College of Pharmacy and Pharmaceutical Sciences
WASHINGTON STATE UNIVERSITY

Drug Information Center

Highlights of FDA Activities – 7/1/19 – 7/31/19

FDA Drug Safety Communications & Drug Information Updates:

Oral oxitriptan (5-HTP) Compounding – FDA Guidance Issued 7/5/19
The FDA issued a guidance informing stakeholders that it does not plan to take regulatory action against compounders who use oxitriptan bulk substance to compound oral drugs for identified individuals with tetrahydrobiopterin (BH4) deficiency. The FDA had previously evaluated oxitriptan for inclusion on the bulk products available for compounding as a treatment for depression or insomnia, and did not include it for these uses.

Tofacitinib (Xeljanz, Xeljanz XR) – Increased Clot Risk at Higher Doses 07/26/19
The FDA approved warnings about an increased risk of blood clots and death with the 10 mg twice daily dose of tofacitinib used in ulcerative colitis, and limited use in ulcerative colitis to patients who are not treated effectively or who experience severe side effects with other medications. The higher dose should only be used for the shortest duration needed. Tofacitinib therapy should be discontinued in patients with symptoms of thrombosis, and tofacitinib use should be avoided in those at higher risk for thrombosis.

Curaleaf Inc. Cannabidiol Products – Unsubstantiated Claims 7/23/19
The FDA issued a warning letter to Curaleaf Inc with regard to selling unapproved cannabidiol products which have been marketed online with unsubstantiated claims that the products treat cancer, Alzheimer's disease, opioid withdrawal, pain, and pet anxiety.

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

SmartSite Syringe from Becton Dickinson & Company: Recall – Risk of Leaks 7/1/19
Becton Dickinson (BD) recalled SmartSite Syringe Administration Sets (Lot number 18045218) distributed from 5/11/18 to 9/14/18 due to leaking of the sets. The infusion sets are intended to be used with the BD Alaris or Medley Syringe Pumps, Module 8110, and are primarily used to provide therapies in neonatal intensive care units.

Fluorouracil injection from Fresenius Kabi USA: Recall - Potential for Glass Particulate 7/2/19
Fresenius Kabi recalled Fluorouracil injection, USP 5 g/100 ml (50 mg/ml), 100 ml fill in 100 ml vials (lot numbers 6120341 and 6120420) distributed between 12/6/18 and 2/20/19, after finding glass particulate in five vials retained for quality control inspection.

Ophthalmic Products from Altaire Pharmaceuticals, Inc: Recall – Lack of Sterility Assurance 7/2-3/19
Altaire Pharmaceuticals, Inc. recalled multiple prescription and over-the-counter ophthalmic formulations marketed under Perrigo, CVS Health, and Walgreens labels including neomycin and polymyxin B and bacitracin zinc ophthalmic ointment, neomycin and polymyxin B and dexamethasone ophthalmic ointment, neomycin and polymyxin B and bacitracin zinc and hydrocortisone acetate ophthalmic ointment, polymyxin B and bacitracin zinc ophthalmic ointment, bacitracin ophthalmic ointment, sulfacetamide sodium ophthalmic ointment, Puralube ophthalmic ointment, lubricant eye drops, gel drops, and ointments, and ophthalmic decongestants. Refer to the FDA website for specific NDC and lot numbers for Perrigo, CVS Health and Walgreens products recalled.

Alaris Pump Model 8100 Infusion Sets by Becton Dickinson: Recall – Over-infusion or Unintentional Delivery 7/18/19
Becton Dickinson (BD) recalled infusion sets for use with the Alaris Pump due to a variation in the wall thickness that may prevent full occlusion by the pump, leading to faster than planned drug delivery or unintentional drug delivery. A complete list of recalled infusion sets can be found at the BD site.

Antihemophilic Factor (Recombinant), Kogenate from Bayer: Recall - Mislabeling of Drug Vials 7/22/19

Bayer recalled 2 lots of Kogenate FS antihemophilic factor (recombinant) 2000 IU vials (lot numbers 27118RK & 27119CG) due to mislabeling. Certain vials in these lots were labeled as Kogenate FS but contain antihemophilic factor (recombinant) pegylated-aucl 3000 IU (Jivi). The affected lots were distributed from 2/5/19 to 7/15/19.

Drospirenone and Ethinyl Estradiol 3 mg/0.02 mg from Jubilant Cadista Pharmaceuticals: Recall-Dissolution Issues 7/25/19

Jubilant Cadista Pharmaceuticals recalled drospirenone and ethinyl estradiol tablets USP 3 mg/0.02 mg 28 x 3 blister packs (lot number 183222, NDC 59746-763-43, exp 11/2020) due to impaired tablet dissolution.

Dietary Supplement Recalls & Public Notifications

Notifications were issued regarding undeclared active ingredients or contaminants in the following products. Patients are advised not to purchase or use these products.

Product	***Promoted Use***	***Undeclared Ingredient(s) or Contaminants***
Big Penis	Sexual Enhancement	Sildenafil[1]
Black Storm	Sexual Enhancement	Sildenafil[1]
Boss Lion 9000	Sexual Enhancement	Sildenafil[1]
De Guo Heijin Gang	Sexual Enhancement	Sildenafil[1]
Herb Viagra	Sexual Enhancement	Sildenafil[1]
Herbal Doctor Remedies*	Various	43 products recalled; marketed without FDA approval for treatment of disease
Le Pepa Negra	Sexual Enhancement	Sildenafil[1]
Odimafo Powerful tablet 200 mg	Sexual Enhancement	Sildenafil[1]
Omega-3 1000 (DaVinci Labs, Lot 35532200)*	Omega-3 supplement	Undeclared fish allergen
Plant VIgra	Sexual enhancement	Sildenafil[1]
Reduktis Max	Weight loss	Sibutramine[2]
Shengjingpian	Sexual Enhancement	Sildenafil[1]
Vigour 800 mg	Sexual Enhancement	Sildenafil[1]

*recalled

[1]Sildenafil is an active ingredient in Viagra, an FDA- approved prescription drug for erectile dysfunction; it may interact with nitrates to lower blood pressure to dangerous levels.

[2]Sibutramine has been associated with increased cardiovascular events; it was removed from market for safety reasons in 2010[FDA]

New Product Shortages	***Date Initially Posted***
Primaquine phosphate	7/19/19
Vinblastine sulfate injection	7/23/19

Product Discontinuations/Withdrawals	***Date Posted***
Metaproterenol sulfate tablets USP (Par); a syrup formulation currently remains available.	7/12/19
Ribavirin capsules, tablet (Kadmon Pharmaceuticals); remains available from other manufacturers	7/12/19
Stavudine Capsules 20 and 40 mg (Mylan); remains available from other manufacturers	7/17/19
Omeprazole 40 mg capsules (Teva); remains available from other manufacturers	7/17/19
Naratriptan hydrochloride 1 mg tablets (Mylan); remains available from other manufacturers	7/17/19
Gadopentetate dimeglumine (Magnevist, Bayer) injection; alternative imaging agents are available	7/17/19
Epirubicin Hydrochloride 2 mg/ 1 ml injection (Cipla); remains available from other manufacturers	7/17/19
Epirubicin Hydrochloride 2 mg/ 1 ml injection (Teva); remains available from other manufacturers	7/17/19
Carbidopa/levodopa SR tablet (Sinemet CR, MSD); remains available from generic manufacturers	7/17/19
Flumazenil injection 0.1 mg/1 mL (Mylan); remains available from other manufacturers	7/19/19
Metformin hydrochloride 500 mg, 750 mg ER tablets (Teva); remains available from other manufacturers	7/22/19
Vardenafil 5 mg (Levitra, Bayer); Bayer will continue to market the 10 mg and 20 mg strengths	7/25/19
Mometasone furoate 0.1% cream (Elocon, MSD); remains available from other manufacturers	7/29/19

New Drug Approvals:	***Description (See Attached Drug Summaries)***	***Date Approved***
Selinexor / Xpovio/ Karyopharm Therapeutics Inc.	A nuclear export inhibitor indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody	7/3/19
Imipenem, cilastatin, and relebactam / Recarbrio / Merck Sharp & Dohme	Antibacterial for treatment of complicated urinary tract infections and complicated intra-abdominal infections	7/17/19
Ferric maltol / Accrufer / Shield Therapeutics	Oral iron product for treatment of iron deficiency in adults	7/25/19
Darolutamide / Nebeqa / Bayer	Androgen receptor inhibitor for treatment of non-metastatic castration-resistant prostate cancer	7/31/19

New Indications:	***Description***	***Date Approved***
Gadobutrol / Gadavist / Bayer	To assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease (CAD)	7/12/19
Apremilast / Otezla / Celgene	Treatment of adult patients with oral ulcers associated with Behcet's disease	7/19/19
Pembrolizumab / Keytruda / Merck Sharp & Dohme Corp.	Treatment of patients with recurrent locally advanced or metastatic esophageal squamous cell cancer with tumors expressing PD-L1 and with disease progression after one or more lines of systemic therapy	7/31/19

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Immune globulin subcutaneous, human-klhw / Xembify / Grifols Therapeutics	A 20% immune globulin solution for subcutaneous injection indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older.	7/3/19
Amlodipine / Katerzia / Slivergate Pharmaceuticals	Oral suspension, 1 mg/ml, for the treatment of hypertension and coronary artery disease	7/8/19
Adelimumab-bwwd / Hadlima / Samsung Bioepis	Biosimilar to Humira (adalimumab), marketing delayed until 2023	7/23/19
Duloxetine delayed-release capsules / Drizalma Sprinkle /	Delayed-release capsules: 20, 30, 40, and 60 mg. Capsules may be swallowed whole or opened and sprinkled over applesauce or administered via nasogastric tube.	7/19/19
Inuslin human in 0.9% sodium chloride injection / Myxredlin / Baxter	Ready-to-use insulin for intravenous infusion	7/23/19
Rituximab-pvvr / Ruxience / Pfizer	Biosimilar to Rituxan, approved for treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and granulomatosis with polyangiitis and microscopic polyangiitis	7/23/19
Glucagon nasal / Baqsimi / Eli Lilly & Co	Nasal powder, for treatment of severe hypoglycemia (see attached drug summary)	7/24/19
Bivalirudin / Angiomax RTU / Maia	Injection: 250 mg/50 mL in a single-dose ready-to-use vial	7/25/19

Compiled by:

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Selinexor / Xpovio / Karyopharm Therapeutics	
Generic Name / Brand Name / Company	Selinexor / Xpovio / Karyopharm Therapeutics
Date of approval	7/3/19
Drug Class (Mechanism of Action if novel agent)	Reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus, reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells.
Indication	Indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths	Tablet: 20 mg tablet
Common Dose/sig	Starting dose: 80 mg (four 20 mg tablets) by mouth on days 1 and 3 of each week until disease progression or unacceptable toxicity. Consult prescribing information for dosage reductions for adverse reactions.
DEA Schedule	None
Date of market availability	Available
Similar Medication Names	Seladin, Selara
Clinical Use Evaluation	
Common Adverse Effects	>20%: thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, upper respiratory tract infections
Severe Adverse Effects	Thrombocytopenia, hemorrhage, neutropenia, gastrointestinal toxicity, hyponatremia, infection, neurologic toxicity
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.	CBC, standard blood chemistry, and body weight at baseline and during treatment as clinically indicated. Monitor more frequently during the first two months of treatment.
Used in Pediatric Areas	Safety and efficacy not established in pediatric patients.
Renal or Hepatic Dosing	No clinically significant differences in the pharmacokinetics of selinexor were observed in mild to severe renal impairment or mild hepatic impairment. The effect of end-stage renal disease (Cl_{CR} <15 mL/min) or hemodialysis on selinexor is unknown. The effect of moderate and severe hepatic impairment on selinexor pharmacokinetics is unknown.

Selinexor continued…	
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	No contraindications Warnings: Thrombocytopenia: monitor platelet counts at baseline, during treatment and as clinically indicated. Monitor for bleeding. Manage thrombocytopenia with dose interruption, reduction, and supportive care. Neutropenia: Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Manage with dose interruption and/or reduction and granulocyte colony-stimulating factors (G-CSFs). Gastrointestinal Toxicity: Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetics and supportive care. Hyponatremia: Monitor serum sodium levels at baseline, during treatment, and as clinically indicated. Correct for concurrent hyperglycemia and high serum paraprotein levels. Infections: Monitor for signs/symptoms of infection and treat promptly. Neurological Toxicity: Avoid taking selinexor with other medications that may cause dizziness or confusion. Avoid situations where dizziness or confusional state may be a problem. Optimize hydration status, blood counts and concomitant medications to avoid dizziness or confusion. Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential, and males with a female partner of reproductive potential, of the potential risk to a fetus and use of effective contraception.
Special administration technique or considerations	Take each dose at approximately the same time of day, swallowing tablets whole with water. Starting dosage of dexamethasone is 20 mg by mouth with each dose of selinexor on days 1 and 3 of each week. Provide concomitant 5-HT3 antagonist and/or other anti-nausea agents prior to and during treatment. Advise patients to maintain adequate fluid and caloric intake during treatment; consider IV hydration for patients at risk of dehydration.
Prepared by	Diana Forrest
Source	Xpovio [prescribing information] Newton, MA: Karyopharm Therapeutics Inc.; July 2019.

Imipenem, cilastatin, and relebactam / Recarbrio / Merck	
Generic Name / Brand Name / Company	Imipenem, cilastatin, and relebactam / Recarbrio / Merck
Date of approval	7/16/19
Drug Class (Mechanism of Action if novel agent)	Carbapenem antibacterial (imipenem) with renal dehydropeptidase inhibitor (cilastatin) and beta-lactamase inhibitor (relebactam)
Indication	Treatment of complicated urinary tract infection or complicated intra-abdominal infection caused by susceptible gram-negative bacteria in adults with limited or no treatment alternatives
Comparative agent – Therapeutic interchange?	Colistin; determined by culture and sensitivity
Dosage forms/strengths	Injection: 1.25 g as sterile powder in single-dose vial containing imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg
Common Dose/sig	Dose: 1.25 g by IV infusion over 30 minutes every 6 hours
DEA Schedule	None
Date of market availability	Later this year
Similar Medication Names	Imipenem/cilastatin
Clinical Use Evaluation	
Common Adverse Effects	>2%: diarrhea, nausea, headache, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, phlebitis/infusion site reactions, pyrexia, hypertension
Severe Adverse Effects	Hypersensitivity reactions, seizures
Severe Drug-Drug Interactions	Avoid concomitant use with ganciclovir, valproic acid, divalproex sodium
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Renal function, to determine dose
Used in Pediatric Areas	Efficacy and safety not established in pediatric patients
Renal or Hepatic Dosing	Adjust dose in renal impairment: 1 g every 6 hours if CrCl 60 to 89 mL/min, 0.75 g every 6 hours if CrCl 30 to 59 mL/min, and 0.5 g every 6 hours if CrCl 15 to 29 mL/min or end-stage renal disease on hemodialysis; no adjustment required in hepatic impairment
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Use only to treat infections caused by susceptible organisms and when limited or no other treatment alternatives are available. Contraindicated in patients with known severe hypersensitivity to any of the product ingredients Warnings: Hypersensitivity reactions Seizures Clostridium difficile-associated diarrhea
Special administration technique or considerations	Infuse over 30 minutes
Prepared by	Terri Levien
Source	Recarbrio (imipenem, cilastatin, and relebactam) for injection [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; July 2019.

Ferric maltol / Accrufer / Shield Therapeutics	
Generic Name / Brand Name / Company	Ferric maltol / Accrufer / Shield Therapeutics
Date of approval	7/25/19
Drug Class (Mechanism of Action if novel agent)	Non-salt-based iron replacement product
Indication	Treatment of iron deficiency in adults
Comparative agent – Therapeutic interchange?	Ferric pyrophosphate, ferrous gluconate, ferrous sulfate, ferrous fumarate, ferrous carbonate, carbonyl iron
Dosage forms/strengths	Capsules: 30 mg
Common Dose/sig	Dose: 30 mg twice daily
DEA Schedule	None
Date of market availability	Not known
Similar Medication Names	Accupril, ferric polymaltose
Clinical Use Evaluation	
Common Adverse Effects	>1%: flatulence, diarrhea, constipation, feces discolored, abdominal pain, nausea, vomiting, abdominal discomfort/distension
Severe Adverse Effects	None reported
Severe Drug-Drug Interactions	Dimercaprol: increased nephrotoxicity risk, avoid concomitant use Separate administration from oral medications by at least 4 hours for medications where reductions in bioavailability may have clinically important effects on efficacy or safety
Severe Drug-Food Interactions	Food decreases bioavailability of iron after ferric maltose administration
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Ferritin levels
Used in Pediatric Areas	Safety and efficacy have not been established
Renal or Hepatic Dosing	No adjustments required
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindicated in patients with history of hypersensitivity to any of the product ingredients, hemochromatosis or other iron overload syndromes, or receiving repeated blood transfusions Warnings: Inflammatory bowel disease: avoid use in patients with an active IBD flare Iron overload Risk of overdose with accidental ingestion: keep out of reach of children
Special administration technique or considerations	Administer 1 hour before or 2 hours after a meal
Prepared by	Terri Levien
Source	Accrufer (ferric maltose) capsules [prescribing information]. Gateshead Quays, UK: Shield Therapeutics; July 2019.

Darolutamide / Nubeqa / Bayer	
Generic Name / Brand Name / Company	Darolutamide / Nubeqa / Bayer
Date of approval	7/30/19
Drug Class (Mechanism of Action if novel agent)	Androgen receptor inhibitor
Indication	Treatment of patients with non-metastatic castration-resistant prostate cancer
Comparative agent – Therapeutic interchange?	Apalutamide, enzalutamide
Dosage forms/strengths	Tablets: 300 mg
Common Dose/sig	Dose: 600 mg (two 300 mg tablets) orally twice daily
DEA Schedule	None
Date of market availability	Available
Similar Medication Names	Daratumumab
Clinical Use Evaluation	
Common Adverse Effects	>2%: fatigue, pain in extremity, rash
Severe Adverse Effects	Adverse reactions most commonly prompting dose reduction included fatigue, hypertension, and nausea
Severe Drug-Drug Interactions	Combined P-glycoprotein and strong/moderate CYP3A inducers: avoid concomitant use Combined P-glycoprotein and strong CYP3A inhibitors: monitor for adverse reactions BCRP substrates: avoid if possible
Severe Drug-Food Interactions	Increased bioavailability with food; administer with food
Important Labs Values to assess prior to order entry or at point of clinical follow up.	None
Used in Pediatric Areas	Safety and efficacy not established in pediatric patients
Renal or Hepatic Dosing	In severe renal impairment and in moderate hepatic impairment, reduce dose to 300 mg twice daily. No dosage adjustment is required in mild to moderate renal impairment or mild hepatic impairment. There is no data in end stage renal disease or severe hepatic impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	No contraindications listed in product labeling. Warnings: Embryo-fetal toxicity: advise males with female partners of reproductive potential to use effective contraception
Special administration technique or considerations	Patients should receive gonadotropin-releasing hormone analog concurrently or have had bilateral orchiectomy. Administer with food. Tablets should be swallowed whole.
Prepared by	Terri Levien
Source	Nubeqa (darolutamide) tablets [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019.

Glucagon / Baqsimi / Lilly USA	
Generic Name / Brand Name / Company	Glucagon / Baqsimi / Lilly USA
Date of approval	7/24/19
Drug Class (Mechanism of Action if novel agent)	Antihypoglycemic agent
Indication	Treatment of severe hypoglycemia in patients with diabetes ages 4 years and older
Comparative agent – Therapeutic interchange?	Glucagon injection
Dosage forms/strengths	Nasal powder: 3 mg supplied in an intranasal device
Common Dose/sig	Dose: 3 mg administered as one actuation of the intranasal device into one nostril; dose does not need to be inhaled. If no response after 15 minutes, an addition dose may be administered while awaiting emergency assistance
DEA Schedule	None
Date of market availability	August 2019
Similar Medication Names	Glucagon Emergency Kit
Clinical Use Evaluation	
Common Adverse Effects	>10%: nausea, vomiting, headache, upper respiratory tract irritation, watery eyes, redness of eyes, itchy nose, throat and eyes
Severe Adverse Effects	Anaphylaxis
Severe Drug-Drug Interactions	Beta-blockers: patients taking beta-blockers may have a transient increase in heart rate and blood pressure Indomethacin: nasal glucose may lose its ability to raise glucose or may product hypoglycemia Warfarin: increased anticoagulant effect of warfarin
Severe Drug-Food Interactions	None known. Oral carbohydrates should be administered once patient responds
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Blood glucose at follow-up
Used in Pediatric Areas	Safety and efficacy have not been established in children younger than 4 years
Renal or Hepatic Dosing	No dosing adjustments required
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindicated in patients with pheochromocytoma, insulinoma, or known hypersensitivity to any of the product ingredients Warnings: Lack of efficacy in patients with decreased hepatic glycogen, such as states of starvation, adrenal insufficiency, or chronic hypoglycemia
Special administration technique or considerations	Keep in shrink wrapped tube until ready to use Administer by inserting the tip into one nostril and pressing the device plunger all the way until the green line no longer shows
Prepared by	Terri Levien
Source	Baqsimi (glucagon) nasal powder [prescribing information]. Indianapolis, IN: Lilly USA, LLC; July 2019.