PharmNotes

Monthly Communications

October 2024

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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 October.

New FDA-Approved Drug Products

New Molecular Entity

Itovebi™ (inavolisib) tablet for oral use

Specialty

FDA-Approved Indication

In combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer.

Dosage & Administration

9 mg orally once daily, with or without food, until disease progression or unacceptable toxicity occurs.

Dosage Forms & Strengths

Tablets: 3 mg and 9 mg.

Common Adverse Reactions

Decreased neutrophils, hemoglobin, platelets, and lymphocytes. Increased fasting glucose, creatinine, and ALT. Stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, nausea, rash, decreased appetite, and headache.

Warnings & Precautions

- Hyperglycemia
- Stomatitis
- Diarrhea
- Embryo-Fetal Toxicity

Use in Specific Populations

Lactation: Advise not to breastfeed during treatment and 1 week after.

Clinical Studies

The approval was based on the Phase III INAVO120 study, a randomized, double blind, placebo-controlled trial. This trial showed as a result significant improvement in progression-free survival for patients treated with Itovebi in combination with palbociclib and fulvestrant, compared to placebo. Itovebi-based regimen reduced the risk of disease worsening or death by 57% compared with palbociclib and fulvestrant alone (15.0 months vs. 7.3 months; hazard ratio [HR]=0.43, 95% CI: 0.32-0.59, $p<0.0001$) in the first-line setting

Place in Therapy

Itovebi is positioned as a targeted therapy for patients with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative breast cancer, particularly in those who have progressed following adjuvant endocrine therapy. Itovebi helps to address an urgent unmet need in breast cancer for people with a PIK3CA mutation, one of the most commonly mutated genes in HR-positive disease, associated with poor prognosis

New FDA-Approved Drug Products

New Molecular Entity

Hympavzi™ (marstacimab) subcutaneous injection

Specialty | Orphan Drug

FDA-Approved Indication

For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients (12 years and older) with hemophilia A (without factor VIII inhibitors) or hemophilia B (without factor IX inhibitors).

Dosage & Administration

300 mg (two 150 mg subcutaneous injections) loading dose, followed by maintenance dose of 150 mg weekly by subcutaneous injection starting one week after the loading dose. Dose adjustment to 300 mg weekly can be considered based on the control of bleeding events.

Dosage Forms & Strengths

Prefilled Syringe and Pen: 150 mg/mL single-dose.

Common Adverse Reactions

Injection site reactions, pruritus, and headache.

Warnings & Precautions

- Thromboembolic Events
- Hypersensitivity
- Embryo Fetal toxicity.

Clinical Studies

Approval came from results of the Phase 3 BASIS trial. The results demonstrated the efficacy of Hympavzi in reducing annualized bleeding rate (ABR) for treated bleeds by 35% and 92% after a 12-month active treatment period compared to routine prophylaxis and on-demand treatment, respectively, in patients with hemophilia A or B without inhibitors.

Place in Therapy

Many patients with hemophilia continue to experience bleeding episodes and have to manage their condition via frequent intravenous infusions. Hympavzi is the first and only anti-tissue factor pathway inhibitor approved for the treatment of hemophilia A or B and the first hemophilia medicine to be administered via a pre-filled, auto-injector pen. Hympavzi can offer a subcutaneous treatment option with a once-weekly dosing schedule and minimal preparation required for each individual administration. Hympavzi aims to reduce the current treatment burden of patients that require frequent, time-consuming intravenous treatment infusion regimens. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the use of marstacimab.

New FDA-Approved Drug Products

New Molecular Entity

Vyloy™ (inavolisib) injection for intravenous use

Specialty | Orphan Drug

FDA-Approved Indication

In combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are CLDN18.2 positive as determined by an FDA-approved test.

Dosage & Administration

The recommended first dose is 800 mg/m^2 intravenously, followed by 600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks.

Dosage Forms & Strengths

Injection: 100 mg lyophilized powder in a single-dose vial.

Common Adverse Reactions

Nausea, vomiting, fatigue, decreased appetite, diarrhea, peripheral sensory neuropathy, abdominal pain, constipation, weight loss, hypersensitivity reactions, and fever.

Warnings & Precautions

- Hypersensitivity Reactions
- Severe Nausea and Vomiting

Use in Specific Populations

Lactation: Advice not to breastfeed.

Clinical Studies

The FDA approval came from SPOTLIGHT and GLOW, two randomized (1:1) double-blind, multicenter trials that enrolled patients with CLDN18.2 positive advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. The major efficacy outcome measure in both trials was progression-free survival (PFS). In SPOTLIGHT, median PFS was 10.6 months in the zolbetuximab-clzb chemotherapy arm and 8.7 months in the placebo chemotherapy arm (hazard ratio [HR] 0.751 [95% CI: 0.598, 0.942]; 1-sided p-value=0.0066). In GLOW, median PFS was 8.2 months in the zolbetuximab-clzb chemotherapy arm and 6.8 months in the placebo chemotherapy arm (hazard ratio [HR] 0.687 [95% CI: 0.544, 0.866]; 1-sided p-value=0.0007).

Place in Therapy

Vyloy is the first and only targeted therapy for CLDN18.2-positive patients. CLDN18.2 is an emerging biomarker in gastric and GEJ cancers and helps predict the likelihood of response to targeted therapy.

New FDA-Approved Drug Products

New Molecular Entity

Orlynavah™ (sulopenem etzadroxil; probenecid) tablets for oral use

FDA-Approved Indication

For the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

Dosage & Administration

One tablet orally twice daily for 5 days.

Dosage Forms & Strengths

Tablets: 500 mg sulopenem etzadroxil and 500 mg probenecid.

Contraindications

- Patients with a history of hypersensitivity to the components of Orlynavah or other beta lactam antibacterial drugs
- Patients with known blood dyscrasias
- Patients with known uric acid kidney stones
- Concomitant use of Orlynavah and ketorolac tromethamine is contraindicated.

Common Adverse Reactions

Diarrhea, nausea, vulvovaginal mycotic infection, headache and vomiting.

Warnings & Precautions

- Hypersensitivity Reactions
- *Clostridiodies difficile* – Associated Diarrhea (CDAD)
- Exacerbation of Gout

Drug Interactions

- Ketoprofen

Clinical Studies

The FDA approval of Orlynvah was based on two pivotal, Phase 3 clinical trials (SURE 1 and REASSURE) that evaluated the safety and efficacy of Orlynvah compared to ciprofloxacin (SURE 1) and Augmentin (REASSURE) in the treatment of adult women with uUTI. SURE 1 showed superiority to ciprofloxacin in fluoroquinolone resistant infections, while REASSURE showed non-inferiority and statistical superiority to Augmentin in the Augmentin susceptible population. Orlynvah was generally well tolerated in both SURE 1 and REASSURE clinical trials.

Place in Therapy

uUTIs are infections of the bladder occurring mainly in women, with approximately 1% of those infections being caused by pathogens that are resistant to all commonly available classes of oral antibiotics. Orlynvah™ is the first oral penem approved that offers an alternative way to combat antimicrobial resistance in patients suffering difficult-to-treat uUTIs.

New FDA-Approved Drug Products

New Biosimilar Product

Imuldosa™ (ustekinumab-srlf) injection for subcutaneous or intravenous use

Specialty

FDA-Approved Indication

For adult patients with moderate to severe plaque psoriasis (PsO), active psoriatic arthritis (PsA), moderately to severely active Crohn's disease (CD), and moderately to severely active ulcerative colitis (UC). It is also indicated for pediatric patients (6 years and older) with moderate to severe plaque psoriasis and active psoriatic arthritis (PsA).

Dosage & Administration

Weight-based dosing is recommended. Refer to package insert for more details.

Dosage Forms & Strengths

- Subcutaneous Injection: 45 mg/0.5 mL or 90 mg/mL in a prefilled syringe.
- Intravenous Infusion: 130 mg/26 mL (5 mg/mL) in a single-dose vial.

Contraindications

Clinically significant hypersensitivity to ustekinumab or any of the excipients in Imuldosa.

Common Adverse Reactions

Nasopharyngitis, upper respiratory infection, headache, fatigue, vomiting, injection site reactions, bronchitis, diarrhea, abdominal pain, urinary tract infection, mycotic infection.

Warnings & Precautions

- Infections
- Theoretical Risk for Particular Infections
- Tuberculosis
- Malignancies
- Hypersensitivity Reactions
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Noninfectious Pneumonia
- Avoid Live Vaccines

Clinical Studies

The FDA approval of Imuldosa came from a comprehensive clinical development program. Data showed that Imuldosa is similar to its reference product Stelara in terms of pharmacokinetic characteristics, safety, tolerability, and efficacy.

Place in Therapy

Ustekinumab products are used to treat several conditions such as moderate to severe plaque psoriasis, psoriatic arthritis, Crohn disease, and ulcerative colitis. Imuldosa is the fifth ustekinumab biosimilar referencing Stelara to receive regulatory approval in the US.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Vyalev™ (foscarbidopa and foslevodopa) subcutaneous injection

Specialty | Orphan Drug

FDA-Approved Indication

For the treatment of motor fluctuations in adults with advanced Parkinson's disease (PD).

Dosage & Administration

For subcutaneous use only via the Vyafuser pump. The dosage involves a continuous subcutaneous infusion, with an optional loading dose. The maximum recommended daily dose is 3,525 mg of foslevodopa (equivalent to approximately 2,500 mg levodopa).

Dosage Forms & Strengths

Injection: 120 mg foscarbidopa and 2,400 mg foslevodopa per 10 mL (12 mg foscarbidopa and 240 mg foslevodopa per mL).

Contraindications

Vyalev is contraindicated in patients who are currently taking a nonselective monoamine oxidase (MAO) inhibitor or have recently (within 2 weeks) taken a nonselective MAO inhibitor.

Common Adverse Reactions

Infusion/catheter site reactions and/or infections, hallucinations, and dyskinesia.

Warnings & Precautions

- May cause falling asleep during activities of daily living
- Hallucinations/psychosis
- Impulse Control Behaviors
- Infusion Site Reactions and Infections
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion
- May cause or exacerbate dyskinesia

Drug Interactions

- Selective MAO-B inhibitors
- Antihypertensive drugs
- Dopamine D2 receptor antagonists and isoniazid

Use in Specific Populations

Pregnancy: Based on animal data, may cause fetal harm.

Clinical Studies

The approval is based on the results from the pivotal Phase III M15-736 study, a 12-week trial that assessed the efficacy of its continuous infusion in advanced PD patients against oral immediate-release carbidopa levodopa (CD/LD IR). The primary endpoint was the quality of "on" time, averaged over three consecutive days and normalized to a waking period of 16 hours. Results demonstrated that patients treated with Vyalev experienced significant improvements in motor fluctuations and had an increased "on" time and decreased "off" time without troublesome dyskinesia, compared to those receiving oral CD/LD IR.

Place in Therapy

In PD, "on" time indicates when patients have optimal motor symptom control, while "off" time refers to the return of symptoms. Vyalev is intended for patients with advanced Parkinson's disease experiencing motor fluctuations not adequately managed by other treatments, providing continuous subcutaneous infusion of levodopa and carbidopa. This is the first and only subcutaneous 24-hour infusion of levodopa-based therapy approved for this indication.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Selarsdi™ (ustekinumab-aekn), injection for intravenous use

Specialty

FDA-Approved Indication

The intravenous use is indicated for the treatment of Crohn's Disease and Ulcerative Colitis.

Dosage & Administration

A single intravenous infusion using weight-based dosing. Please refer to package insert for details.

Dosage Forms & Strengths

Intravenous Infusion: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial.

Contraindications

Clinically significant hypersensitivity to ustekinumab products or to any of the excipients in ustekinumab-aekn.

Common Adverse Reactions

Vomiting, nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, headache, diarrhea, fatigue, nausea, bronchitis, pruritus, urinary tract infection, and sinusitis.

Warnings & Precautions

- Infections
- Theoretical Risk for Particular Infections
- Tuberculosis
- Malignancies
- Hypersensitivity Reactions
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Noninfectious Pneumonia
- Avoid Live Vaccines

Clinical Studies

Clinical studies have shown Selarsdi is similar to its reference product Stelara in terms of pharmacokinetic characteristics, safety, tolerability, and efficacy.

Place in Therapy

Ustekinumab is used for treating immune-mediated diseases like psoriasis, psoriatic arthritis, ulcerative colitis and Crohn's disease. This approval paves the way for Selarsdi to further align its label with the indications of the reference product Stelara (ustekinumab). The FDA previously approved Selarsi 45 mg/0.5 mL and 90 mg/mL in a single-dose prefilled syringe for subcutaneous injection in the beginning of 2024.

Other notable new approvals include:

Bimzelx™ (bimekizumab-bkzx) injection, for subcutaneous use

- The FDA has approved a 2 mL pre-filled syringe and pre-filled autoinjector, each containing 320 mg of bimekizumab-bkzx. This new device strength means that patients requiring a 320 mg dose of bimekizumab-bkzx will have options for single-injection administration. Before, Bimzelx was only available as a 1 mL administration option containing 160 mg of bimekizumab-bkzx

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)
Octreotide acetate	Teva	Sandostatin LAR Depot	Endocrine and Metabolic Agents – Misc.	[1] Acromegaly; [2] Severe diarrhea and flushing episodes associated with carcinoid tumors; [3] Profuse diarrhea associated with Vasoactive Intestinal Peptide (VIP)-secreting tumors
Minocycline Hydrochloride Injection	Nexus Pharmaceuticals, Inc	Minocin Injection	Tetracyclines	Bacterial Infections

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
Opdivo (nivolumab) From: Bristol Myers Squibb	[1] Unresectable or metastatic melanoma; [2] Adjuvant treatment of melanoma; [3] Metastatic NSCLC; [4] Malignant pleural mesothelioma; [5] Advanced RCC; [6] Classical HL; [7] SCCHN; [8] UC; [9] Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer; [10] Hepatocellular carcinoma; [11] Esophageal carcinoma; [12] Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.	For the treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by single-agent Opdivo as adjuvant treatment after surgery – otherwise referred to as perioperative therapy, which is used before and after surgery.
Lumryz (sodium oxybate) From: Avadel CNS	For the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.	For the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.
Abrysvo (respiratory syncytial virus vaccine) From: Pfizer	[1] Immunization of pregnant individuals; [2] Immunization of individuals 60 years of age and older	Active immunization for the prevention of LRTD caused by RSV in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV.
Jylamvo (methotrexate) From: Shorla	[1] Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen; [2] Treatment of adults with mycosis fungoides; [3] Treatment of adults with relapsed or refractory non Hodgkin lymphoma as part of a metronomic combination regimen; [4] Treatment of adults with rheumatoid arthritis; [5] Treatment of adults with severe psoriasis.	[1] Treatment of adults and pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen; [2] Treatment of adults with mycosis fungoides; [3] Treatment of adults with relapsed or refractory non Hodgkin lymphoma as part of a metronomic combination regimen; [4] Treatment of adults with rheumatoid arthritis; [5] Treatment of pediatric patients with polyarticular juvenile

		idiopathic arthritis (pJIA); [6] Treatment of adults with severe psoriasis.
Scemblix (asciminib) From: Novartis	[1] Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs); [2] Ph+ CML in CP with the T315I mutation.	Newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

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
Reprolalap From: Aldeyra Therapeutics	Dry eye disease	NDA resubmitted	Low
Elinzanetant From: Bayer	Hot Flashes, Menopausal Disorders	NDA accepted	High
TNX-102 (cyclobenzaprine hydrochloride) From: Tonix Pharmaceuticals	Fibromyalgia	NDA submitted	Moderate
UGN-102 (mitomycin) From: UroGen	Bladder cancer	NDA submitted	High
LNZ100 (aceclidine) From: LENZ Therapeutics	Presbyopia	NDA accepted	Moderate