Highlights of FDA Activities – 4/1/18 – 4/30/18

FDA Drug Safety Communications & Drug Information Updates:

Essure Permanent Birth Control System by Bayer Healthcare: Announcement – FDA Restricts the Sale and Distribution 4/9/18

The FDA restricted sales of the Essure device to only doctors and healthcare facilities who use the FDA-approved "Patient-Doctor Discussion Checklist – Acceptance of Risk and Informed Decision Acknowledgement." Sale and distribution of Essure is limited to healthcare providers who agree to review this checklist with patients, and give them the opportunity to sign it, before Essure implantation. The checklist is part of the patient information booklet and contains information about the device and its safety and effectiveness outcomes that patients should be aware of prior to selecting this permanent birth control option.

Lamotrigine (Lamictal) Drug Safety communication – Serious immune system reaction. 4/25/18

The FDA warned that lamotrigine can cause hemophagocytic lymphohistiocytosis (HLH), an uncontrolled response by the immune system that typically presents as a persistent fever, usually greater than 101°F, and can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs. Lamotrigine labeling has been updated with warnings about HLH. Healthcare professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis can be complicated by the nonspecific nature of the early signs and symptoms, such as fever and rash. In addition, HLH may be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Patients who develop fever or rash should be promptly evaluated. Lamotrigine should be discontinued if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. Advise patients to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms: fever/rash; enlarged spleen; cytopenia; elevated levels of triglycerides or low blood levels of fibrinogen; high levels of blood ferritin; hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy; decreased or absent Natural Killer cell activity; or elevated blood levels of CD25 showing prolonged immune cell activation.

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

Prothrombin Complex Concentrate (Human), Kcentra: Recall – Risk of Vial Breakage 4/5/18

CSL Behring recalled Kcentra 1000 U lots M9560111E, N1260111A, and N1360111A distributed through March 2018 due to an increased risk of breakage of the glass vials during transport and handling.

Sterile Injectable Products by Premier Pharmacy Labs: Recall – Lack of Sterility 4/11/18

Premier Pharmacy Labs recalled select lots of injectable morphine sulfate, hydromorphone HCl, and neostigmine methylsulfate due to a potential lack of sterility assurance. Microbial contamination was detected during routine testing of subsequent unreleased product lot. The recalled products were distributed nationwide.

Sterile Products from Coastal Meds: Recall – Lack of Sterility 4/13/18

Coastal Meds LLC of Biloxi, Mississippi recalled all non-expired products marketed as sterile due to visible particles in some of the drug vials for injection.

Dietary Supplement Recalls & Public Notifications

In April, the FDA issued notifications to the public 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***
Cali Green Malay by NutriZone*	Opioid alternative	Salmonella
Cali Maeng Da by Nutrizone*	Opioid alternative	Salmonella
Cali Thai by Nutrizone*	Opioid alternative	Salmonella
Euphoric capsules by Epic Products*	Sexual enhancement	Sildenafil and tadalifil[1]
Ignite High Endurance Pre-Workout Supplement*	Exercise supplement	Undeclared milk
Kratom from Triangle Pharmanaturals*	Opioid alternative	Salmonella
Kratom powder by Viable Solutions*	Opioid alternative	Salmonella
Maeng Da Red Kratom capsules & powder by Club 13*	Opioid alternative	Salmonella
Maeng Da Red XS kratom capsules by Club 13*	Opioid alternative	Salmonella
Muscle Strength by Advocare*	Exercise supplement	Undeclared milk
Nighttime Recovery by Advocare*	Exercise supplement	Undeclared milk
Nirvanio Bali by Nutrizone*	Opioid alternative	Salmonella
Nirvanio Green Malay by Nutrizone*	Opioid alternative	Salmonella
Nirvanio Maeng Da by Nutrizone*	Opioid alternative	Salmonella
Nirvanio Special Reserve by Nutrizone*	Opioid alternative	Salmonella
NxtGen Botanicals Maeng Da Kratom by NGB Corp	Opioid alternative	Salmonella
Pain Out Green Malay by Nutrizone*	Opioid alternative	Salmonella
Pain Out Maeng Da by Nutrizone*	Opioid alternative	Salmonella
Pain Out Malay by Nutrizone*	Opioid alternative	Salmonella
Pain Out Thai by Nutrizone*	Opioid alternative	Salmonella
Rhino 69 Extreme 50000*	Sexual enhancement	Tadalafil[1]

*Recalled

[1]Sildenafil/tadalafil/vardenafil may interact with nitrates to lower blood pressure to dangerous levels

New Product Shortages Reported by the FDA:	***Date Initially Posted***
Abciximab injection	4/11/18
Eflornithine hydrochloride cream	4/18/18
Leuprolide acetate injection	4/11/18
Magnesium sulfate injection	4/27/18
Ondansetron hydrochloride injection	4/10/18

Product Discontinuations/Withdrawals	***Date Posted***
Diclofenac sodium extended-release tablets (Mylan); remains available from other manufacturers.	4/4/18
Exenatide extended release injectable suspension (Bydureon, AstraZeneca) 2 mg single dose tray (NDC 0310-6520-04); other delivery options for exenatide extended release remain available.	4/3/18
Lidocaine topical jelly (Teva); remains available from other manufacturers.	4/27/18
Lisinopril tablets (Mylan); remains available from other manufacturers.	4/11/18
Pentazocine lactate injection (Talwin, Hospira); there are no other manufacturers of this product.	4/16/18
Stavudine capsules (Mylan); remains available from other manufactures.	4/30/18
Trandolapril tablets (Teva); remains available from other manufacturers.	4/18/18
Vinorelbine tartrate injection (Hospira); remains available from other manufacturers.	4/16/18

New Drug Approvals:	***Description (See Attached Drug Summaries)***	***Date Approved***
Burosumab-twza / Crysvita / Ultragenyx and Kyowa Kirin	For the treatment of x-linked hypophosphatemia, a rare form of inherited rickets.	4/17/18
Fostamatinib / Tavalisse / Rigel pharmaceuticals, INC	For the treatment of thrombocytopenia in adults with chronic idiopathic thrombocytopenia who have had an insufficient response to a previous treatment.	4/17/18

New Indications:	***Description***	***Date Approved***
Fosaprepitant dimeglumine / Emend / Merck & Co	Indication expanded for prevention of chemotherapy-induced nausea and vomiting in patients ages 6 months of age and older	4/3/18
Rucaparib / Rubraca / Clovis Oncology, Inc.	Maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults who are in a complete or partial response following platinum-based chemotherapy.	4/6/18
Bupivacaine liposome injectable suspension / Exparel / Pacira Pharmaceuticals	Interscalene brachial plexus nerve block to produce postsurgical regional analgesia	4/6/18
Everolimus tablets for oral suspension / Afinitor Disperz / Novartis	Adjunctive treatment of adults and pediatric patients 2 years and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures	4/10/18
Ipilimumab / Yervoy / Bristol Myers Squibb	Use in combination with nivolumab for the treatment of patients with untreated advanced renal cell carcinoma	4/16/18
Nivolumab / Opdivo / Bristol Myers Squibb	Use in combination with ipilimumab for the treatment of patients with untreated advanced renal cell carcinoma	4/16/18
von Willebrand factor [recombinant] / Vonvendi / Shire	Perioperative management of bleeding in adults with von Willebrand disease	4/17/18
Osimertinib / Tagrisso / AstraZeneca	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA approved test.	4/18/18
Tolvaptan / Jynarque / Otsuka	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD); available only through a restricted distribution system due to risk of liver injury	4/23/18
Mirabegron / Myrbetriq / Astellas	For co-administration with solifenacin succinate for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency	4/27/18
Dabrafenib / Tafinlar / Novartis	Use in combination with trametinib for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations and involvement of lymph node(s), following complete resection	4/30/18
Trametinib / Mekinist / Novartis	Use in combination with dabrafenib for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations and involvement of lymph node(s), following complete resection	4/30/18

New Dosage Forms or Formulation:	***Description***	***Date Approved***
Sarilumab / Kevzara / Sanofi	Single-dose prefilled pen injection	4/13/18
Fosnetupitant; palonosetron / Akynzeo / Helsinn Therapeutics	IV formulation for the prevention of chemotherapy-induced nausea and vomiting	4/20/18

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Burosumab-twza / Crysvita / Ultragenyx Pharmaceutical Inc.	
Generic Name / Brand Name / Company	Burosumab-twza / Crysvita / Ultragenyx Pharmaceutical Inc.
Date of approval	4/17/18
Drug Class (Mechanism of Action if novel agent)	X-linked hypophosphatemia is caused by excess fibroblast growth factor 23 (FGF23) which suppresses renal tubular phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D. Burosumab-twza binds to and inhibits the biological activity of FGF23 restoring renal phosphate reabsorption and increasing serum concentration of 1,25 dihydroxy-Vitamin D.
Indication	Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.
Comparative agent – Therapeutic interchange?	First drug approved for this indication
Dosage forms/strengths. Common Dose/sig	Injection: 10 mg/mL, 20 mg/mL, and 30 mg/mL in a single dose vial. Pediatric XLH: Starting dose is 0.8 mg/kg of body weight rounded to nearest 10 mg subcutaneously, administered every 2 weeks. Minimum starting dose is 10 mg up to a maximum dose of 90 mg. Dose may be increased up to approximately 2 mg/kg (max 90 mg), administered every 2 weeks to achieve normal serum phosphorus. Adult XLH: Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum of 90 mg administered subcutaneously every 4 weeks.
DEA Schedule	Not applicable
Date of market availability	Available
Similar Medication Names	Cryselle
Clinical Use Evaluation	
Common Adverse Effects	Pediatrics (>25%): headache, injection site reaction, vomiting, pyrexia, pain in extremity, vitamin D decrease Adults (> 5% and at least 2 more patients than placebo): back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, blood phosphorus increase
Severe Adverse Effects	Hypersensitivity, hyperphosphatemia and risk of nephrocalcinosis, Injection site reaction.

Severe Drug-Drug Interactions	Do not use with oral phosphate and active vitamin D analogs
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Fasting serum phosphorus level: prior to initiation in all patients, and then: Pediatric: every 4 weeks for the first 3 months and then as clinically indicated Adults: monthly, 2 weeks after dose is given, for the first 3 months and then as clinically indicated.
Used in Pediatric Areas	Safety and efficacy established in patients 1 year and older
Renal or Hepatic Dosing	Not studied; dose is titrated based on serum phosphorus level. Contraindicated in severe renal impairment or end-stage renal disease.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Contraindications: Do not use with oral phosphate and active Vit D analogs. Do not initiate if serum phosphorus is within or above the normal range for age. Contraindicated in patients with severe renal impairment or end stage renal disease. Warnings: Hypersensitivity reactions have been reported. Discontinue if serious hypersensitivity reaction occurs. Hyperphosphatemia may be associated with increased risk of nephrocalcinosis. Monitor serum phosphorus and adjust therapy accordingly. Discontinue if severe injection site reactions occur.
Special administration technique or considerations	Should be administered by a healthcare provider. Discontinue oral phosphate and active vitamin D analogs 1 week prior to initiation of treatment. Fasting serum phosphorus concentration should be below the reference range for age prior to initiation of treatment. Administered subcutaneously at a maximum volume of 1.5 mL per injection site; if more than 1.5 mL is required split the total volume and administered at two different injection sites.
Prepared by	Garret Mann
Source	Crysvita (burosumab-twza) injection [prescribing information]. Novato, CA: Ultragenyx Pharmaceutical Inc.; 2018.

Fostamatinib disodium hexahydrate / Tavalisse / Rigel Pharmaceuticals, Inc.	
Generic Name / Brand Name / Company	Fostamatinib disodium hexahydrate / Tavalisse / Rigel Pharmaceuticals, Inc.
Date of approval	4/17/18
Drug Class (Mechanism of Action if novel agent)	Tyrosine kinase inhibitor with activity against spleen tyrosine kinase
Indication	Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
Comparative agent – Therapeutic interchange?	None; in studies was used after corticosteroids, immunoglobulins, splenectomy and/or thrombopoietin receptor agonists, and was permitted concurrently with corticosteroids, azathioprine, and danazol.
Dosage forms/strengths. Common Dose/sig	Tablets: 100 mg and 150 mg Dose: Initiate at 100 mg orally twice daily with or without food. After 4 weeks, increase to 150 mg twice daily if needed to achieve platelet count at least 50 x 10^9/L as necessary to reduce risk of bleeding
DEA Schedule	Not applicable

Date of market availability	Late May 2018
Similar Medication Names	Fosamax, Tavaborole
Clinical Use Evaluation	
Common Adverse Effects	Most common (>5%): diarrhea, hypertension, nausea, respiratory infection, dizziness, ALT/AST increased, rash, abdominal pain, fatigue, chest pain, and neutropenia
Severe Adverse Effects	Hypertension, hepatotoxicity, diarrhea, neutropenia
Severe Drug-Drug Interactions	Effects of other drugs on fostamatinib/metabolite: CYP3A4 inhibitors – increase exposure to R406 (major active metabolite) – monitor toxicity CYP3A4 inducer – reduce R406 – concomitant use is not recommended Effects of fostamatinib/metabolite on other drugs: CYP3A4 Substrates: may increase concentrations of some 3A4 substrate drugs. Monitor for toxicity of 3A4 substrates BCRP substrates: may increase concentrations of BCRP substrate drugs – monitor for toxicity P-gp substrates: may increase concentrations of P-gp substrates (digoxin). Monitor for toxicity of P-gp substrates.
Severe Drug-Food Interactions	None known
Important Labs Values to assess prior to order entry or at point of clinical follow up.	Baseline and monthly: CBC, including platelets and neutrophils, and liver function tests. Pregnancy status – prior to initiation
Used in Pediatric Areas	Safety and efficacy have not been established
Renal or Hepatic Dosing	Pharmacokinetics are not altered in renal or hepatic impairment. Dose interruption, adjustment, or discontinuation may be necessary in patients developing hepatotoxicity.
Critical Issues (i.e., contraindications, warnings, etc) that should be emphasized	Monitor CBC, LFTs and blood pressure. Monitor for diarrhea. Manage adverse reactions using dose reduction, interruption of treatment, or discontinuation. Can cause fetal harm. Discontinue after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.
Special administration technique or considerations	May be taken with or without food.
Prepared by	Garret Mann
Source	Tavalisse (fostamatinib disodium hexahydrate) tablets [prescribing information]. South San Francisco, CA: Rigel Pharmaceuticals, Inc.; 2018.