PharmNotes

Monthly Communications

February 2024

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Pharmacy Benefit Management
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Drug Safety Alert Notification

The Drug Safety Communications are provided by the U.S. Food and Drug Administration and are intended to offer important information to patients and health care providers about new safety issues regarding certain medications. This helps prescribers and health care professionals be informed so that decisions regarding the treatment of patients are made accordingly.

No Drug Safety Alert Notification was released during February.

New FDA-Approved Drug Products

New Molecular Entity

Amtagvi™ (lifileucel) Suspension

Specialty | Orphan Drug

FDA-Approved Indication

Tumor-derived autologous T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

Dosage & Administration

Between 7.5 x 10^9 and 72 x 10^9 viable cells. Administer IL-2 (aldesleukin) after infusion. Refer to prescribing information for more details.

Dosage Forms & Strengths

Cell suspension for intravenous infusion: a single dose contains 7.5 x 10^9 to 72 x 10^9 viable cells suspended in 1 to 4 patient-specific infusion bag(s)

Contraindications

None

Warnings & Precautions

- Hypersensitivity Reactions

Common Adverse Reactions

Chills, pyrexia, fatigue, tachycardia, diarrhea, febrile neutropenia, edema, rash, hypotension, alopecia, infection, hypoxia, and dyspnea

Clinical Studies

Approval came from a pivotal Phase 2 C-144-01 study which included patients with unresectable or metastatic melanoma who had previously received one or more systemic therapies, including anti-PD-1/PD-L1 and a BRAF inhibitor with or without a MEK inhibitor for those with a BRAF V600 mutation. The primary endpoint of the trial was objective response rate. Among the 73 patients treated with Amtagvi at the recommended dose, 31.5% exhibited an objective response rate, including three patients (4.1%) who had a complete response and 20 patients (27.4%) who had a partial response. A confirmatory trial is ongoing to verify Amtagvi's clinical benefit.

Place in Therapy

Amtagvi has the potential to provide several advantages for the treatment of advanced melanoma. There is an unmet need for therapies among the population of patients with melanoma who have progressed on immunotherapy and, if they are BRAF mutation–positive, on a BRAF inhibitor with or without a MEK inhibitor. In this setting, there is currently no approved treatment, and these patients typically resort to chemotherapy, which offers a low response rate and short duration of response. There is some evidence indicating favorable responses when reattempting treatment with both immune checkpoint inhibitors and BRAF-targeted therapy. The NCCN Panel recommends that patients who achieve disease control with these agents and experience no lingering side effects, but subsequently face disease progression or relapse more than 3 months after stopping treatment, may consider reinitiating the same treatment or a similar class of treatments.

New FDA-Approved Drug Products

New Molecular Entity

Exblifep™ (cefepime and enmetazobactam) Injection, for intravenous use

FDA-Approved Indication

For the treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible microorganisms.

Dosage & Administration

2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam) every 8 hours by intravenous infusion over 2 hours for 7 days to 14 days, in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR) between 60 to 129 mL/min. Dosage adjustment is recommended in patients with renal impairment who have an eGFR < 60 mL/min or > 130 mL/min.

Dosage Forms & Strengths

Sterile powder for reconstitution in single-dose vials containing 2 grams cefepime and 0.5 grams enmetazobactam.

Contraindications

History of serious hypersensitivity reactions to the components of Exblifep (cefepime and enmetazobactam), or other beta-lactam antibacterial drugs

Common Adverse Reactions

Transaminases increased, increased bilirubin, headache, and phlebitis/infusion site reactions.

Warnings & Precautions

- Hypersensitivity Reactions
- Neurotoxicity
- *Clostridioides difficile*-Associated Diarrhea (CDAD)

Clinical Studies

The randomized, controlled, double-blind, global Phase III ALLIUM trial, which compared the treatment with the current standard of care of piperacillin/tazobactam. Exblifep achieved the trial's primary outcome of clinical cure and microbiological eradication for non-inferiority and superiority compared with piperacillin/tazobactam. The trial enrolled 1,041 patients, 18 years of age and above, with a clinical diagnosis of cUTI or acute pyelonephritis caused by gram-negative urinary pathogens. Patients were randomly assigned to receive either Exblifep or piperacillin/tazobactam by two-hour infusion every eight hours for seven days. The results showed that 79.1% of patients administered Exblifep achieved the primary outcome vs. 58.9% of those administered piperacillin/tazobactam.

Place in Therapy

Complicated UTI is commonly caused by *E. coli, Klebsiella, Enterobacter, Serratia, Pseudomonas, Enterococci*, or *Staphylococci*. Results of urine culture and susceptibility testing should be used to tailor the regimen, if appropriate. In many cases, broad-spectrum empiric regimens can be replaced by a more narrow-spectrum agent. Antimicrobial resistance mediated by ESBLs is a critical clinical challenge and this novel drug has a potential to become a replacement for piperacillin/tazobactam and an alternative to the use of carbapenems.

New FDA-Approved Drug Products

New Biosimilar Product

Simlandi™ (adalimumab-ryvk) Suspension

Specialty

FDA-Approved Indication

[1] Moderate to severe rheumatoid arthritis; [2] Moderately to severely active polyarticular JIA in patients 2 years of age and older; [3] Active psoriatic arthritis; [4] Active ankylosing spondylitis; [5] Moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older; [6] Moderately to severely active ulcerative colitis in adult patients; [7] Moderate to severe chronic plaque psoriasis; [8] Moderate to severe hidradenitis suppurativa; [9] Non-infectious intermediate, posterior, and panuveitis.

Dosage & Administration

By subcutaneous injection

- Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: 40 mg every other week
- JIA: 40 mg every other week (66 lbs and greater)
- Crohn's Disease: 160 mg on Day 1, 80 mg on Day 15, and 40 mg every other week starting on Day 29.
- UC: 160 mg on Day 1, 80 mg on Day 15, and 40 mg every other week starting on Day 29.
- Plaque Psoriasis or Adult Uveitis: 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.
- Hidradenitis Suppurativa: 160 mg on Day 1, 80 mg on Day 15, and 40 mg every week (or 80 mg every other week) starting on Day 29.

Dosage Forms & Strengths

Injection: 40 mg/0.4 mL single dose autoinjector

Contraindications

None

Common Adverse Reactions

Infections, injection site reactions, headache, and rash.

Warnings & Precautions

- ***BBW***: Serious infections & Malignancies
- Invasive fungal infections
- Anaphylaxis or serious hypersensitivity reactions
- Hepatitis B virus reactivation
- Demyelinating disease
- Cytopenias, pancytopenia
- Heart failure
- Lupus-like syndrome

Clinical Studies

Various clinical studies demonstrated pharmacokinetics, safety, tolerability, and efficacy of Simlandi comparable to Humira.

Place in Therapy

A total of nine Humira biosimilars are on the market in the United States. Simlandi will be the 10th when it launches and it is the first high-concentration, citrate-free biosimilar to Humira. Simlandi is the third interchangeable Humira biosimilar, joining Abrilada and Cyltezo. All of the Humira biosimilars on the U.S. market are citrate-free formulations. However, Simlandi is also a high-concentration version of adalimumab. Most of Humira prescriptions are for high-concentration formulations. Abrilada and Cyltezo are low-concentration formulations, so for now, Simlandi has the high-concentration, citrate-free and interchangeable Humira biosimilar market to itself.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Eohilia™ (budesonide) Oral Suspension

Specialty | Orphan Drug

FDA-Approved Indication

Corticosteroid indicated for 12 weeks of treatment in adult and pediatric patients 11 years of age and older with eosinophilic esophagitis (EoE).

Dosage & Administration

2 mg orally twice daily for 12 weeks.

Dosage Forms & Strengths

Oral suspension: 2 mg/10 mL single-dose stick packs.

Contraindications

Hypersensitivity to budesonide.

Warnings & Precautions

- Hypercorticism and Adrenal Axis Suppression
- Immunosuppression and Increased Risk of Infection
- Erosive Esophagitis
- Effect on Growth
- Symptoms of Steroid Withdrawal in Patients Transferred from Other Systemic Corticosteroids
- Other Corticosteroids Effects
- Kaposi's Sarcoma

Common Adverse Reactions

Respiratory tract infection, gastrointestinal mucosal candidiasis, headache, gastroenteritis, throat irritation, adrenal suppression, and erosive esophagitis

Use in Specific Population

- Pregnancy: May cause fetal harm.
- Hepatic Impairment: Use is not recommended in severe hepatic impairment. Monitor patients with moderate hepatic impairment for signs and/or symptoms of hypercorticism.

Clinical Studies

Two multicenter, randomized, double-blind, parallel-group, placebo-controlled 12-week studies in patients (ages 11 to 56 and 11 to 42, respectively) with EoE.1 In both studies, patients received at least one dose of either Eohilia 2 mg twice daily or placebo orally twice daily. Efficacy endpoints included histologic remission and the absolute change from baseline in patient-reported Dysphagia Symptom Questionnaire (DSQ) combined score after 12 weeks of treatment. Significantly more patients receiving Eohilia achieved histologic remission vs. placebo in Study 1 (53.1% vs. 1%). In Study 2, 38% of Eohilia patients achieved histologic remission vs. 2.4% of those in the placebo group. Absolute change from baseline in DSQ combined score in the Eohilia vs. placebo groups in Study 1 was -10.2 (1.5) vs. -6.5 (1.8) and in Study 2, -14.5 (1.8) vs. -5.9 (2.1).

Place in Therapy

Eohilia joins Sanofi/Regeneron's Dupixent (dupilumab), a subcutaneously administered drug, as the second treatment option in the EoE space. Prior to the approval of Dupixent and Eohilia, management of EoE included off-label proton pump inhibitors or swallowing inhaled corticosteroids used for asthma. The American Gastroenterological Association Guideline for the Management of Eosinophilic Esophagitis suggest topical glucocorticosteroids over no treatment (strong recommendation). In patients with EoE, the AGA suggests topical glucocorticosteroids rather than oral glucocorticosteroids (conditional recommendation).

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Legubeti™ (acetylcysteine) Oral Solution

FDA-Approved Indication

Antidote to prevent or lessen hepatic injury, which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen, in adults and pediatric patients.

Dosage & Administration

Obtain a plasma or serum sample to assay for acetaminophen concentration at least 4 hours after acetaminophen ingestion. Loading dose: 140 mg/kg. Maintenance dose: 70 mg/kg repeated every 4 hours for a total of 17 doses.

Dosage Forms & Strengths

Oral solution: 500 mg and 2.5 grams of acetylcysteine.

Contraindications

None

Warnings & Precautions

- Hypersensitivity Reactions, including urticaria, angioedema, bronchospasm, pruritus, flushing, other rash, chest tightness, and hypotension.
- Risk of Upper Gastrointestinal Hemorrhage

Common Adverse Reactions

Nausea and vomiting, other gastrointestinal symptoms, and rash with or without fever.

Clinical Studies

NDA submitted pursuant to section 505(b)(2) of the FDCA.

Place in Therapy

To prevent hepatotoxicity, acetaminophen overdose must be identified early and the antidote, N-acetylcysteine (NAC) given quickly. The acetaminophen level (drawn 4 to 24 hours after ingestion) is used as basis for treatment. The levels are plotted on the Rumack-Matthew nomogram to determine the risk of hepatotoxicity.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Aurlumyn™ (iloprost) Injection

Orphan Drug

FDA-Approved Indication

Prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations.

Dosage & Administration

Initiate intravenous infusion at 0.5 ng/kg/minute and titrate in 0.5 ng/kg/minute increments based on tolerability at intervals of 30 minutes to a maximum of 2 ng/kg/minute. Infuse continuously for 6 hours each day up to a maximum of 8 consecutive days.

Dosage Forms & Strengths

Injection: 100 mcg per mL in a single dose vial.

Contraindications

None

Warnings & Precautions

- Symptomatic hypotension

Common Adverse Reactions

Headache, flushing, palpitations/tachycardia, nausea, vomiting, dizziness, and hypotension.

Use in Specific Population

- Dose adjustment in patients with renal impairment with eGFR less than 30 mL/min.
- Dose adjustment in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C.

Clinical Studies

The study was an open-label, controlled trial that randomized 47 adults with severe frostbite, who all received aspirin by vein and standard of care, into one of three treatment groups. One of these groups (Group 1) received iloprost by vein (intravenously) for 6 hours daily for up to 8 days. The two other groups received other medications that are unapproved for frostbite, given with iloprost (Group 2) or without iloprost (Group 3). The primary measure of efficacy was a bone scan obtained 7 days after initial frostbite that was used to predict the need for amputation of at least one finger or toe. On day 7, the bone scan finding predictive of needing amputation was observed in 0% (0 of 16) patients receiving iloprost alone (Group 1) compared to 19% (3 of 16) patients in Group 2 and 60% (9 of 15) patients in Group 3.

Place in Therapy

Frostbite can occur in several stages, ranging from mild frostbite that does not require medical intervention and does not cause permanent skin damage, to severe frostbite when both the skin and underlying tissue are frozen and blood flow is stopped, sometimes requiring amputation. The Wilderness Medical Society guidelines recommend iloprost for deep frostbite to or proximal to the proximal interphalangeal joint; within 48 hours after injury, when angiography is not available or when contraindications to thrombolysis are present.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Pantoprazole Sodium in 0.9% Sodium Chloride Injection

FDA-Approved Indication

For the short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE), and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults.

Dosage & Administration

GERD Associated with EE: 40 mg given once daily by intravenous infusion administered over 15 minutes for 7 to 10 days.

Pathological Hypersecretion Conditions: 80 mg administered every 12 hours by intravenous infusion administered over 15 minutes.

Dosage Forms & Strengths

Injection: 40 mg/100 mL (0.4 mg/mL) pantoprazole in a single-dose container, 40 mg/50 mL (0.8 mg/mL) pantoprazole in a single-dose container, 80 mg/100 mL (0.8 mg/mL) pantoprazole in a single-dose container.

Contraindications

- Patients with a known hypersensitivity to any component of the formulation or to substituted benzimidazoles.
- Patients receiving rilpivirine-containing products.

Common Adverse Reactions

Nausea and vomiting, other gastrointestinal symptoms, and rash with or without fever.

Warnings & Precautions

- Gastric Malignancy
- Injection Site Reactions
- Potential Exacerbation of Zinc Deficiency
- Acute Tubulointerstitial Nephritis
- *Clostridioides difficile*-Associated Diarrhea
- Bone Fracture
- Severe Cutaneous Adverse Reactions
- Cutaneous and Systemic Lupus Erythematosus
- Hepatic Effects
- Hypomagnesemia and Mineral Metabolism
- Fundic Gland Polyps

Clinical Studies

NDA submitted pursuant to section 505(b)(2) of the FDCA.

Place in Therapy

Proton Pump Inhibitors are mainstays of the treatment of several gastrointestinal-related conditions such as GERD and EE.

New First-Time Generic Approvals

First-Time Generics are the first generic forms of brand name drugs. The generic version is formulated to work in the same way as the brand-name product and provides the same clinical benefit.

Product	Manufacturer	Generic For	Therapeutic Class	Indication(s)
Bromfenac Sodium Sesquihydrate Ophthalmic Solution 0.075%	Lupin Pharmaceuticals, Inc.	BromSite	Ophthalmic Agents - Misc	Postoperative Ocular Inflammation
Deflazacort Tablets 6 mg, 18 mg, 30 mg and 36 mg	Aurobindo Pharma Limited	Emflaza	Glucocorticosteroids	Duchenne Muscular Dystrophy
Ospemifene Tablets 60 mg	Hetero Labs Limited	Osphena	Hormone Receptor Modulators	Menopause Symptoms
Brimonidine Tartrate Ophthalmic Solution 0.025%	Dr.Reddy's Laboratories Inc.	Lumify	Ophthalmic Adrenergic Agents	Eye Redness
Nitroglycerin Intra-Anal Ointment 0.4%	Cosette Pharmaceuticals, Inc	Rectiv	Vasodilating Agents	Anal Fissure

New FDA-Approved Indications for Existing Drugs

The following table contains drugs that have gained FDA approval for the treatment of additional diseases or conditions.

Drug Name and Manufacturer	Previous Indication(s)	New Indication
Onivyde (irinotecan liposomal) From: Ipsen	In combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.	In combination with oxaliplatin, fluorouracil and leucovorin, for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma,
Tagrisso (osimertinib) From: AstraZeneca	[1] Adjuvant treatment of EGFR mutation-positive NSCLC; [2] First-line treatment of EGFR mutation-positive metastatic NSCLC; [3] Previously treated EGFR T790M mutation-positive metastatic NSCLC.	In combination with pemetrexed and platinum-based chemotherapy, the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.
Xolair (omalizumab) From: Genentech	[1] Asthma; [2] Chronic rhinosinusitis with nasal polyps; [3] Chronic spontaneous urticaria.	IgE Mediated Food Allergy.
Biktarvy (bictegravir, emtricitabine and tenofovir alafenamide) From: Gilead Sciences, Inc	HIV-1 infection in patients with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.	HIV-1 infection in patients with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no known or suspected substitutions associated with resistance to bictegravir or tenofovir.

Pipeline

The goals of the NDA (or BLA) are to provide enough information to permit FDA approval of a new pharmaceutical for sale and marketing in the U.S.

Drug Name and Manufacturer	Indication(s)	Additional Information	Impact
Nemolizumab From: Galderma	Prurigo nodularis and for adolescents and adults with moderate to severe atopic dermatitis.	BLA accepted	High
Lymphir (denileukin diftitox-cxdl) From: Citius Pharmaceuticals, Inc.	Relapsed or refractory cutaneous T-cell lymphoma.	BLA resubmitted	High High
Dasynoc (dasatinib) - formerly XS004 From: Xspray Pharma AB	Chronic myeloid leukemia and acute lymphoblastic leukemia.	NDA resubmitted	High
Midomafetamine From: Lykos Therapeutics	FPost-traumatic stress disorder	NDA accepted	Moderate
Linvoseltamab From: Regeneron Pharmaceuticals, Inc.	Adult patients with relapsed/refractory (R/R) multiple myeloma (MM) that has progressed after at least three prior therapies.	BLA accepted for Priority Review	High High
Acoramidis From: BridgeBio Pharma, Inc.	Transthyretin Amyloid Cardiomyopathy	NDA accepted	High
Datopotamab deruxtecan From: AstraZeneca and Daiichi Sankyo	Adult patients with locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) who have received prior systemic therapy.	BLA accepted	High High