	February 25, 2015
Drug Class (Mechanism of Action if novel agent)	Third-generation, antipseudomonal, cephalosporin plus beta-lactamase inhibitor
Indication	Treatment of adults 18 years or older with complicated intra-abdominal infections (cIAI), in combination with metronidazole; and complicated urinary tract infections (cUTI), including kidney infections (pyelonephritis) caused by certain Enterobacteriaceae and *Pseudomonas aeruginosa*. Due to limited clinical safety and efficacy data, use should be reserved for patients with limited or no alternative treatment options.
Comparative agent – Therapeutic interchange?	Ceftolozane/tazobactam
Dosage forms/strengths. Common Dose/sig	Single-use vials: 2 grams ceftazidime and 0.5 grams avibactam (2.5 g) cIAI : 2.5 g IV every 8 hrs for 5-15 days [used in combination with metronidazole] cUTI: 2.5 grams IV every 8 hrs for 7-14 days
DEA Schedule	Not applicable
Date of market availability	Second quarter of 2015
Similar Medications (Look-Alike Sound-Alike)	Ceftazidime
CLINICAL USE EVALUATION	
Common Adverse Effects	(Incidence >10%) Vomiting, nausea, constipation, and anxiety
Severe Adverse Effects	Rash, thrombocytopenia, eosinophilia, hypokalemia, acute renal failure
Severe Drug-Drug Interactions	Probenecid – decreased elimination of avibactam due to OAT inhibition
Severe Drug-Food Interactions	None
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Serum creatinine/creatinine clearance should be monitored daily in patients with changing renal function to permit dosage adjustment.
Used in Pediatric Areas	Safety and effectiveness have not been established.
Renal or Hepatic Dosing	CrCl > 50 mL/min: 2.5 grams every 8 hrs IV over 2 hrs CrCl 31-50 mL/min: 1.25 grams every 8 hrs IV over 2 hrs CrCl 16-30 mL/min: 0.94 grams every 12 hrs IV over 2 hrs CrCl 6-15 mL/min: 0.94 grams every 24 hrs IV over 2 hrs CrCl less than or equal to 5 mL/min: 0.94 grams every 48 hrs IV over 2 hrs

Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	• AVYCAZ is contraindicated in patients with known serious hypersensitivity to the drug, avibactam-containing products, ceftazidime, or other members of the cephalosporin class. • Decreased efficacy in patients with baseline CrCl of 30 to 50 mL/min • Hypersensitivity reactions • Clostridium difficile-associated diarrhea • Seizures and other neurologic events may occur
Special administration technique or considerations	• Administer IV over 2 hours. • Constitute powder with 10 mL of either: sterile water for injection, normal saline, 5% of dextrose injection, all combinations of dextrose injection and sodium chloride injection containing up to 2.5% dextrose, and 0.45% sodium chloride, or lactated Ringer's injection. Mix gently and further dilute with the same diluent (except sterile water) to achieve a total volume between 50 mL to 250 mL. • Use diluted solution within 12 hours when stored at room temperature. May be stored under refrigeration at 36 to 46°F up to 24 hours following dilution and use within 12 hours of subsequent storage at room temperature.
Prepared by	Jessica Wu, Pharm.D. Candidate 2015