

Highlights of FDA Activities – 04/1/16 – 04/30/16

FDA Drug Safety Communications & Drug Information Updates:

FDA Alert: Sterile Drug Products by Medaus Pharmacy - Lack of Sterility Assurance 4/1/16

An inspection of Medaus' facility in Birmingham, AL raised concerns about Medaus' ability to assure the sterility of drug products that it produced. The Alabama Board of Pharmacy ordered Medaus to cease sterile compounding operations on 3/22/16. On 3/29/16, the FDA recommended Medaus recall all unexpired drug products intended to be sterile. To date, Medaus has not voluntarily recalled any drug products intended to be sterile. Therefore, FDA alerts health care professionals and patients not to use drug products marketed as sterile from Medaus.

Drug Safety Communication: Heart Failure Risk with Alogliptin and Saxagliptin 4/5/16

An FDA safety review has found that saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. The FDA is adding new warnings to the labeling for all saxagliptin- and alogliptin-containing medications. Patients should be aware of signs of symptoms of heart failure (unusual shortness of breath during daily activities, trouble breathing when lying down, tiredness/weakness/fatigue or weight gain or swelling of the ankles) and know to call their health care professional if they develop any of the listed symptoms. Health care professionals should consider discontinuing the medicine in patients who develop heart failure and monitor diabetes control.

Drug Safety Communication: Metformin-containing Drugs - Revised Warnings for use in Patients With Reduced Kidney Function 4/8/16

The FDA is requiring labeling changes expanding metformin's use in certain patients with reduced kidney function. Following the review of studies published in the medical literature, the FDA concluded that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function. FDA is also requiring manufacturers to revise the labeling to recommend that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (serum creatinine concentration) to one that provides a better estimate of renal function (glomerular filtration rate estimating equation (eGFR)). New labeling states that metformin is contraindicated in patients with eGFR below 30 mL/min/1.73 m² and that starting metformin is not recommended in patients with eGFR between 30-45 mL/min/1.73 m². eGFR should be monitored at least annually, and if eGFR falls below 45 mL/min/1.73 m² benefits and risks of continued treatment should be assessed.

Drug Safety Communication: Use of Oral Fluconazole (Diflucan) in Pregnancy 4/26/16

The FDA is currently evaluating a Danish study that concludes there is a possible increased risk of miscarriage with the use of oral fluconazole for yeast infections. The current FDA drug label states that data from studies in people do not suggest an increased risk of problems during pregnancy or abnormalities in developing babies when women are exposed to a single 150 mg dose of fluconazole for vaginal yeast infections. However, higher doses of oral fluconazole (400-800 mg/day) taken for longer than a single dose have resulted in reports of abnormalities. In the Danish study, most of the oral fluconazole use appeared to be one or two doses of 150 mg. Until the FDA review is complete, it is advised that caution be used prescribing oral fluconazole in pregnancy. Health care professionals should also be aware that the Centers for Disease Control and Prevention guidelines recommend only using topical antifungal products to treat pregnant women with vulvovaginal yeast infections, including longer periods than usual if these infections persist or recur.

Major Product Recalls Announced Through MedWatch:

G4 Platinum and G5 Mobile Continuous Glucose Monitoring System Receivers: Recall – Alarm Failure 4/11/16

Dexcom, Inc. is recalling the following continuous glucose monitoring system receivers (all model numbers and all lot numbers): Dexcom G4 PLATINUM Receiver, Dexcom G4 PLATINUM (Pediatric) Receiver, Dexcom G4 PLATINUM

(Professional) Receiver, Dexcom G4 PLATINUM Receiver with Share, Dexcom G4 PLATINUM (Pediatric) Receiver with Share, Dexcom G5 Mobile Receiver. The audible alarms may not activate in the receiver when hypoglycemia or hyperglycemia is detected.

50% Magnesium Sulfate Injection by Hospira: Recall – Particulate Matter 4/13/16

Hospira issued a recall of Magnesium Sulfate Injection, USP, 10 g/20 mL (0.5 g/mL), 20 mL Single-dose vials, Lot 50-343-DK, Expiration 01FEB2017, NDC 0409-2168-02 following a confirmed customer complaint of the presence of particulate matter within one single-dose flip top vial. A previous recall was issued on this same lot on 3/23/16 due to a confirmed high out of specification result for pH.

Focus Diagnostic Laboratory Examination Kits: Class I Recall – Inaccurate Test 4/14/16

Focus Diagnostics is recalling Simplexa Herpes Simplex Virus 1 & 2 and Simplexa Group A Strep Direct kits containing Direct Amplification Discs (Model Numbers: MOL2150, MOL1451, MOL2850, and MOL1455; manufacturing dates: 7/30/15 to 2/11/16; distribution dates: 9/16/15 to 2/11/16). Due to poor lamination between the sample reaction wells there is a possibility of leakage of samples into adjacent wells causing cross contamination between samples which could result in a false positive, false negative or invalid test.

Compounded Products from Pharmakon Pharmaceuticals, Inc: Recall – Lack of Sterility Assurance 4/19/16

Pharmakon Pharmaceuticals, Inc. is voluntarily recalling all lots of sterile products aseptically compounded and packaged by Pharmakon Pharmaceuticals, Inc. due to FDA concern over a lack of sterility assurance and other quality issues. All recalled products have a label that includes the Pharmakon Pharmaceuticals, Inc. name, address and expiration date. The sterile products were distributed nationwide to hospitals between 3/4/16 and 4/15/16.

Sensorcaine-MPF (bupivacaine HCl) from Fresenius Kabi: Recall - Glass Particulate Matter 4/25/16

Fresenius Kabi USA announced a voluntarily recall of a single lot (Lot Number 6111504; Product Code 470237) of Sensorcaine-MPF (bupivacaine HCl) Injection, USP, 0.75%, 7.5 mg/mL, 30 mL fill in a 30 mL vial due to visible particulate matter characterized as glass observed by the company during inspection of reserve samples.

Dietary Supplement Recalls & Public Notifications

In April, 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.

<u>Product</u>	<u>Promoted Use</u>	<u>Hidden/Undeclared Drug Ingredient(s)</u>
3 rd Degree*	Weight Loss	Sibutramine
Angel Wings Daily Multi 120 caps	Multivitamin	Milk and Soy (undeclared allergens)
Black Gold X Advanced*	Weight Loss	Sibutramine
Black Label X*	Weight Loss	Sildenafil
LGD-Xtreme 3 mg*	Gain of lean muscle mass	LGD-4033 (Ligandrol)
Life's Qik Fix	Multivitamin	Milk and Soy (undeclared allergens)
Re-VITA-lize	Liquid Vitamin	Milk and Soy (undeclared allergens)
StemVitae 30 oz Liquid	Multivitamin	Milk and Soy (undeclared allergens)
SUPER HERBS*	Weight Loss	Sibutramine, desmethyilsibutramine, and/or phenolphthalein
Zuma Supreme	Multivitamin	Milk and Soy (undeclared allergens)

*Recalled

New Product Shortages Reported by the FDA:

	<u>Date Initially Posted</u>
Theophylline extended-release tablets and capsules	4/5/16
Bleomycin sulfate for injection	4/17/16
Penicillin G Benzathine (Bicillin L-A) injection	4/29/16

Product Discontinuations/Withdrawals

Fluphenazine HCl tablets (Sandoz)

Generic fluphenazine HCl tablets remain available from Lannett and Mylan

Date Posted

4/26/16

New Drug Approvals:

Infliximab-dyyb / Inflectra / Hospira

Description

Infliximab biosimilar indicated for use in:

- Adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy
- Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
- Patients with moderately to severely active rheumatoid arthritis in combination with methotrexate
- Patients with active ankylosing spondylitis
- Patients with active psoriatic arthritis
- Adult patients with chronic severe plaque psoriasis

Date Approved

4/5/16

Venetoclax/ Venclexta/ AbbVie Inc.

Treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy; see attached drug summary

4/11/16

Riboflavin ophthalmic / Photrexa / Avedro

Treatment of progressive keratoconus, a degenerative disease that causes thinning and distortion of the cornea; see attached drug summary

4/18/16

Pimavanserin / Nuplazid / Acadia

Treatment of hallucinations and delusions associated with Parkinson's disease psychosis; see attached drug summary

4/29/16

New Indications:

Afatinib / Gilotrif / Boehringer Ingelheim

Description

Treatment of metastatic, squamous, non-small cell lung cancer progressing after platinum-based chemotherapy

Date Approved

4/15/16

Gadobutrol / Gadavist / Bayer

Evaluation of known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including term neonates)

4/27/16

Albuterol sulfate powder for inhalation/ ProAir RespiClick / Teva

Indication expanded to include 4-11 year old patients

4/28/16

New Dosage Forms or Formulations:

Emtricitabine & tenofovir alafenamide / Descovy / Gilead

Description

Combination tablet for use with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

Date Approved

4/4/16

Glycopyrrolate-formoterol fumarate / Bevespi Aerosphere / AstraZeneca

Long-acting muscarinic antagonist/long-acting beta-2 agonist combination in a pressurized metered-dose inhaler (pMDI) for chronic obstructive pulmonary disease (COPD)

4/25/16

Nitisinone oral suspension / Orfadin / Swedish Orphan

New oral suspension formulation of nitisinone for the treatment of hereditary tyrosinemia type 1

4/22/16

Cabozantinib tablets / Cabometyx / Exelixis

New dosage form for the treatment of advanced renal cell carcinoma in patients who have received prior antiangiogenic therapy

4/24/16

Oxycodone extended-release capsules / Xtampza ER / Collegium Pharms	Abuse deterrent oxycodone formulation for the treatment of severe pain	4/26/16
Ciprofloxacin 0.3% & fluocinolone acetonide 0.025% otic solution / Otovel / Laboratorios Salvat	Treatment of acute otitis media with tympanostomy tubes in pediatric patients aged 6 months and older	4/29/16
Perampanel oral suspension / Fycompa / Eisai	New oral suspension formulation of perampanel for the adjunctive treatment of partial onset seizures and primary generalized tonic-clonic seizures	4/29/16

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Venetoclax / Venclexta / AbbVie Inc.	
Generic Name / Brand Name / Company	Venetoclax / Venclexta / AbbVie Inc.
Date of approval	April 11, 2016
Drug Class (Mechanism of Action if novel agent)	Selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein that helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases
Indication	Treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy
Comparative agent – Therapeutic interchange?	n/a
Dosage forms/strengths. Common Dose/sig	Tablets: 10 mg, 50 mg, 100 mg Initiate therapy at 20 mg once daily with a meal and water for 7 days, followed by a 5-week ramp-up dosing schedule to the recommended daily dose of 400 mg
DEA Schedule	n/a
Date of market availability	April 2016
Similar Medications (Look-Alike Sound-Alike)	n/a
CLINICAL USE EVALUATION	
Common Adverse Effects	(all \geq 20%) neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue
Severe Adverse Effects	Pneumonia, febrile neutropenia, autoimmune hemolytic anemia, anemia, tumor lysis syndrome (TLS)
Severe Drug-Drug Interactions	Avoid concomitant use with moderate CYP3A inhibitors strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic index P-gp substrates; dosage adjustment recommended if concomitant use is unavoidable
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?)	Presence of 17p deletions in blood specimens (must be FDA approved test); patients without 17p deletion at diagnosis should be retested at relapse because acquisition of 17p deletion can occur. Complete blood counts throughout treatment period. TLS: assess risk based on radiographic evaluation (CT scan) and blood chemistry (potassium uric acid, phosphorus, calcium, and creatinine); monitor blood chemistry pre-dose and at 6-8 hours and 24 hours after each dose increase.
Used in Pediatric Areas	Safety and effectiveness have not been established in pediatric patients
Renal or Hepatic Dosing	Patients with reduced renal function (CrCl <80 mL/min) are at increased risk of TLS and require intensive prophylaxis and monitoring when initiating treatment Patients with moderate hepatic impairment should be monitor more closely for signs of toxicity during the initiation and dose ramp-up phase (trend for increased adverse events was observed)
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindication <ul style="list-style-type: none"> Concomitant use of venetoclax with strong inhibitors of CYP3A at initiation and during ramp-up phase is contraindicated Warnings & Precautions <ul style="list-style-type: none"> Anticipate TLS; institute prophylaxis and monitoring Neutropenia: monitor blood counts and signs of infection Immunization: do not give live vaccines prior to, during, or after Embryo-fetal toxicity: advise females of reproductive potential of embryo-fetal harm and to use effective contraception during treatment Lactation: discontinue breastfeeding
Special administration technique or considerations	Perform prophylaxis for tumor lysis syndrome <ul style="list-style-type: none"> Premedicate with anti-hyperuricemics and ensure adequate hydration Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases Administer with a meal and water at approximately the same time each day. Swallow tablets whole; do not crush, chew or break tablets
Prepared by	Jennifer Nguyen, Pharm.D. Candidate 2016

Riboflavin 5'-Phosphate Ophthalmic Solution 0.146% / Photrexia / Avedro, Inc.	
Generic Name / Brand Name / Company	Riboflavin 5'-phosphate ophthalmic solution 0.146% / Photrexia / Avedro
Date of approval	April 15, 2016
Drug Class (Mechanism of Action if novel agent)	Riboflavin is a water-soluble vitamin that is the parent of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze many oxidation/reduction reactions. The intent of corneal collagen crosslinking is to biomechanically strengthen and stabilize the cornea to delay progression of the deformation associated with keratoconus and postoperative corneal ectasia. Collagen cross-linking occurs when the riboflavin solutions are exposed to the KXL™ UVA light and the drug product emits a singlet oxygen species. The singlet oxygen forms intermolecular bonds to cross-link the corneal collagen. In addition there is literature suggesting that riboflavin is absorbed into the corneal stroma, providing a degree of protection to structures interior to the stroma, corneal endothelium, lens and retina.
Indication	A photoenhancer indicated for use in corneal collagen cross-linking for the treatment of progressive keratoconus

Comparative agent – Therapeutic interchange?	None
Dosage forms/strengths. Common Dose/sig	<p>Photrexa Viscous: 3 mL glass syringe containing sterile 0.146% riboflavin ophthalmic solution with 20% dextran for topical administration</p> <p>Photrexa: 3 mL glass syringe containing sterile 0.146% riboflavin ophthalmic solution for topical administration</p> <p>For use with the KXL™ system</p> <ul style="list-style-type: none"> • Following epithelial debridement, administer 1 drop of the solution topically every 2 minutes for 30 minutes; if yellow flare is not observed via slit lamp examination at the end of this period, administer 1 drop every 2 minutes for an additional 2 to 3 drops; may repeat as necessary until yellow flare is observed • Once yellow flare is observed and if corneal thickness is less than 400 microns, administer 2 drops of solution every 5 to 10 seconds until corneal thickness is at least 400 microns; may perform irradiation once yellow flare is observed and corneal thickness is at least 400 microns • During the entire irradiation period (30 minutes), administer 2 drops of solution every 2 minutes
DEA Schedule	N/A
Date of market availability	By the end of 2016
Similar Medications (Look-Alike Sound-Alike)	Phacotrex
CLINICAL USE EVALUATION	
Common Adverse Effects	Corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision
Severe Adverse Effects	Ulcerative keratitis can occur. Monitor for resolution of epithelial defects.
Severe Drug-Drug Interactions	No adverse drug interactions have been identified
Severe Drug-Food Interactions	No adverse food interactions have been identified
Important Labs Values to assess prior to order entry or at point of clinical follow up. (Need Pop Up?)	Ocular Examination
Used in Pediatric Areas	No recommendation for below age of 14.
Renal or Hepatic Dosing	Unknown
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Ulcerative keratitis can occur. Monitor for resolution of epithelial defects.
Special administration technique or considerations	For use with the KXL™ system only
Prepared by	Amanda Helmann, PharmD Candidate 2016

Pimavanserin / Nuplazid / Acadia Pharmaceuticals	
Generic Name / Brand Name / Company	Pimavanserin / Nuplazid / Acadia Pharmaceuticals
Date of approval	April 29, 2016
Drug Class (Mechanism of Action if novel agent)	Atypical antipsychotic. Selective serotonin antagonist at the 5-HT _{2A} receptor without antagonistic dopaminergic effects (lacks affinity for the DA ₂ receptor).
Indication	Pimavanserin is indicated for the treatment of Parkinson's disease related hallucinations and delusions (psychosis).
Comparative agent – Therapeutic interchange?	Quetiapine or clozapine (atypical antipsychotics used off-label for Parkinson's disease related psychosis)
Dosage forms/strengths. Common Dose/sig	<p>Tablet: 17 mg</p> <p>Dose: 34 mg (two 17 mg tablets) by mouth once a day. No titration necessary. Can be taken without regard to food.</p>
DEA Schedule	Not a controlled substance
Date of market availability	June 2016

Similar Medications (Look-Alike Sound-Alike)	Flibanserin; Prevacid
CLINICAL USE EVALUATION	
Common Adverse Effects	All \geq 5% and twice the rate of placebo: peripheral edema, confusion
Severe Adverse Effects	Increased mortality in elderly with dementia-related psychosis, QT interval prolongation
Severe Drug-Drug Interactions	Strong CYP3A4 inhibitors: reduce pimavanserin dose by 1/2. CYP3A4 Inducers: an increased pimavanserin dose may be needed. Avoid co-administration with class 1A and 3A antiarrhythmic agents.
Severe Drug-Food Interactions	None
Important Labs Values to assess prior to order entry or at point of clinical follow up.	None
Used in Pediatric Areas	Safety and effectiveness have not been established.
Renal or Hepatic Dosing	Renal dosing: No adjustment needed for CrCL \geq 30 mL/min. Use is not recommended in patients with CrCL < 30 mL/min since it has not been evaluated in this population. Hepatic dosing: Use of pimavanserin has not been evaluated in patients with hepatic impairment; therefore it is not recommended in this population.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Increased mortality in elderly with dementia-related psychosis. <ul style="list-style-type: none"> Elderly patients who have dementia-related psychosis, and are treated with antipsychotic drugs, are at increased risk of all-cause mortality. Pimavanserin is not approved for patients who have dementia-related psychosis that is not related to Parkinson's disease. QT prolongation <ul style="list-style-type: none"> Pimavanserin use should be avoided in patients who are taking cardiovascular medications and/or have a history of cardiovascular disease or anomalies.
Special administration technique or considerations	Recommended dose is <u>two</u> tablets once daily.
Prepared by	Alice Knotts, PharmD. Candidate 2018