College of Pharmacy and Pharmaceutical Sciences
WASHINGTON STATE UNIVERSITY

Drug Information Center

Highlights of FDA Activities – 3/1/19 – 3/31/19

FDA Drug Safety Communications & Drug Information Updates:

ARB Drug Products and Nitrosamine Impurity 3/1/19
The FDA provided updated information on the recall of multiple generic angiotensin II receptor blocker products containing an impurity N-nitroso-N-methyl-4-aminobutyric acid (NMBA), a potential human carcinogen. This is in addition to the previously identified nitrosamines N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA). Updated information on the ARB recalls can be found on the FDA site.

Risks Associated with Investigational Use of Venetoclax (Venclexta) in Multiple Myeloma 3/21/19
The provided a warning about the risks associated with the investigational use of venetoclax for multiple myeloma. Interim results of a study evaluating venetoclax combined with bortezomib and dexamethasone demonstrated an increased risk of death in patients receiving venetoclax compared with control. Enrollment in the study was discontinued, and enrollment in other studies of venetoclax for multiple myeloma were suspended. Patients taking venetoclax for approved indications should continue taking their medication.

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

ARB Recalls March 2019
The FDA site was updated on 3/1, 3/20, 3/22, 3/25, and 3/29 with additional information on ARB recalls due to impurities in the active pharmaceutical ingredient. In March AurobindoPharma expanded its recall to include 38 additional lots of valsartan and amlodipine/valsartan combination tablets due to the presence of NDEA. Repackager American Health Packaging also recalled one lot of valsartan manufactured by AurobindoPharma and packaged by American Health Packaging. Torrent Pharmaceuticals Limited expanded its recall to include 144 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide tablets due to the presence of NMBA. Legacy Pharmaceutical Packaging recalled 40 repackaged lots of losartan following the recall initiated by Camber Pharmaceuticals in February. Updated information on the ARB recalls can be found on the FDA site.

Drospirenone and ethinyl estradiol tablets by Apotex Corp: Recall – Incorrect tablet arrangement 3/4/19
Apotex recalled four lots of drospirenone 3 mg and ethyl estradiol 0.3 mg tablets, USP (NDC 60505-4183-3) that may contain defective blisters with incorrect tablet arrangements or missing tablets. The affected product is packaged in packs of 3 within an outer carton. The recalled lots are 7DY008A, 7DY009A, 7DY010A, and 7DY011A.

Pilocarpine 0.1% Ophthalmic Solution from Stokes Healthcare Inc.: Recall - High Level of Preservative 3/13/19
Stokes Healthcare Inc. recalled 1 lot of 81 units of Pilocarpine 0.1% Ophthalmic Solution, to the consumer and veterinarian office levels. The ophthalmic solution has been found to contain a higher level of the preservative benzalkonium chloride than is typical and could result in irreversible dry eye syndrome.

Sodium Bicarbonate Injection, 8.4% USP from Hospira, Inc.: Recall - Particulate Matter 3/15/19
Hospira, Inc., recalled lot numbers 79-238-EV, 79-240-EV and 80-088-EV, NDC# 0409-6625-02, of 8.4% Sodium Bicarbonate Injection USP, 50 mEq/50 mL (1 mEq/mL), to the Hospital/Institution level following observation of particulate matter, confirmed as glass.

Levoleucovorin Injection from Mylan Institutional LLC: Recall - Particulate Matter 3/18/19
Mylan Institutional LLC recalled two lots (APB032 and APB033) of Levoleucovorin Injection, 250 mg/25 mL (NDC 67457-601-30) to the consumer/user level following detection of particulate matter, later identified as copper salts, during 12-month stability testing. The lots were manufactured by Alidac Pharmaceuticals Limited and distributed by Mylan Institutional LLC.

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***
Bluefusion capsules, Ata Int*	Sexual enhancement	Sildenafil[1], tadalafil[1], desmethyl carbodenafil[1], dithiodesmethyl carbodenafil[1], scutellarin, daidzein
DG/Health NATURALS Baby Cough Syrup + Mucus, Kingston Pharma*	Cough, Throat irritation	Bacillus cereus / Bacillus circulans
Leopard Miracle Honey, by USA Less*	Sexual enhancement	Sildenafil[1]
Sunstone Organics White Vein Kratom capsules and powder (Lot 119)*	Pain	Salmonella
Sunstone Organics Maeng Da Kratom capsules and powder (Lot 124A)*	Pain	Salmonella

*recalled

[1]Sildenafil, tadalafil, and PDE-5 inhibitor analogs may interact with nitrates to lower blood pressure to dangerous levels

New Product Shortages	***Date Initially Posted***
Erythromycin ophthalmic ointment	3/5/19
Eprosartan Mesylate Tablets	3/11/19
Hydroxyzine Pamoate Capsules	3/12/19
Olmesartan Medoxomil Tablets	3/12/19
Dicyclomine Hydrochloride	3/13/19
Flurazepam HCl capsules	3/14/19
Enalaprilat injection USP	3/29/19

Product Discontinuations/Withdrawals	***Date Posted***
Cefepime for injection 1 g (Apotex), remains available from other manufacturers	3/1/19
Amlodipine Besylate/Olmesartan Medoxomil (Azor) Tablet (Actavis): amlodipine/olmesartan medoxomil remains available from other manufacturers.	3/11/19
Lisinopril (Prinivil) Tablet (Merck Sharp & Dohme Corp.): 5-mg tablets, unit-of-use bottle/90 (NDC 0006-0019-54); lisinopril remains available from other manufacturers.	3/11/19
Vincristine sulfate injection USP (VINCASAR PFS, Teva) 2 mg/2 mL vial (NDC 0703-4412-11). However, vincristine sulfate injection USP (VINCASAR PFS), NDC 0703-4402-11 (1 mg/1 mL vial) has not been discontinued.	3/20/19
Acyclovir capsules USP (Teva), remains available from other manufacturers	3/21/19
Acyclovir tablets USP (Teva), remains available from other manufacturers	3/21/19
Dicyclomine HCl capsules and tablets (Bentyl, Allergan), remains available from generic manufacturers	3/29/19

New Drug Approvals:	***Description (See Attached Drug Summaries)***	***Date Approved***
Spravato / Esketamine / Janssen Pharmaceuticals, Inc.	Nasal spray used in conjunction with an oral antidepressant for treatment-resistant depression	3/5/19
Brexanolone / Zulresso / Sage Therapeutics, Inc.	GABA receptor modulator for treatment of postpartum depression	3/19/19
Solriamfetol / Sunosi / Jazz Pharmaceuticals	Dopamine and norepinephrine reuptake inhibitor to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea.	3/20/19
Siponimod / Mayzent / Novartis	Sphingosine-1-phosphate receptor modulator for the treatment of relapsing forms of multiple sclerosis	3/26/19

New Indications:	***Description***	***Date Approved***
Atezolizumab / Tecentriq / Genentech Inc.	Use in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1.	3/3/19
Dupilumab / Dupixent / Regeneron and Sanofi	Indication expanded to include patients aged 12 to 18 years for the treatment of moderate-to-severe atopic dermatitis.	3/11/19
Fulvestrant / Faslodex / AstraZeneca	Treatment of HR-positive, HER-2 negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine based therapy or following disease progression on endocrine therapy	3/11/19
Atezolizumab / Tecentriq / Genentech Inc.	Use in combination with carboplatin and etoposide for the first-line treatment of adults with extensive-stage small cell lung cancer	3/18/19
Ceftazidime and avibactam / Avycaz / Allergan	Indication expanded to include treatment of complicated intra-abdominal infections and complicated urinary tract infections in patients 3 months to 18 years of age	3/14/19
Certolizumab / Cimzia / UCB, Inc.	Treatment of adults with non-radiographical axial spondyloarthritis	3/28/19
Tegaserod / Zelnorm / US Worldmeds LLC	Product reintroduced with labeling revised to limit the indication to treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation	3/29/19

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Trazimera / trastuzumab-qyyp / Pfizer	Biosimilar to Herceptin (trastuzumab), indicated for treatment of HER2-overexpressing breast cancer, metastatic gastric, or gastroesophageal junction adenocarcinoma	3/11/19
Acyclovir 3% ophthalmic ointment / Avaclyr / Fera Pharmaceuticals	Ophthalmic ointment indicated in the treatment of acute herpetic keratitis in patients with herpes simplex (HSV-1 and HSV-2) virus	3/29/19
Testosterone undecanoate / Jatenzo / Clarus Therapeutics	Oral testosterone for the treatment of male hypogonadism resulting from specific medical conditions	3/27/19
Aclidinium bromide and formoterol fumarate inhalation powder / Duaklir Pressair / AstraZeneca	Inhaler for maintenance treatment of patients with chronic obstructive pulmonary disease	3/29/19
Cladribine / Mavenclad / EMD Serono	Oral formulation for the treatment of relapsing forms of multiple sclerosis	3/29/19

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Esketamine / Spravato / Janssen Pharmaceuticals Inc	
Generic Name / Brand Name / Company	Esketamine / Spravato / Janssen Pharmaceuticals Inc
Date of approval	3/5/19
Drug Class (Mechanism of Action if novel agent)	NMDA receptor antagonist
Indication	Treatment-resistant depression in conjunction with an oral antidepressant
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	Nasal spray: 28 mg per device (two sprays delivers 28 mg) Induction phase (weeks 1 to 4) – administer twice per week • Day 1 starting dose: 56 mg • Subsequent doses: 56 – 84 mg Maintenance phase (weeks 5 to 8) – administer 56 or 84 mg once weekly Maintenance phase (week 9 and after) – administer 56 or 84 mg every 2 weeks or once weekly
DEA Schedule	CIII
Date of market availability	Available; restricted distribution through a REMS program
Similar Medication Names	Ketamine, Spiriva
Clinical Use Evaluation	
Common Adverse Effects	>5%: disassociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, feeling intoxicated
Severe Adverse Effects	Extreme sedation and disassociation, suicidal thoughts and behaviors
Severe Drug-Drug Interactions	• CNS depressants • If used, nasal corticosteroid or nasal decongestant should be administered 1 hour before esketamine nasal spray
Severe Drug-Food Interactions	Avoid food for at least 2 hours before administration and avoid liquids at least 30 minutes prior to administration
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
Renal or Hepatic Dosing	Exposure increased in moderate hepatic impairment; monitor for longer period. Use not recommended in severe hepatic impairment. No adjustments in renal impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	• Contraindication – aneurysmal vascular disease or arteriovenous malformation, intracerebral hemorrhage • Boxed warning - May impair attention, judgment, thinking, reaction speed, and motor skills. Potential for misuse and abuse, suicidal thoughts. • Patients with unstable or poorly controlled hypertension or pre-existing aneurysmal vascular disorders may be at increased risk for adverse cardiovascular or cerebrovascular effects • May cause fetal harm, women should not become pregnant or breastfeed
Special administration technique or considerations	Patient self-administers esketamine nasal spray under the supervision of a health care professional in a doctor's office/clinic. Do not prime before use. Recline head at about 45 degrees during administration. Wait 5 minutes between use of each device. Patients must be monitored for at least 2 hours after receiving dose. Monitor blood pressure prior to dosing, at 40 minutes after administration, and as clinically indicated.
Prepared by	Rachel Lindgren
Source	Spravato (esketamine) nasal spray [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019.

Brexanolone / Zulresso / Sage Pharmaceuticals, Inc.	
Generic Name / Brand Name / Company	Brexanolone / Zulresso / Sage Pharmaceuticals, Inc.
Date of approval	3/19/19
Drug Class (Mechanism of Action if novel agent)	Neuroactive steroid GABA receptor positive modulator
Indication	Postpartum depression
Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	Injection: 100 mg/20 mL single dose vial Dose: Continuous intravenous infusion over 60 hours 0 to 4 hrs: 30 mcg/kg/hr 4 to 24 hrs: 60 mcg/kg/hr 24 to 52 hrs: 90 µg/kg/hr or 60 µg/kg/hr 52 to 56 hrs: 60 mcg/kg/hr 56 to 60 hrs: 30 mcg/kg/hr
DEA Schedule	Pending
Date of market availability	Late June 2019; restricted distribution through a REMS program
Similar Medication Names	Brexpiprazole
Clinical Use Evaluation	
Common Adverse Effects	>5%: sleepiness, dry mouth, loss of consciousness, and flushing
Severe Adverse Effects	Excessive sedation, sudden loss of consciousness
Severe Drug-Drug Interactions	CNS depressants, antidepressants
Severe Drug-Food Interactions	None known
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
Renal or Hepatic Dosing	No dosage adjustment required in hepatic impairment or mild to severe renal impairment. Avoid in end stage renal disease (eGFR less than 15 mL/min/1.73 m^2) due to potential accumulation of solubilizing agent
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Monitor for excessive sedation and loss of consciousness. Interrupt therapy for excessive sedation; discontinue therapy in patients experiencing loss of consciousness. Patient also needs to be monitored during interactions with their child.
Special administration technique or considerations	Administered as a continuous intravenous infusion in a certified center. Healthcare provider must be available on site to continuously monitor the patient. Monitor for hypoxia using continuous pulse oximetry with alarm. Assess for sedation every 2 hours during planned, non-sleep periods. Initiate therapy early in the day to allow for recognition of excessive sleepiness. Each prepared bag for IV infusion may be used for up to 12 hours.
Prepared by	Boris Zhang
Source	Zulresso (brexanolone) injection [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc.; March 2019.

Solriamfetol / Sunosi / Jazz Pharmaceuticals, Inc.	
Generic Name / Brand Name / Company	Solriamfetol / Sunosi / Jazz Pharmaceuticals, Inc.
Date of approval	3/20/19
Drug Class (Mechanism of Action if novel agent)	Dopamine and norepinephrine reuptake inhibitor
Indication	To improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea
Comparative agent – Therapeutic interchange?	Methylphenidate, amphetamines
Dosage forms/strengths. Common Dose/sig	Tablets: 75 mg (functionally scored), 150 mg Narcolepsy starting dose: 75 mg once daily Obstructive sleep apnea starting dose: 37.5 mg once daily Dose increased every 3 days with a maximum dose of 150 mg once daily
DEA Schedule	Pending
Date of market availability	Pending
Similar Medication Names	Solifenacin, sunitinib
Clinical Use Evaluation	
Common Adverse Effects	>5%: headache, nausea, decreased appetite, insomnia, anxiety
Severe Adverse Effects	Increase in systolic blood pressure, diastolic blood pressure, and heart rate in dose-dependent fashion; psychiatric reactions have been observed including anxiety, insomnia, and irritability
Severe Drug-Drug Interactions	Monoamine oxidase inhibitors, drugs increasing blood pressure and/or heart rate, and dopaminergic drugs.
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up.	None
Used in Pediatric Areas	Safety and efficacy have not been established
Renal or Hepatic Dosing	Moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) start at 37.5 mg once daily and titrate to maximum of 75 mg once daily after at least 7 days; severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) administer at 37.5 mg daily. Avoid use in end stage renal disease (eGFR less than 15 mL/min/1.73 m^2). No dosage adjustments in hepatic impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindicated with concomitant use of monoamine oxidase (MAO) inhibitors or within 15 days following discontinuation of a MAO inhibitor. Ensure blood pressure is adequately controlled prior to initiation; monitor blood pressure and heart rate regularly. Use with caution in patients at increased risk for major adverse cardiovascular events. Psychiatric adverse reactions have been observed in patients treated with solriamfetol; use with caution in patients with a history of psychosis or bipolar disorders.
Special administration technique or considerations	Administer once daily upon awakening with or without food; avoid administration within 9 hours of planned bedtime.
Prepared by	Boris Zhang
Source	Sunosi (solriamfetol) tablets [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; March 2019

Siponimod / Mayzent / Novartis	
Generic Name / Brand Name / Company	Siponimod / Mayzent / Novartis
Date of approval	3/26/19
Drug Class (Mechanism of Action if novel agent)	Sphinogosine 1-phosphate receptor modulator
Indication	Treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease
Comparative agent – Therapeutic interchange?	Fingolimod
Dosage forms/strengths. Common Dose/sig	Tablets: 0.25 mg, 2 mg Dose: Initiated with a 5-day titration starting with a 0.25 mg dose on day 1 Maintenance dose depends upon CYP2C9 genotype.
DEA Schedule	None
Date of market availability	Available
Similar Medication Names	None identified
Clinical Use Evaluation	
Common Adverse Effects	>5%: headache, increased blood pressure, transaminase increase, falls, peripheral edema, nausea, dizziness, diarrhea, bradycardia, pain in extremity
Severe Adverse Effects	Infection, macular edema, bradyarrhythmia, and atrioventricular conduction delay, respiratory effects, liver injury, increased blood pressure, fetal risk, posterior reversible encephalopathy syndrome, unintended additive immunosuppressive effects from prior treatment with immunosuppressive or immune-modulating therapies, severe increase in disability upon discontinuation, immune system effects upon discontinuation
Severe Drug-Drug Interactions	Avoid live attenuated vaccines for up to 4 weeks after treatment with siponimod; not recommended with concomitant moderate CYP2C9 and/or moderate/strong CYP3A4 inhibitors, as well as not recommended with moderate CYP2C9 and strong CYP3A4 inducers; prior immunosuppressive therapies, avoid use after treatment with alemtuzumab
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Complete blood count, liver function tests, CYP2C9 genotyping
Used in Pediatric Areas	Safety and efficacy not established
Renal or Hepatic Dosing	No dosage adjustments in renal impairment or hepatic impairment.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindications: CYP2C9*3/*3 genotype, history of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure in the last 6 months, and presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome unless patient has a functioning pacemaker. Warnings: Risk of infection: obtain completed blood count prior to initiation Macular edema: ophthalmic evaluation recommended before initiation Bradyarrhythmia: titrate dose, obtain ECG prior to initiation Respiratory effects, liver injury (monitor), increased blood pressure (monitor), fetal risk, posterior reversible encephalopathy syndrome
Special administration technique or considerations	Titration and maintenance doses vary by CYP2C9 genotype. First-dose 6-hour monitoring of heart rate is recommended for patients with cardiac conditions. If miss doses for 4 or more consecutive days, reinitiate with titration.
Prepared by	Boris Zhang
Source	Mayzent (siponimod) [package insert]. Novartis Pharmaceuticals Corp., East Hanover, NJ; March, 2019.