College of Pharmacy and Pharmaceutical Sciences
WASHINGTON STATE UNIVERSITY

**Drug Information Center**

# Highlights of FDA Activities – 3/1/2020 – 3/31/2020

## *FDA Drug Safety Communications & Drug Information Updates:*

**Singulair (montelukast): Boxed Warning About Serious Mental Health Side Effects** 3/4/20
The FDA strengthened existing warnings about serious behavior and mood-related changes with montelukast. Due to these side effects they recommend that montelukast be reserved to treat only allergic rhinitis in patients who have inadequate response or cannot tolerate other medications. For asthma they recommend considering the risks and benefits when deciding to prescribe or continue this medication. A boxed warning has been added to the prescribing information.

**Chloroquine Phosphate Intended for Fish – MedWatch Safety Alert** 3/28/20
The FDA advised that consumers may mistake chloroquine phosphate used to treat disease in aquarium fish for the chloroquine that is being studied in COVID-19. One fatality has been reported after a man took the product in an attempt to prevent COVID-19; his wife also became seriously ill.

**EpiPen Malfunctions** 3/23/20
The FDA issued an alert regarding malfunctions with the EpiPen 0.3 mg and EpiPen Jr 0.15 mg autoinjectors and the authorized generics. The autoinjectors may have delayed injection or failure to inject associated with use of sideways force to remove the blue safety release, inadvertent or spontaneous activation due to a raised blue safety release, difficulty removing the device from the carrier tube, or user errors. Healthcare providers, patients, and caregivers should periodically review the user instructions and practice using an EpiPen trainer.

**COVID-19 Information** March 2020
The FDA maintained a link on its main page (www.fda.gov) to COVID-19 information. Additional information on the FDA site of particular interest to pharmacy can be found at:
Medical countermeasures
Therapeutics with Emergency Use Authorizations: this site includes chloroquine and hydroxychloroquine fact sheets for health care providers and patients

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

**Ketorolac Tromethamine Injection, Hikma Pharmaceuticals USA: Recall - Small Particulates** 3/5/20
Extended the previously announced recall of 8 lots of ketorolac tromethamine injection USP 30 mg/mL, 1 mL fill in 2 mL vials due to the presence of small visible black particulate matter of a gelatinous/oily nature in some of the recalled lots. The recalled lots are 019413, 029353, 038366, 048365, 048367, 078301, 0378303, and 118358.

**Alaris System Infusion Pumps, Becton Dickinson (BD) CareFusion 303: Recall – Software/System Errors** 3/6/20
Software and system errors on modules with software version 9.33 or earlier and version 12.1.0 may lead to delay or interruption of infusion, under-infusion or over-infusion of medication. Serious adverse events have been reported due to these errors.

**Phytonadione Injectable Emulsion USP, Dr. Reddy's Laboratories: Recall – Ampules Shattering** 3/27/20
Dr. Reddy's Laboratories Ltd recalled 4 lots (ACB902, ACB903, ACB904, ACB905) of phytonadione injectable emulsion USP, 10 mg/mL single dose ampules to the hospital level due to reports of the product breaking and shattering upon opening.

**BodyGuard Infusion Pump System, CME America: Recall – Risk of Over- and Under-Infusion** 3/30/20
CME America recalled the BodyGuard Infusion Pump System following reports of slower and faster than expected rates of medication delivery. The cause is unknown. The pumps must not be used to deliver critical medications or those where infusion accuracy is important. The pumps may have a delivery inaccuracy of up to ±13%.

## *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* |
|---|---|---|
| Active Male 500 mg* | Sexual enhancement | Tadalafil[1] |
| Kudzu root, Mountain Rose Herbs* | Herbal supplement | Salmonella |

*recalled

[1]Tadalafil may interact with nitrates to lower blood pressure to dangerous levels

| *New Product Shortages* | *Date Initially Posted* |
|---|---|
| Amoxapine tablets | 3/9/20 |
| Chloroquine phosphate tablets | 3/31/20 |
| Hydroxychloroquine sulfate tablets | 3/31/20 |
| Nizatidine capsules | 3/27/20 |
| Rifapentine tablets | 3/25/20 |

| *Product Discontinuations/Withdrawals* *(sole source products discontinued)* | *Date Posted* |
|---|---|
| Indacaterol Maleate and Glycopyrrolate inhalation powder (Utibron Neohaler, Sunovion) | 3/10/20 |
| Indacaterol Maleate Inhalation Powder (Arcapta Neohaler, Sunovion) | 3/10/20 |
| Glycopyrrolate Inhalation Powder (Seebri Neohaler, Sunovion) | 3/10/20 |
| Indinavir capsules 400 mg (Crixivan, Merck Sharp & Dohme) | 3/31/20 |

| *New Drug Approvals:* | *Description (See Attached Drug Summaries)* | *Date Approved* |
|---|---|---|
| Isatuximab-irfc / Sarclisa / Sanofi-Aventis U.S. LLC | CD38-directed cytolytic antibody, used with pomalidomide and dexamethasone for the treatment of adults with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor | 3/2/20 |
| Osilodrostat / Isturisa / Novartis | Cortisol synthesis inhibitor for the treatment of adults with Cushing's disease | 3/6/20 |
| Ozanimod / Zeposia / Bristol Myers Squibb | Relapsing forms of multiple sclerosis | 3/26/20 |

| *New Indications:* | *Description* | *Date Approved* |
|---|---|---|
| Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide / Symtuza / Janssen Therapeutics | As a complete regimen for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg | 3/2/20 |
| Nintedanib / Ofev / Boehringer Ingelheim | Treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype | 3/9/20 |
| Nivolumab / Opdivo / Bristol Myers Squibb | With ipilimumab for hepatocellular carcinoma in patients who have received prior therapy with sorafenib | 3/11/20 |
| Ipilimumab / Yervoy / Bristol Myers Squibb | With nivolumab for hepatocellular carcinoma in patients who have received prior therapy with sorafenib | 3/11/20 |
| Durvalumab / Imfinzi / AstraZeneca | First line treatment for adult patients with extensive-stage small cell lung cancer in combination with standard-of-care chemotherapies, etoposide plus carboplatin or cisplatin | 3/30/20 |

| ***New Dosage Forms or Formulation:*** | ***Description*** | ***Date Approved*** |
|---|---|---|
| Bimatoprost / Durysta / Allergan | Intracameral biodegradable implant: 10 mcg; for reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension | 3/4/20 |
| Ferric pyrophosphate citrate / Triferic AVNU / Rockwell Medical | Intravenous solution: 6.75 mg per 4.5 mL; for iron replacement in patients with hemodialysis-dependent chronic kidney disease | 3/27/20 |

***Compiled by:***

Terri Levien, Pharm.D.
Brittany Craft, Pharm.D., PGY1 Drug Information Resident
Tracie Comer, Doctor of Pharmacy Candidate 2020
Vanessa Gutierrez, Doctor of Pharmacy Candidate 2020

**Drug Information Center**
College of Pharmacy and Pharmaceutical Sciences
Washington State University
412 E. Spokane Falls Blvd.
Spokane, WA 99202-2131
(509) 358-7662
Pharmacy.druginfo@wsu.edu

| **Isatuximab-irfc / Sarclisa / Sanofi-Aventis** | |
|---|---|
| Generic Name / Brand Name / Company | Isatuximab-irfc / Sarclisa / Sanofi-Aventis |
| Date of approval | 3/2/2020 |
| Drug Class (Mechanism of Action if novel agent) | IgG1- derived monoclonal antibody that binds to CD38 expressed on hemopoietic and tumor cells, inducing apoptosis of tumor cells and activation of immune effector mechanisms. |
| Indication | In combination with pomalidomide and dexamethasone, for treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. |
| Comparative agent – Therapeutic interchange? | Daratumumab (Darzalex, Janssen) |
| Dosage forms/strengths | Injection: 100 mg/5 ml (20 mg/ml) and 500 mg/25 ml (20 mg/ml) solution in single-dose vials |
| Common Dose/sig | Recommended dose is 10 mg/kg as an IV infusion every week for 4 weeks then every 2 weeks until disease progression or unacceptable toxicity. |
| DEA Schedule | Not applicable |
| Date of market availability | 2nd quarter 2020 |
| Similar Medication Names | Tarceva |
| **Clinical Use Evaluation** | |
| Common Adverse Effects | ≥ 20%: neutropenia, infusion-related reactions, pneumonia, upper respiratory infection, and diarrhea.<br>≥ 80%: anemia, neutropenia, lymphopenia, thrombocytopenia |
| Severe Adverse Effects | Infusion-related reactions, pneumonia, upper respiratory tract infections, febrile neutropenia, neutropenia, lymphopenia, thrombocytopenia |
| Severe Drug-Drug Interactions | Interference with serological testing and serum protein electrophoresis and immunofixation tests |
| Severe Drug-Food Interactions | None known |
| Important Labs Values to assess prior to order entry or at point of clinical follow up. | Monitor complete blood count |
| Used in Pediatric Areas | Safety and efficacy have not been established in pediatric patients |
| Renal or Hepatic Dosing | No dose reductions recommended |

| Isatuximab-irfc continued…. | |
|---|---|
| Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized | Contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.<br>Warnings:<br>- Infusion related reactions observed in 39% of patients– to decrease risk and severity premedicate with acetaminophen, H2 antagonist, diphenhydramine, dexamethasone.<br>- Neutropenia occurred in 85 – 96% of patients<br>- Second primary malignancies were reported in 3.9% of patients<br>- Embryo-fetal toxicity |
| Special administration technique or considerations | Premedicate with dexamethasone, acetaminophen, an H2 antagonist, and diphenhydramine 15 to 60 minutes before starting the isatuximab infusion. Must be administered by healthcare professional with immediate access to emergency equipment and medical support to manage infusion-related reactions. Incremental escalation of the infusion rate should only be considered in the absence of infusion-related reactions. The first infusion should be initiated at a rate of 24 mL/hour; subsequent infusions may be initiated at a greater rate. Isatuximab is used in combination with pomalidomide and dexamethasone |
| Prepared by | Tracie Comer |
| Source | Sarclisa (isatuximab-irfc) [package insert]. Bridgewater, NJ: Sanofi-Aventis; Revised March. 2020. |

| **Osilodrostat / Isturisa / Novartis** | |
|---|---|
| Generic Name / Brand Name / Company | Osilodrostat / Isturisa / Novartis |
| Date of approval | 3/6/20 |
| Drug Class (Mechanism of Action if novel agent) | Cortisol synthesis inhibitor |
| Indication | Treatment of adults with Cushing's disease for whom pituitary surgery is not an option or has not been curative. |
| Comparative agent – Therapeutic interchange? | Metyrapone, mitotane |
| Dosage forms/strengths | Tablets: 1 mg, 5 mg, and 10 mg |
| Common Dose/sig | Initiate dosing at 2 mg twice daily. The maintenance dosage is individualized and titrated based on cortisol and patient's signs and symptoms. |
| DEA Schedule | None |
| Date of market availability | 2nd or 3rd quarter of 2020 |
| Similar Medication Names | Orlistat |
| **Clinical Use Evaluation** | |
| Common Adverse Effects | >10%: adrenal insufficiency, fatigue, nausea, headache, edema, nasopharyngitis, vomiting, arthralgia, back pain, rash, diarrhea, blood corticotropin increased, dizziness, abdominal pain, hypokalemia, myalgia, decreased appetite, hormone level abnormal, hypotension, urinary tract infection, blood testosterone increased, pyrexia, anemia, cough, hypertension, and influenza. |
| Severe Adverse Effects | Clinically significant adverse reactions include hypocortisolism, QT prolongation, and elevations in adrenal hormone precursors and androgens. |

| Osilodrostat continued… | |
|---|---|
| Severe Drug-Drug Interactions | Strong CYP3A4 inhibitors: reduce the dose of osilodrostat by half with concomitant use of a strong CYP3A4 inhibitor.<br>Strong CYP3A4 and CYP2B6 inducers: during concomitant use of osilodrostat, monitor cortisol concentration and patient's signs and symptoms; an increase in osilodrostat dosage may be needed. Upon discontinuation of strong CYP3A4 and CYP2B6 inducer during treatment with osilodrostat, monitor cortisol concentration and patient's signs and symptoms; a reduction in osilodrostat dosage may be needed. |
| Severe Drug-Food Interactions | None known |
| Important Labs Values to assess prior to order entry or at point of clinical follow up. | Correct hypokalemia and hypomagnesemia prior to starting osilodrostat. Cortisol levels from 24-hour urine free cortisol collections every 1 to 2 weeks until maintenance dose is established, then every 1 to 2 months. |
| Used in Pediatric Areas | Safety and effectiveness in pediatric patients have not been established. |
| Renal or Hepatic Dosing | Renal Impairment: No dosage adjustment is required. In patients with moderate to severe renal impairment, use caution in interpreting urine free cortisol levels due to reduced urine free cortisol excretion.<br>Hepatic Impairment: The recommended starting dose is 1 mg twice daily for patients with moderate hepatic impairment (Child-Pugh B) and 1 mg once daily in the evening in patients with severe hepatic impairment (Child-Pugh C). No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A). In all patients with hepatic impairment more frequent monitoring of adrenal function may be required. |
| Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized | Contraindications: none<br>Warnings and Precautions:<br>• Hypocortisolism: monitor 24-hour urine free cortisol, serum or plasma cortisol, and patient's sign and symptoms periodically during osilodrostat treatment. Stop treatment and administer exogenous glucocorticoid replacement therapy if serum or plasma cortisol levels are below target range and patient has symptoms of adrenal insufficiency.<br>• QTc Prolongation: dose-dependent QT interval prolongation may cause cardiac arrhythmias. Perform a baseline ECG and correct hypokalemia/hypomagnesemia prior to initiation. Obtain baseline electrocardiogram and repeat within one week after treatment initiation, and as clinically indicated thereafter. Use caution and consider more frequent ECG monitoring with concomitant medications known to prolong the QT interval and in patients with risk factors for QT prolongation.<br>• Elevations in adrenal hormone precursors and androgens: osilodrostat may increase circulating levels of cortisol, aldosterone precursors and androgens. If hypokalemia results, treat with IV or oral potassium supplementation. Patients should be advised to contact a healthcare provider if symptoms associated with hyperandrogenism occur. |
| Special administration technique or considerations | Take orally, with or without food. |
| Prepared by | Vanessa Gutierrez |
| Source | Isturisa (osilodrostat) [prescribing information]. Lebanon, NJ: Recordati Rare Disease, Inc.; March 2020. |

| Ozanimod / Zeposia / Bristol Myers Squibb | |
|---|---|
| Generic Name / Brand Name / Company | Ozanimod / Zeposia / Bristol Myers Squibb |
| Date of approval | 3/25/20 |
| Drug Class (Mechanism of Action if novel agent) | Sphingosine 1-phosphate receptor modulator |
| Indication | Indicated for the treatment of adults with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. |
| Comparative agent – Therapeutic interchange? | Fingolimod, siponimod |
| Dosage forms/strengths | Capsules: 0.23 mg, 0.46 mg, and 0.92 mg |
| Common Dose/sig | Initiate once daily with a 7-day titration (days 1-4: 0.23 mg, days 5-7: 0.46 mg). Maintenance dosage is 0.92 mg once daily beginning on day 8. |
| DEA Schedule | None |
| Date of market availability | Unknown |
| Similar Medication Names | Zepatier, isoniazid |
| **Clinical Use Evaluation** | |
| Common Adverse Effects | ≥4%: upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension. |
| Severe Adverse Effects | Severe adverse reactions include infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, fetal risk, increased blood pressure, respiratory effects, macular edema, and posterior reversible encephalopathy syndrome. |
| Severe Drug-Drug Interactions | Strong CYP2C8 Inhibitors: co-administration is not recommended.<br>Strong CYP2C8 Inducers: co-administration is not recommended<br>Breast Cancer Resistance Protein (BCRP) Inhibitors: co-administration is not recommended.<br>Monoamine Oxidase (MAO) Inhibitors: co-administration is contraindicated. At least 14 days should elapse between discontinuation of ozanimod and initiation of treatment with MAO inhibitors.<br>Vaccinations: live attenuated vaccines may carry the risk of infections and should be avoided during ozanimod therapy with and for up to 3 months after discontinuation of ozanimod.<br>QT-Prolonging Agents: ozanimod treatment should not be initiated in patients who are being treated with QT prolonging drugs. If concomitant treatment with these agents is initiated, seek advice from a cardiologist.<br>Adrenergic and Serotonergic Drugs: Co-administration is not recommended; monitor patients for hypertension with concomitant use. |
| Severe Drug-Food Interactions | Tyramine: aged, fermented, cured, smoked, and pickled foods containing large amounts of exogenous amines may cause a rise in blood pressure. Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ozanimod. |
| Important Labs Values to assess prior to order entry or at point of clinical follow up. | Before initiation of treatment with ozanimod: CBC (including lymphocyte count), ECG, liver function tests, an ophthalmic assessment, and test for antibodies to varicella zoster virus. |
| Used in Pediatric Areas | Safety and effectiveness in pediatric patients have not been established. |
| Renal or Hepatic Dosing | Renal Impairment: no clinically important effects on pharmacokinetics<br>Hepatic Impairment: the effect on the pharmacokinetics of the ozanimod major active metabolites is unknown; use is not recommended. |

| Ozanimod continued… | |
|---|---|
| Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized | Contraindicated in patients who:<br>• In the last 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure.<br>• Have the presence of Mobitz type II second-degree or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker.<br>• Have severe untreated sleep apnea.<br>• Are taking a monoamine oxidase (MAO) inhibitor.<br>Warnings and Precautions:<br>• Risk of infections: obtain a recent CBC before initiation of ozanimod; delay initiation in patients with an active infection until it is resolved. Consider interruption of treatment if a patient develops a serious infection while taking ozanimod.<br>• Bradyarrhythmia and atrioventricular conduction delays: an up-titration schedule should be used to reach the maintenance dosage due to a possible result of transient decreased heart rate and atrioventricular conduction delay with initiation of ozanimod.<br>• Liver injury: elevations of aminotransferases may occur; obtain transaminase and bilirubin levels before initiation of ozanimod treatment.<br>• Fetal risk: based on animal studies, ozanimod may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after discontinuation of ozanimod.<br>• Increased blood pressure: monitor and manage blood pressure during treatment.<br>• Respiratory effects: dose-dependent reductions in absolute forced expiratory volume over 1 second ($FEV_1$) were observed during ozanimod treatment.<br>• Macular edema: ophthalmic evaluation of the fundus is recommended in all patients if there is any change in vision while taking ozanimod.<br>• Posterior Reversible Encephalopathy Syndrome (PRES): a complete physical and neurological examination should be performed if the patient develops any unexpected neurological or psychiatric symptoms. Discontinue treatment if PRES is suspected.<br>• Unintended additive immunosuppressive effects from prior treatment with immunosuppressive or immune-modulating drugs: consider the half-life and mode of action of drugs with prolonged immune effects.<br>• Severe increase in disability after stopping ozanimod: observe patients upon discontinuation and institute appropriate treatment as required.<br>• Immune system effects after stopping ozanimod: use caution when initiating other immunosuppressants 4 weeks after the last dose of ozanimod. |
| Special administration technique or considerations | Swallow capsules whole; may be administered with or without food. If a dose of ozanimod is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen. |
| Prepared by | Vanessa Gutierrez |
| Source | Zeposia (ozanimod) [prescribing information]. Summit, NJ: Celgene Corporation; March 2020. |