Highlights of FDA Activities – 2/1/18 – 2/28/18

FDA Drug Safety Communications & Drug Information Updates:

Ocaliva (obeticholic acid): Drug Safety Communication - Boxed Warning To Highlight Correct Dosing 02/01/18
The FDA warned that Ocaliva (obeticholic acid) has been incorrectly dosed daily instead of weekly in patients with moderate to severe primary biliary cholangitis (PBC) increasing the risk of serious liver injury. To ensure correct dosing and reduce the risk of liver problems, FDA is clarifying the current recommendations for screening, dosing, monitoring, and managing PBC patients with moderate to severe liver disease taking obeticholic acid. A new Boxed Warning, has been added to the labeling to highlight this information. A Medication Guide will also be required.

Clarithromycin (Biaxin): Drug Safety Communication – Potential Increased Risk of Heart Problems or Death in Patients with Heart Disease 02/22/18
The FDA is advising caution before prescribing the antibiotic clarithromycin to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later. The FDAs recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease from a large clinical trial that first observed this safety issue. The large clinical trial, called the CLARICOR trial, observed an unexpected increase in deaths among patients with coronary heart disease who received a two-week course of clarithromycin that became apparent after patients had been followed for one year or longer. A new warning about this increased risk of death in patients with heart disease has been added to the labeling, and prescribers are advised to consider using other antibiotics in such patients.

Major Medication/Drug-Related Product Recalls Announced Through MedWatch:

Gericare Eye Wash by Kareway: Recall – Lack of Sterility 2/1/18
Kareway Products, Inc recalled 60,000 lots of Gericare Eye Wash, Sterile Eye Irrigation Solution, 4 fluid ounces (UPC 3-57896-18604-3) to the hospital, retail or consumer level due to potential microbial contamination. The affected products include the Lot#86041601 with an expiration date of 09/2019.

Acyclovir 400 mg Tablets by Apace Packaging: Recall - Product Mix-Up 2/13/18
Apace Packaging LLC recalled one lot of Acyclovir Tablet, USP, 400 mg, 50 count Unit Dose, NDC# 50268-0061-15, Lot number 19900, to the retail level due to a product mix-up. A small number of blister cards containing acyclovir tablets, 400 mg, may also include torsemide, 20 mg, tablets.

Kratom products: Recall – Serious Risks 2/21/18
The FDA announced the destruction and recall of kratom-containing dietary supplements manufactured and distributed nationwide under the brand names Botany Bay, Enhance Your Life, and Divinity by Divinity Products Distribution. The FDA reiterated its concerns regarding the safety of kratom due to its opioid content and encouraged all companies currently selling products containing kratom to take the products off the market. Companies are also urged to submit evidence to the FDA to allow evaluation of the products based on applicable regulatory pathways.

Labetalol HCl Injection by Hospira: Recall - Potential For Cracked Glass At Rim Surface Of Vials 2/23/18
Hospira recalled 3 lots (74370DD, 75035DD, 75115DD) of Labetalol Hydrochloride Injection, USP, 100 mg/20 mL Vial (NDC 0409-2267-20), and one lot (74230DD) of Labetalol Hydrochloride Injection, USP, Novaplus (NDC 0409-2267-25) to the hospital/institution level. The recall was initiated following discovery of cracks on the rim surface of vials, which is covered by the stopper and crimp seal, and may result in a lack of product sterility. Products were distributed between 4/2017 and 8/2017.

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)***
Bella All Natural Diet Capsules*	Weight Loss	Sibutramine[1]

*Recalled

[1]Sibutramine has been associated with increased cardiovascular events; discontinued 2010[FDA]

New Product Shortages Reported by the FDA:	***Date Initially Posted***
Thioridazine hydrochloride tablets	2/2/18
Deferoxamine mesylate for injection, USP	2/2/18
Fluorescein strips	2/6/18
Remifentanil (Ultiva) lyophilized powder for solution injection	2/6/18
Ketamine injection	2/16/18
Bupivacaine hydrochloride and epinephrine injection, USP	2/20/18
Bupivacaine hydrochloride injection, USP	2/20/18
Diltiazem hydrochloride injection	2/21/18

Product Discontinuations/Withdrawals	***Date Posted***
Saquinavir mesylate (Invirase, Genentech) 200 mg capsules discontinued. Saquinavir mesylate (Invirase) 500 mg tablets are still available.	2/6/18
Simvastatin (Zocor, Merck Sharp & Dohme Corp.) 5 mg tablets in bottles of 30 (NDC: 0006-0726-31) discontinued. Other tablet strengths of Zocor remain available, as do generic 5 mg tablets.	2/6/18
Simvastatin tablets (Teva Pharmaceuticals). Other generics remain available.	2/6/18
Norethindrone tablets (Nor QD, Allergan). A generic remains available.	2/23/18
Amiodarone hydrochloride tablets (Sandoz Inc.). Other generics remain available.	2/23/18
Fluoxetine capsules (Sandoz Inc.): Other generics remain available.	2/23/18
Triamterene and hydrochlorothiazide tablets (Sandoz Inc.): Other generics remain available.	2/23/18
Sumatriptan (Sumavel DosePro, Endo) 6 mg/0.5 mL. Other sumatriptan dosage forms remain available.	2/27/18
Meclizine HCl tablets (Epic). Other generics remain available	2/28/18
Peginterferon alfa-2b (Sylatron, Merck): 200 mcg and 300 mcg will be discontinued on or near December 2019, 600 mcg will be discontinued on or near December 2018. Alternative therapies for melanoma remain available.	2/28/18

New Drug Approvals:	***Description (See Attached Drug Summaries)***	***Date Approved***
Bictegravir; Emtricitabine; Tenofovir Alafenamide / Biktarvy / Gilead	A combination tablet for the treatment of HIV-1 infection in adults who are antiretroviral treatment naive or to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen for at least 3 months.	2/7/18
Tezacaftor; Ivacaftor / Symdeko / Vertex Pharmaceuticals	For the treatment of patients aged 12 years and older with cystic fibrosis who are homozygous for F508del mutation or have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.	2/12/18
Apalutamide / Erleada / Janssen	For the treatment of patients with non-metastatic castration-resistant prostate cancer.	2/14/18
Benzhydrocodone; Acetaminophen / Apadaz / KemPharm	A prodrug for the opioid agonist hydrocodone plus acetaminophen, indicated for short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.	2/23/18

New Indications:	***Description***	***Date Approved***
Ceftazidime and avibactam / Avycaz / Allergan	Treatment of adults with hospital-acquired or ventilator-associated bacterial pneumonia	2/1/18
Abiraterone acetate / Zytiga / Janssen	Use in combination with prednisone for the treatment of patients with metastatic high-risk castration sensitive prostate cancer	2/7/18
Durvalumab / Imfinzi / AstraZeneca	Treatment of patients with unresectable stage III non-small cell lung cancer (NSCLC) whose cancer has not progressed after concurrent platinum-based chemotherapy and radiation therapy.	2/16/18
Luliconazole cream 1% / Luzu Cream / Valeant	Tinea pedis, tinea cruris and tinea corporis indication expanded to include pediatric patients 12 years and older	2/20/18
Abemacilib / Verenzio / Eli Lilly and Co.	Use in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.	2/26/18

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Rabies immune globulin [human] / HyperRab / Grifols	Higher potency formulation (300 International Units/mL) allows for fewer injections	2/6/18
Efavirenz 400 mg, lamivudine 300 mg, tenofovir disoproxil fumarate 245 mg / Symfi Lo / Mylan	Tablet administered once daily as a complete regimen for treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg	2/5/18
Dexamethasone intraocular suspension / Dexycu / Icon Bioscience Inc	9% Intraocular suspension indicated for treatment of postoperative inflammation	2/9/18
Hydroxyprogesterone caproate / Makena / AMAG Pharma	Single-use 275 mg/1.1 mL auto-injector for subcutaneous administration of a dose of 275 mg once weekly	2/14/18
Amantadine extended-release / Osmolex ER / Osmotica	Extended release tablets (129 mg, 193 mg, and 258 mg) for the treatment of Parkinson's disease and drug-induced extrapyramidal reactions	2/16/18
Ibrutinib / Imbruvica / Pharmacyclics	Tablets: 140 mg, 280 mg,420 mg, 560 mg. Replace 140 mg capsules; administered as one tablet once daily	2/16/18
Lidocaine topical system / ZTlido / Scilex	Topical lidocaine 1.8% for relief of post-herpetic neuralgia pain	2/28/18

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Bictegravir + Emtricitabine + Tenofovir Alafenamide / Biktarvy / Gilead	
Generic Name / Brand Name / Company	Bictegravir; emtricitabine; tenofovir alafenamide / Biktarvy / Gilead Sciences Inc
Date of approval	2/7/18
Drug Class (Mechanism of Action if novel agent)	HIV-1 antiretroviral: integrase strand transfer inhibitor (INSTI) / nucleoside analog reverse transcriptase inhibitors (NRTIs)
Indication	A complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to bictegravir, emtricitabine, or tenofovir.
Comparative agent – Therapeutic interchange?	Once daily INSTI-based HIV regimens: Stribild, Genvoya, Triumeq
Dosage forms/strengths. Common Dose/sig	Tablet: bictegravir 50 mg, emtricitabine 200 mg, tenofovir alafenamide 25 mg. Dose: One tablet by mouth daily
DEA Schedule	NA
Date of market availability	Available
Similar Medication Names	None identified
Clinical Use Evaluation	
Common Adverse Effects	>5%: diarrhea, nausea, headache
Severe Adverse Effects	Severe acute exacerbation of hepatitis B, Immune Reconstitution Syndrome, renal impairment, lactic acidosis / severe hepatomegaly with steatosis
Severe Drug-Drug Interactions	Bictegravir inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1). Coadministration with drugs that are substrates of OCT2 and MATE1 may increase their plasma concentrations. (Dofetilide) Bictegravir is a substrate of CYP3A4 and UGT1A1. A drug that is a strong inducer of CYP3A4 and also an inducer of UGT1A1 may decrease the plasma concentrations of bictegravir and lead to loss of therapeutic effect and development of resistance. (Rifampin)
Severe Drug-Food Interactions	Can be taken with or without food
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Hepatitis B virus infection; serum creatinine, estimated creatinine clearance, urine glucose, urine protein
Used in Pediatric Areas	Safety and effectiveness in pediatric patients have not been established
Renal or Hepatic Dosing	Not recommended in patients with severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment (Child-Pugh C). No adjustments are necessary in patients with mild to moderate renal or hepatic impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindicated to be co-administered with - Dofetilide due to potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events - Rifampin due to decreased bictegravir plasma concentrations which may result in the loss of therapeutic effect and development of resistance Test for hepatitis B prior to initiating therapy. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with discontinuation of this combination. Closely monitor hepatic function

	with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue this treatment. If appropriate, anti-hepatitis B therapy may be warranted. Monitor for decreases in renal function.
Special administration technique or considerations	Avoid missing doses as it can result in development of resistance.
Prepared by	Mason McDowell, Pharm.D. Candidate 2018
Source	Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) [prescribing information]. Foster City, CA: Gilead Sciences, Inc; February 2018.

Tezacaftor + Ivacaftor / Symdeko / Vertex Pharmaceuticals	
Generic Name / Brand Name / Company	Tezacaftor; ivacaftor / Symdeko / Vertex Pharmaceuticals
Date of approval	2/12/18
Drug Class (Mechanism of Action if novel agent)	Tezacaftor increases the amount of mature FTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability of the CFTR protein at the cell surface.
Indication	Treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor.
Comparative agent – Therapeutic interchange?	Kalydeco, Orkambi
Dosage forms/strengths. Common Dose/sig	Co-packaged tablets: tezacaftor 100 mg + ivacaftor 150 mg combination tablet, ivacaftor 150 mg tablet Dose: one tezacaftor/ivacaftor tablet in the morning and one ivacaftor tablet in the evening, approximately 12 hours apart
DEA Schedule	NA
Date of market availability	Available
Similar Medication Names	Symbicort, Symadine
Clinical Use Evaluation	
Common Adverse Effects	>3%: headache, nausea, sinus congestion, dizziness
Severe Adverse Effects	Cataracts, elevated liver enzymes
Severe Drug-Drug Interactions	Tezacaftor and ivacaftor are substrates of CYP3A4. Concomitant use of CYP3A4 inducers (eg, rifampin, phenobarbital, St. John's Wort) may result in reduced exposures and reduced efficacy of tezacaftor and ivacaftor. Dose adjustments are needed when tezacaftor/ivacaftor is co-administered with strong CYP3A inhibitors (eg, itraconazole, erythromycin). Concomitant administration with P-gp substrates (eg, digoxin, cyclosporine, everolimus) may result in increased exposure to the P-gp substrates; monitor closely.
Severe Drug-Food Interactions	Ivacaftor exposure increased 3-fold when administered with fat-containing foods. Take with fat-containing foods.
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Hepatic function: AST/ALT elevations prior to initiation and every 3 months during the first year of treatment, and annually thereafter.
Used in Pediatric Areas	Approved use in pediatrics 12 – 17 years of age who are homozygous for the F508del mutation & who are heterozygous for the F508del mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Safety and efficacy in patients younger than 12 years of age has not been studied.
Renal or Hepatic Dosing	No renal adjustment is needed.

	Hepatic impairment adjustment - Mild (Child-Pugh class A) = no adjustment - Moderate (Child-Pugh Class B) = One tablet in the morning of tezacaftor/ivacaftor and no ivacaftor in the evening - Severe (Child-Pugh Class C) = One tablet in the morning (or less frequently) of tezacaftor(/ivacaftor and no ivacaftor in the evening
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	No contraindications Warnings: Elevations in AST/ALT, Concomitant use with CYP3A4 inducers, Cataracts
Special administration technique or considerations	Tablet should be swallowed whole and taken with fat-containing food. If a dose is missed and it has been 6 hours or longer skip the missed dose.
Prepared by	Mason McDowell, Pharm.D. Candidate 2018
Source	Symdeko (tezacaftor/ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals, Inc; February 2018.

Apalutamide / Erleada / Janssen	
Generic Name / Brand Name / Company	Apalutamide / Erleada / Janssen
Date of approval	2/14/18
Drug Class (Mechanism of Action if novel agent)	Androgen receptor inhibitor
Indication	For the treatment of patients with non-metastatic castration-resistant prostate cancer.
Comparative agent – Therapeutic interchange?	Enzalutamide (Xtandi). Apalutamide is the only agent in this class with an indication for non-metastatic prostate cancer.
Dosage forms/strengths. Common Dose/sig	Tablet: 60 mg. Take 240 mg (four 60 mg tablets) by mouth once daily.
DEA Schedule	NA
Date of market availability	Available
Similar Medication Names	Erlotinib
Clinical Use Evaluation	
Common Adverse Effects	>10%: fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, peripheral edema
Severe Adverse Effects	Hypertension, falls and fracture, seizure
Severe Drug-Drug Interactions	Concomitant use of medications that are sensitive substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1 may result in loss of activity of these medications. Apalutamide is a strong inducer of CYP3A4 and CYP2C19.
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up.	None specified
Used in Pediatric Areas	Safety and efficacy have not been established.
Renal or Hepatic Dosing	No renal or hepatic dose adjustment recommendations.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindications – Pregnancy. Advise males with female partners to use effective contraception during treatment and for 3 months after the last dose. Warnings and precautions: Increased risk of falls and fractures. Seizures occurred on 0.2% of patients. Discontinue permanently in patients who experience a seizure while on apalutamide. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Special administration technique or considerations	Take at the same time each day. Swallow the tablets whole. Take with or without food.
Prepared by	Megan Lenz, Pharm.D. Candidate 2018
Source	Erleada (apalutamide) [prescribing information]. Horsham, PA: Janssen Pharmaceuticals, Inc.; February 2018.

Benzhydrocodone + Acetaminophen / Apadaz / KemPharm Inc.	
Generic Name / Brand Name / Company	Benzhydrocodone, acetaminophen / Apadaz / KemPharm Inc.
Date of approval	2/23/18
Drug Class (Mechanism of Action if novel agent)	Analgesic combination; Opioid agonist and acetaminophen Benzhydrocodone is a hydrocodone prodrug; benzhydrocodone is equivalent to 4.54 mg hydrocodone or 7.5 mg hydrocodone bitartrate.
Indication	Short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Comparative agent – Therapeutic interchange?	Norco, Vicodin
Dosage forms/strengths. Common Dose/sig	Immediate-release tablet: benzhydrocodone 6.12 mg, acetaminophen 325 mg Dose: one or two tablets every 4 to 6 hours as needed for pain; do not exceed 12 tablets in a 24-hour period.
DEA Schedule	Schedule II
Date of market availability	Pending
Similar Medication Names	None identified
Clinical Use Evaluation	
Common Adverse Effects	>5%: nausea, somnolence, vomiting, constipation, pruritus, dizziness, headache
Severe Adverse Effects	Addiction, abuse, misuse, respiratory depression, neonatal opioid withdrawal syndrome, hepatotoxicity, adrenal insufficiency, severe hypotension, serious skin reactions, anaphylaxis, seizures, withdrawal
Severe Drug-Drug Interactions	Benzodiazepines and other CNS depressants can cause excessive respiratory depression. Concomitant use with CYP3A4 and CYP2D6 inhibitors can increase plasma concentration of hydrocodone. Concomitant use with CYP3A4 and inducers can decrease plasma concentration of hydrocodone. Concomitant use of serotonergic drugs with opioids can result in serotonin syndrome. Concomitant use of monoamine oxidase inhibitors and opioids can manifest in serotonin syndrome or opioid toxicity. Concomitant use of mixed agonists/antagonists and partial opioid analgesics may reduce analgesic effect. Concomitant use of muscle relaxants and hydrocodone may result in enhanced neuromuscular blocking action and respiratory depression. Concomitant use of diuretics and opioids can reduce efficacy of diuretics. Concomitant use with anticholinergic drugs may increase risk of urinary retention and/or severe constipation.
Severe Drug-Food Interactions	None identified
Important Labs Values to assess prior to order entry or at point of clinical follow up.	None specified
Used in Pediatric Areas	Safety and effectiveness have not been established

Renal or Hepatic Dosing	Use low initial doses in renal or hepatic impairment and monitor closely for adverse effects.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, cytochrome P450 3A4 interaction, acetaminophen hepatotoxicity, risk from concomitant use with benzodiazepines or other CNS depressants
Special administration technique or considerations	Use the lowest effective dosage for the shortest duration consistent with individual treatment goals.
Prepared by	Mason McDowell, Pharm.D. Candidate 2018
Source	Apadaz (benzhydrocodone and acetaminophen) [prescribing information]. Coralville, IA: KemPharm, Inc.; February 2018.