Highlights of FDA Activities – 5/1/16 – 5/31/16

FDA Drug Safety Communications & Drug Information Updates:

Drug Safety Communication: vortioxetine (Brintellix) brand name to change to Trintellix 5/2/16
The brand name of vortioxetine will change from Brintellix to Trintellix in order to prevent the risk of prescribing and dispensing errors with the blood-thinner Brilinta (ticagrelor). The appearance of the tablets will remain the same, however the National Drug Code (NDC) number will change along with the brand name.

Drug Safety Communication: new impulse–control problems due to aripiprazole 5/3/16
The FDA is warning that rare compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported to occur with the use of aripiprazole. New warnings about these compulsive behaviors will be added to drug labels and medication guides for all aripiprazole products. Health care professionals are advised to consult with patients and caregivers about the risks of these compulsive urges before prescribing, and monitor any new or increasing urges in patients already being treated with aripiprazole.

Drug Safety Communication: rare but serious skin reactions caused by olanzapine 5/10/16
A new warning is currently being added to the drug labels for all olanzapine-containing products describing a rare but serious skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Patients taking olanzapine-containing products who develop a fever with a rash and swollen lymph glands, or swelling in the face, should seek medical care right away. DRESS can result in injury to the liver, kidneys, lungs, heart, or pancreas.

Drug Safety Communication: fluoroquinolone risks outweigh benefits for certain infections 5/12/16
For patients suffering from sinusitis, bronchitis, or uncomplicated UTI, who have other treatment options, systemic fluoroquinolone treatment should be avoided as the risks outweigh their benefits. Fluoroquinolones are associated with disabling, sometimes permanent, adverse effects on tendons, muscles, joints, and the central nervous system.

FDA Alert: carmustine for injection (BiCNU) counterfeit product discovered in foreign countries 5/13/16
The FDA has identified counterfeit anti-cancer agent carmustine for injection in a few foreign countries. So far there has been no indication that counterfeit drug has entered the US or that any US patients have received a counterfeit version of this drug, but health care professionals are advised to carefully inspect product vials.

Drug Safety Communication: canagliflozin (Invokana) and increased risk of leg and foot amputations 5/18/16
The FDA warns that an ongoing clinical trial has found increased leg and foot amputations in patients being treating with canagliflozin. The FDA has not yet determined if the drug increased the risk, but advised health care professionals to follow the prescribing information and monitor patients for any new pain or tenderness, sores or ulcers, or infections in the feet or legs.

Drug Safety Communication: ketoconazole use for skin and nail infections linked to patient death 5/19/16
The FDA issued a warning urging prescribers to avoid using ketoconazole for skin and nail fungal infections due to risk of serious liver damage, adrenal gland problems, and drug interactions. Ketoconazole should not be used for skin and nail infections since they are not approved indications and the risks outweigh the benefits.

Major Product Recalls Announced Through MedWatch:

PharMEDium Sterile Preparations Compounded with Fresenius Kabi Sensorcaine-MPF (bupivacaine HCl): Recall - Presence of Glass Particulate Matter 5/9/16
PharmMEDium services, LLC recalled a number of sterile preparations that were compounded with a single recalled lot of Fresenius Kabi Sensorcaine-MPF (bupivacaine HCl). During a sample inspection, particulate matter in solution, characterized as glass was found causing Fresenius Kabi to recall that specific lot. The complete list of recalled products can be found at: http://www.pharmedium.com/

Pharmakon Pharmaceuticals: Recall of sterile drug products—possibly not sterile 5/6/16
Pharmakon is voluntarily recalling all compounded drug products distributed from March 4, 2016—April 15, 2016. The products were distributed nationwide. The recall is due to quality issues and inadequate sterility assurance.

Well Care Compounding Pharmacy (Las Vegas): Recall of all sterile products—possibly not sterile 5/18/16
Well Care is voluntarily recalling all sterile compounded products due to concerns with sterility. This applies to all compounds distributed between January 1, 2016 – April 29, 2016.

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)*
3rd Degree by Making it A Lifestyle FDA	Weight loss	Sibutramine[1] and sildenafil[2]
Black Gold X Advanced by Making it A Lifestyle FDA	Weight loss	Sibutramine[1] and sildenafil[2]
Black Label X by Making it A Lifestyle FDA	Weight loss	Sibutramine[1] and sildenafil[2]
Ginseng Powder X by SOS Telecom, Inc. FDA *	Male sexual enhancement	Sildenafil[2]
Ninja-X by SOS Telecom, Inc. FDA *	Male sexual enhancement	Sildenafil[2]
Step 2 by The Body Shot Bar FDA	Weight loss	Sibutramine[1]
Super Samurai-X by SOS Telecom, Inc. FDA *	Male sexual enhancement	Sildenafil[2]
Tiger-X by SOS Telecom, Inc. FDA *	Male sexual enhancement	Sildenafil[2]

[1]Sibutramine: oral anorexiant; risk - increased cardiovascular events; discontinued 2010FDA
[2]Sildenafil: PDE5 inhibitor; risk - interaction with nitrates leading to dangerously low blood pressure
*Recalled

New Product Shortages Reported by the FDA:

Date Initially Posted

No new shortages were announced in May 2016

Product Discontinuations/Withdrawals

Date Posted

Cyclosporine capsules Sandoz/Novartis will permanently discontinue cyclosporine 25 mg and 100 mg capsules with supply likely depleted in early 2017. An AB-rated generic remains available. 5/10/16

Imipenem and cilastatin for injection, USP Merck is discontinuing Primaxin I.V. 250 mg imipenem equivalent in trays of 25 vials, but it will continue other NDCs of Primaxin. 5/10/16

Terbinafine (Lamisil) Oral Granules Novartis is discontinuing the oral granules; no other manufacturer supplies that dosage form. Oral tablets remain available from multiple manufacturers 5/24/16

New Drug Approvals:	*Description*	*Date Approved*
Atezolizumab / Tecentriq / Genentech	See attached drug summary	5/18/16
Fluciclovine (18F) / Axumin / Blue Earth Diagnostics Ltd	Radioactive diagnostic agent for injection for use with positron emission tomography imaging in men with suspected prostate cancer recurrence	5/27/16
Daclizumab / Zinbryta / Biogen	See attached drug summary	5/27/16
Obeticholic acid / Ocaliva / Intercept Pharmaceuticals	See attached drug summary	5/27/16

New Indications:	***Description***	***Date Approved***
Ibrutinib / Imbruvica /Pharmacyclics & Janssen	Now also indicated for small lymphocytic lymphoma (SLL) with 17p deletion, a type of non-Hodgkin's lymphoma which presents primarily in the lymph nodes.	5/6/16
Lenvatinib / Lenvima / Eisai	Now also indicated for advanced renal cell carcinoma in combination with everolimus.	5/16/16
Nivolumab / Opdivo / Bristol-Myers Squibb	Now also indicated for classical Hodgkin Lymphoma (cHL) relapse or progression after hematopoietic stem cell transplantation post brentuximab.	5/17/16
Ceftaroline fosamil injection / Teflaro / Cerexa	Indication expanded to include pediatric patients 2 months to 18 years of age for acute bacterial skin and skin structure infections and community acquired pneumonia	5/27/16

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Aminolevulinic acid hydrochloride 10% gel / Ameluz gel / Biofrontera Pharma	Topical gel intended for use with photodynamic therapy using BF-RhodoLED lamp.	5/10/16
Influenza vaccine / Flucelvax Quadrivalent / Seqirus	Inactivated quadrivalent influenza vaccine for use in persons 4 years of age and older	5/10/16
Buprenorphine HCl implant / Probuphine / Braeburn Pharmaceuticals	See attached drug summary	5/26/16
Linagliptin & metformin extended-release / Jentadueto XR / Boehringer Ingelheim & Eli Lilly	Combination dosage form for once daily administration in adults with type 2 diabetes; contains 2.5 mg or 5 mg linagliptin and 1000 mg metformin	5/31/16

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Atezolizumab / Tecentriq / Genentech	
Generic Name / Brand Name / Company	Atezolizumab / Tecentriq / Genentech
Date of approval	5/18/16
Drug Class (Mechanism of Action if novel agent)	Programmed death-ligand (PD-L1) blocking antibody
Indication	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who: 1) have disease progression during or following platinum-containing chemotherapy or 2) have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	Injection: 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. Dilute prior to intravenous infusion.
DEA Schedule	Not scheduled
Date of market availability	06/2016
Similar Medications (Look-Alike Sound-Alike)	Alemtuzumab, pembrolizumab

CLINICAL USE EVALUATION	
Common Adverse Effects	Fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation.
Severe Adverse Effects	Pneumonitis, hepatitis, diarrhea, colitis, meningitis/encephalitis, neuropathy, pancreatitis, sepsis, urinary tract infections, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, acute kidney injury, pneumonia, dyspnea, abdominal pain, confusional state
Severe Drug-Drug Interactions	None known
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Monitor AST, ALT, bilirubin, and thyroid function prior to and periodically during treatment.
Used in Pediatric Areas	Safety and effectiveness have not been established in pediatric patients
Renal or Hepatic Dosing	No renal or hepatic adjustment is necessary
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Immune-mediated pneumonitis, immune-related hepatitis, immune-related colitis, immune-related endocrinopathies, other immune-related adverse reactions (meningitis/encephalitis, motor and sensory neuropathy, pancreatitis), ocular inflammatory toxicity, infection, infusion reactions have occurred. Patients should be closely monitored, and appropriate treatment administered; labeling should be consulted for recommendations on withholding or permanently discontinuing atezolizumab treatment. Embry-Fetal Toxicity- can cause fetal harm when administered to a pregnant woman.
Special administration technique or considerations	Administer the initial infusion over 60 minutes through an intravenous line. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not co-administer other drugs through the same intravenous line.
Prepared by	William Yordy, Pharm.D. Candidate 2017
Source	Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc.; May 2016.

Buprenorphine Subdermal Implant / Probuphine / Braeburn Pharmaceuticals, Inc.	
Generic Name / Brand Name / Company	Buprenorphine subdermal implant / Probuphine / Braeburn Pharmaceuticals, Inc.
Date of approval	5/26/16
Drug Class (Mechanism of Action if novel agent)	Semisynthetic mixed opiate agonist-antagonist
Indication	Opioid dependence; only indicated for use in patients stable on transmucosal buprenorphine at a dose of 8 mg per day or less
Comparative agent – Therapeutic interchange?	Compare to other forms of buprenorphine
Dosage forms/strengths. Common Dose/sig	Each implant contains 74.2 mg of buprenorphine (equivalent to 80 mg buprenorphine hydrochloride) 4 implants are inserted subdermally in the upper arm for 6 months.
DEA Schedule	Schedule III
Date of market availability	Summer 2016; restricted distribution program
Similar Medications (Look-Alike Sound-Alike)	Other buprenorphine dosage forms
CLINICAL USE EVALUATION	
Common Adverse Effects	Implant-site pain, pruritus, erythema, headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain
Severe Adverse Effects	Serotonin syndrome, adrenal insufficiency, anaphylaxis, complications from insertion and removal
Severe Drug-Drug Interactions	• CYP3A4 inhibitors (increase buprenorphine levels)

	o -azole antifungals o Macrolides (erythromycin) o HIV protease inhibitors (ritonavir, indinavir, saquinavir) • CYP3A4 inducers (induce buprenorphine metabolism, decreasing buprenorphine levels) • Antiretrovirals - possible interaction but no evaluations have been preformed • Benzodiazepines (use with caution) • Serotonergic Drugs (use with caution)
Severe Drug-Food Interactions	N/A
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Liver function tests prior to initiation and periodically during treatment
Used in Pediatric Areas	Safety and effectiveness have not been established in patients <16 years old
Renal or Hepatic Dosing	Patients with moderate or severe hepatic impairment are <u>not</u> candidates for treatment Lack of data for renal impairment, but no differences have been reported in pharmacokinetics thus far
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindications: patients sensitive to buprenorphine Warnings: o Serious complications from insertion and removal o Addiction, abuse and misuse o Respiratory depression o Central nervous system depression o Neonatal opioid withdrawal syndrome o Adrenal insufficiency o Unintentional pediatric exposure to expelled implants o Risk of opioid withdrawal with abrupt discontinuation o Risk of hepatitis, hepatic events o Risk of withdrawal in patients dependent on full agonist opioids o Treatment of emergent acute pain
Special administration technique or considerations	Implants must be inserted and removed by a trained healthcare professional. Implant is placed just under the skin on the inside of the upper arm. Follow-up with healthcare provider 1 week after insertion.
Prepared by	Shelby Denney, Pharm.D. Candidate 2017
Source	Probuphine [package insert]. Princeton, NJ: Braeburn Pharmaceuticals, Inc.; May 2016.

Daclizumab / Zinbryta / Biogen	
Generic Name / Brand Name / Company	Daclizumab / Zinbryta / Biogen
Date of approval	5/27/16
Drug Class (Mechanism of Action if novel agent)	Interleukin-2 receptor antagonist
Indication	Treatment of adult patients with relapsing forms of multiple sclerosis (MS).
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	Injection: 150 mg/mL solution in a single-dose prefilled syringe. Administer 150 milligrams subcutaneously once monthly.
DEA Schedule	Not scheduled
Date of market availability	September 2016; restricted distribution program

Similar Medications (Look-Alike Sound-Alike)	Daclizumab (Zenapax, 25 mg/5 mL) previously available for prophylaxis of acute organ rejection in patients receiving renal transplants
CLINICAL USE EVALUATION	
Common Adverse Effects	Nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, lymphadenopathy, upper respiratory tract infection, depression, rash, pharyngitis, and increased alanine aminotransferase (ALT)
Severe Adverse Effects	Hepatic injury, immune-mediated disorders, acute hypersensitivity, infections, depression, and suicidal ideation
Severe Drug-Drug Interactions	Caution using hepatotoxic drugs, especially non-prescription drugs. There were no significant affects with the systemic exposure of concomitantly administered oral midazolam (CYP3A substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), omeprazole (CYP2C19 substrate), or caffeine (CYP1A2 substrate).
Severe Drug-Food Interactions	N/A
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Monitor ALT, AST, and total bilirubin levels. Screen for tuberculosis, hepatitis B and hepatitis C prior to initiating therapy.
Used in Pediatric Areas	Safety and effectiveness in patients less than 17 years old have not been established.
Renal or Hepatic Dosing	Patients with signs and symptoms of hepatic impairment may be at increased risk for hepatotoxicity; patients with ALT or AST more than 2 times ULN were excluded from clinical trials. No renal dosage adjustments required.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindications • Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN • History of autoimmune hepatitis or other autoimmune condition involving the liver • History of hypersensitivity to daclizumab or any other component of the formulation Warnings and Precautions • Hypersensitivity reactions: Risk of anaphylaxis and angioedema. Infections: Increased risk of infections. • Immune-mediated disorders • Depression and suicide • Increased infection risk – withhold therapy if serious infection develops
Special administration technique or considerations	Administer the contents of one prefilled syringe one time every month subcutaneously in the thigh, abdomen, or back of the upper arm. Patients may be trained to self-administer. Remove from refrigerator 30 minutes prior to injection and allow to warm to room temperature.
Prepared by	Uzoma Mbogu, Pharm.D. Candidate 2018
Source	Zinbryta [package insert]. North Chicago, IL: Biogen Inc.; May 2016.

Obeticholic acid / Ocaliva / Intercept Pharmaceuticals, Inc	
Generic Name / Brand Name / Company	Obeticholic acid/Ocaliva/Intercept Pharmaceuticals, Inc
Date of approval	May 27, 2016
Drug Class (Mechanism of Action if novel agent)	Famesoid X receptor (FXR) agonist

Indication	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.
Comparative agent – Therapeutic interchange?	none
Dosage forms/strengths. Common Dose/sig	Tablets: 5 mg, 10 mg Starting dosage: 5 mg orally once daily in those who have not achieved an adequate response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA. Dosage titration: if adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of obeticholic acid 5 mg once daily and the patient is tolerating therapy, increase dosage to 10 mg once daily Maximum dosage: 10 mg once daily
DEA Schedule	Not scheduled
Date of market availability	June 2016
Similar Medications (Look-Alike Sound-Alike)	Ocusoft, oxacillin, oxaliplatin, oxazepam, oxychlorosene
CLINICAL USE EVALUATION	
Common Adverse Effects	Pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema.
Severe Adverse Effects	Liver-related adverse reactions, severe pruritus
Severe Drug-Drug Interactions	Warfarin: potential for decreased INR; monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range Bile acid binding resins: may reduce absorption of obeticholic acid. Take obeticholic acid at least 4 hours before or after the bile acid binding resin CYP1A2 substrates with narrow therapeutic index: increased exposure. Therapeutic monitoring of CYP1A2 substrates is recommended when co-administered with obeticholic acid.
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Monitor for elevations in liver biochemical tests and development of liver related adverse reactions Monitor for changes in serum lipid levels during treatment
Used in Pediatric Areas	Safety and effectiveness have not been established in pediatric patients
Renal or Hepatic Dosing	Plasma exposure to obeticholic acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C). Dose adjustment of obeticholic is recommended for patients with moderate and severe hepatic impairment, with a starting dose of 5 mg once weekly. No dosage adjustment is needed in patients with mild hepatic impairment or with renal impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindicated in patients with complete biliary obstruction. Monitor for elevations in liver biochemical tests and development of liver related adverse reactions. Monitor for changes in serum lipid levels. Monitor for severe pruritus; if intolerable can consider use of an antihistamine or bile acid binding resin, reduced dose, or temporary interruption in therapy.
Special administration technique or considerations	Take with or without food For patients taking bile acid binding resins, take obeticholic acid at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible.
Prepared by	William Yordy, PharmD Candidate 2017
Source	Ocaliva [package insert]. New York, NY: Intercept Pharmaceuticals, Inc.; May 2016.