PharmNotes

Monthly Communications

April 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 April.

New FDA-Approved Drug Products

New Molecular Entity

Zevtera™ (ceftobiprole medocaril sodium) injection

FDA-Approved Indication

- For the treatment of adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia) (SAB), including those with right-sided infective endocarditis.
- For the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI).
- For the treatment of adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP).

Dosage & Administration

The recommended dosage for adult patients is 667mg (every 6 hours on days 1-8; and then every 8 hours from day 9). The recommended dosage for pediatric patients is based on patient's weight (up to 667mg/dose every 8 hours). The duration of treatment in adult patients is up to 42 days for SAB and 5 -14 days for ABSSSI and CABP. The duration of treatment for CABP in pediatric patients is 7 – 14 days.

Dosage Forms & Strengths

For injection: 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) as a lyophilized powder for reconstitution in a single-dose vial.

Contraindications

In patients with a known history of severe hypersensitivity to Zevtera, or to other members of the cephalosporin class.

Common Adverse Reactions

Anemia, nausea, hypokalemia, vomiting, hepatic enzymes and bilirubin increased, headache, diarrhea, blood creatinine increased, rash, phlebitis, hypertension, leukopenia and pyrexia.

Drug Interactions

- Organic Anion Transporting Polypeptide 1B1/1B3 (OATP1B1/OATP1B3) Substrates

Warnings & Precautions

- Increased mortality with unapproved use in ventilator-associated bacterial pneumonia (VABP) patients.
- Hypersensitivity reactions
- Seizures and other adverse central nervous system (CNS) reactions.
- *Clostridioides difficile*-associated diarrhea (CDAD)

Clinical Studies

The approval was supported by clinical efficacy and safety data from the phase 3 studies ERADICATE (SAB) and TARGET (ABSSSI), and two phase 3 studies in CABP. In the ERADICATE. among a total of 390 patients with SAB, 69.8% of those who received Zevtera achieved overall treatment success, defined as survival, symptom improvement, SAB bloodstream clearance, no new SAB complications, and no use of other potentially effective antibiotics after 70 days of treatment, compared with 68.7% of patients who received daptomycin + optional aztreonam. In the TARGET trial, among a total of 679 patients with ABSSSIs, 91.3% of those who received Zevtera achieved an early CR compared with 88.1% of patients in the vancomycin + aztreonam arm. In the CABP Trial, of the patients who received Zevtera, 76.4% achieved clinical cure compared to 79.3% of patients who received the comparator. An additional analysis considered an earlier timepoint of clinical success at Day 3, which was 71.0% in patients receiving Zevtera and 71.1% in patients receiving the comparator.

Place in Therapy

Zevtera will compete with vancomycin and other antibiotics with activity against MRSA, but will also cover gram-negative pathogens, eliminating the need for multiple antibiotics in mixed infections.

New FDA-Approved Drug Products

New Molecular Entity

Lumisight™ (pegulicianine) injection

FDA-Approved Indication

An optical imaging agent indicated for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity.

Dosage & Administration

1 mg/kg intravenous injection over 3 minutes administered 2 hours to 6 hours prior to imaging.

Dosage Forms & Strengths

For injection: lyophilized powder in a single-dose vial delivering 39mg of pegulicianine after reconstitution.

Contraindications

History of hypersensitivity reaction to pegulicianine.

Common Adverse Reactions

Hypersensitivity and chromaturia.

Warnings & Precautions

- ***BBW:*** Anaphylaxis and other serious hypersensitivity reactions.
- Risk of misdiagnosis
- Interference from dyes used for sentinel lymph node mapping.

Contraindications

History of hypersensitivity reaction to pegulicianine.

Clinical Studies

The efficacy and safety of Lumisight were evaluated in a multicenter, intra-patient controlled clinical trial (NCT03686215) of patients with breast cancer undergoing lumpectomy surgery. A total of 357 patients underwent image-guided surgery with the Lumicell DVS following standard of care lumpectomy. The study assessed the proportion of patients receiving Lumisight who had residual cancer detected and removed after the standard of care lumpectomy. A total of 27 of 357 patients (7.6%) had cancer in at least one Lumisight-guided shave. Sensitivity was 49.1% and specificity was 86.5%. Forty-three percent (43%) of patients had at least one false positive image and 8% of patients had at least one false negative image.

Place in Therapy

This product is the first and only imaging combination product capable of detecting cancerous tissue where it matters most, inside the breast cavity.

New FDA-Approved Drug Products

New Molecular Entity

Anktiva™ (nogapendekin alfa inbakicept-pmln) solution

Specialty

FDA-Approved Indication

Indicated with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

Dosage & Administration

For induction the dose is 400 mcg administered intravesical with BCG once a week for 6 weeks. A second induction course may be administered if complete response is not achieved at month. For maintenance: 400mcg administered intravesical with BCG once a week for 3 weeks at months 4,7,10,13 and 19. For patients with an ongoing complete response at month 25 and later, additional maintenance instillations, with BCG may be administered once a week for 3 weeks at months 25, 31 and 37. Instill intravesically only after dilution. Total time from vial puncture to the completion of the intravesical instillation should not exceed 2 hours.

Dosage Forms & Strengths

400 mcg/0.4 mL, clear to slightly opalescent and colorless to slightly yellow solution in single-dose vials for intravesical instillation after dilution.

Contraindications

None

Common Adverse Reactions

Increased creatinine, dysuria, hematuria, urinary frequency, micturition urgency, urinary tract infection, increased potassium, musculoskeletal pain, chills, and pyrexia.

Warnings & Precautions

- Delaying cystectomy can lead to the development of metastatic bladder cancer, which can be lethal.

Use in Specific Populations

- Pregnancy: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

Clinical Studies

The approval of Anktiva, a first-in-class IL-15 agonist immunotherapy for NMIBC, was supported by results from the Phase 2/3 QUILT-3.032 trial, a single-arm, multicenter study that included 77 patients with BCG-unresponsive, high-risk NMIBC with CIS with or without Ta/T1 papillary disease following transurethral resection. The CR rate was 62%, with the upper end of the 95% confidence interval (CI) being 73%. The final median DOR has yet to be determined. In total, 58% of patients with a CR had a DOR ≥12 months and 40% had a DOR ≥24 months.

Place in Therapy

Intravesical BCG administration is seen as the gold-standard adjuvant immunotherapy for high-risk NMIBC with CIS. Limited treatment options are available for patients who fail to respond to BCG. Cystectomy has been the standard of care in this patient population; however, it is a highly invasive procedure. Keytruda and Adstiladrin are now being used in this population with positive results. Anktiva will compete with Keytruda (pembrolizumab) and Adstiladrin (nadofaragene firadenovec).

New FDA-Approved Drug Products

New Molecular Entity

Ojemda™ (tovorafenib) tablets & suspension

Specialty | Orphan Drug

FDA-Approved Indication

For the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (pLGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

Dosage & Administration

Recommended dosage of Ojemda is based on body surface area. Administer Ojemda orally, once weekly, with or without food.

Dosage Forms & Strengths

Tablets: 100 mg

For Oral Suspension: 25 mg/mL

Contraindications

None

Common Adverse Reactions

Rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection. The most common laboratory abnormalities were decreased phosphate, decreased hemoglobin, increased creatinine phosphokinase, increased alanine aminotransferase, decreased albumin, decreased lymphocytes, decreased leukocytes, increased aspartate aminotransferase, decreased potassium, and decreased sodium.

Warnings & Precautions

- Hemorrhage
- Skin toxicity including Photosensitivity.
- Hepatotoxicity
- Effect on Growth
- Embryo-Fetal Toxicity
- NF1 Associated Tumors

Use in Specific Populations

- Lactation: Advise not to breastfeed.
- Infertility: May impair infertility in males and females.

Drug Interactions

- Moderate and Strong CYP2C8 Inhibitors/Inducers
- Certain CYP3A Substrates
- Hormonal contraceptives

Clinical Studies

The efficacy of Ojemda was established in the Phase 2 FIREFLY-1 trial, an open-label, single-arm, multicenter study that included 76 patients with relapsed or refractory pLGG harboring an activating BRAF alteration. Patients previously received at least one line of systemic therapy. The major efficacy measure was overall response rate (ORR). An additional efficacy measure was duration of response (DOR). The ORR was 51%, and median DOR was 13.8 months.

Place in Therapy

LGG is the most common pediatric brain cancer, accounting for approximately 33% of all childhood brain tumors. Approximately 75% of pLGG cases involve a BRAF alteration; of these, about 80% have BRAF fusions and about 20% have BRAF V600 mutations.Ojemda is the second agent approved for BRAF V600E-mutated pLGG. It will compete with Novartis' BRAF/MEK inhibitor combination Mekinist (dosed once daily) plus Tafinlar (dosed twice daily), which received approval for the treatment of pLGG with BRAF V600E mutations. Mekinist plus Tafinlar combination exhibited an ORR of 47%.

New FDA-Approved Drug Products

New Molecular Entity

Pivya™ (pivmecillinam) tablets, for oral use

FDA-Approved Indication

For the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus*.

Dosage & Administration

One 185 mg tablet orally 3 times a day for 3 to 7 days as clinically indicated.

Dosage Forms & Strengths

Tablets: 185 mg pivmecillinam

Contraindications

- Serious hypersensitivity reactions
- Primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, and other inborn errors of metabolism.
- Acute porphyria.

Common Adverse Reactions

Nausea and diarrhea.

Warnings & Precautions

- Hypersensitivity Reactions
- Severe Cutaneous Adverse Reactions (SCAR)
- Carnitine Depletion
- *Clostridioides difficile*- Associated Diarrhea (CDAD)
- Interference with Newborn Screening Test

Clinical Studies

The efficacy of Pivya was established in three controlled studies comparing different Pivya to placebo, fosfomycin, or ibuprofen. The primary endpoint was the composite response rate, which included clinical cure (resolution of the symptoms of the uncomplicated UTI that were present in patients at trial entry and no new symptoms) and microbiological response (demonstration that the bacteria cultured from patients' urine at trial entry was reduced). In the clinical trial comparing Pivya to placebo, 62% of the 137 subjects who received Pivya achieved the composite response compared to 10% of the 134 who received placebo. In the clinical trial comparing Pivya to fosfomycin, 72% of the 127 subjects who received Pivya achieved composite response compared to 76% of the 132 who received the comparator drug. In the clinical trial comparing Pivya to ibuprofen, 66% of the 105 subjects who received Pivya achieved composite response compared to 22% of the 119 who received ibuprofen.

Place in Therapy

Pivya is the first drug approved for uUTI in the U.S. in over 20 years. It's an aminopenicillin, which is a type of beta-lactam. Pivmecillinam has been used successfully in Europe for the treatment of uUTIs for over 40 years and is included in guidelines from the Infectious Disease Society of America (IDSA) as a first-line option for treatment of uUTI.

New FDA-Approved Drug Products

New Molecular Entity

Xolremdi™ (mavorixafor) capsules, for oral use

Specialty | Orphan Drug

FDA-Approved Indication

For the treatment of patients 12 years of age and older with WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes.

Dosage & Administration

For weight more than 50 kg: 400 mg orally once daily. For weight less than or equal to 50 kg: 300 mg orally once daily. Administer on an empty stomach after an overnight fast, and at least 30 minutes before food.

Dosage Forms & Strengths

Capsules: 100 mg mavorixafor

Contraindications

Use with drugs highly dependent on CYP2D6 for clearance.

Common Adverse Reactions

Thrombocytopenia, pityriasis, rash, rhinitis, epistaxis, vomiting, and dizziness.

Warnings & Precautions

- Embryo-Fetal toxicity
- QTc Interval Prolongation

Drug Interactions

- Strong CYP3A4 Inhibitors/Inducers
- P-gp Inhibitors or Moderate CYP3A4 Inhibitors
- CYP3A4 or P-gp substrates

Use in Specific Populations

- Lactation: Advise females that breastfeeding is not recommended.
- Renal Impairment: Not recommended for use in patients with severe renal impairment or end stage renal disease.
- Hepatic Impairment: Not recommended for use in patients with moderate to severe hepatic impairment.

Clinical Studies

The FDA approval of Xolremdi was based on results of the pivotal, 4WHIM Phase 3 clinical trial, a global, randomized, double-blind, placebo-controlled, 52-week multicenter study that evaluated the efficacy and safety of Xolremdi in 31 people aged 12 years and older diagnosed with WHIM syndrome. The efficacy of Xolremdi was determined by improvement in absolute neutrophil counts (ANC), improvement in absolute lymphocyte counts (ALC), and a reduction in infections. In the trial, Xolremdi treatment demonstrated increased time above threshold (≥500 cells/microliter) for absolute neutrophil count vs. placebo ($p<0.0001$) and increased time above threshold (≥1000 cells/microliter) for absolute lymphocyte count vs. placebo ($p<0.0001$). The efficacy of Xolremdi was further assessed in a composite endpoint consisting of total infection score and total wart change score using a Win-Ratio method.

Place in Therapy

Xolremdi, a selective CXC chemokine receptor 4 (CXCR4) antagonist, is the first therapy specifically indicated in patients with WHIM syndrome, a rare, combined primary immunodeficiency and chronic neutropenic disorder caused by CXCR4 pathway dysfunction. Typical treatment for WHIM syndrome has historically included the use of granulocyte-colony stimulating factor (G-CSF) and intravenous immunoglobulin (IVIG).

New FDA-Approved Drug Products

New Molecular Entity

Beqvez™ (fidanacogene elaparvovec-dzkt) injection, for intravenous use

Specialty | Orphan Drug

FDA-Approved Indication

For the treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who: currently use factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes, and, do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.

Dosage & Administration

For one-time single-dose intravenous infusion only
The recommended dose is 5×10^{11} vector genomes per kg (vg/kg) of body weight. Dose based on adjusted body weight for those with a BMI >30 kg/m^2.

Dosage Forms & Strengths

Suspension for intravenous infusion after dilution. Beqvez has a nominal concentration of 1×10^{13} vg/mL, and each vial contains an extractable volume of 1 mL. The total number of vials will be customized to meet dosing requirements for individual patients based on their weight.

Contraindications

None

Common Adverse Reactions

Increase in transaminases.

Warnings & Precautions

- Hepatotoxicity
- Infusion Reactions
- Malignancy
- Monitoring laboratory test

Use in Specific Populations

- There is limited information on the safety and effectiveness of Beqvez in patients with HIV infection.
- The safety and effectiveness of Beqvez in patients with prior or active factor IX inhibitors have not been established.

Clinical Studies

The approval was based on promising data from the Phase III open-label, single-arm BENEGENE-2 trial, which evaluated the efficacy and safety of Beqvez™ in 45 males aged 18 to 65 years with moderately severe to severe hemophilia B. All participants were required to have completed a minimum of six months routine FIX prophylaxis therapy during the lead-in study, also while receiving a single IV infusion of the therapy. The trial demonstrated noninferiority in annualized bleeding rates (ABR) compared with standard-of-care (SOC) FIX therapy. Treatment with Beqvez resulted in a mean ABR of 2.5 in the efficacy evaluation period between Week 12 and data cutoff (median 1.8 years of follow-up), compared to a mean ABR of 4.5 during the lead-in pretreatment period of at least 6 months (median 1.2 years of follow-up). Bleeds were eliminated in 60% of patients compared to 29% in the prophylaxis arm.

Place in Therapy

Hemophilia is a disease that interferes with the normal coagulation process. Patients with hemophilia B typically receive prophylaxis with factor IX products. Beqvez is the second gene therapy approved for the treatment of hemophilia B, following Hemgenix (etranacogene dezaparvovec-drlb).

New FDA-Approved Drug Products

New Biosimilar Product

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

Specialty

FDA-Approved Indication

- For the treatment of adult and pediatric patients (6 years and older) with moderate to severe plaque psoriasis (PSO) who are candidates to phototherapy or systemic therapy
- For the treatment of adult and pediatric patients (6 years and older) with active psoriatic arthritis

Dosage & Administration

Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter. For 60kg to 100kg: 45mg. For greater than 100kg: 90 mg

Dosage Forms & Strengths

Subcutaneous injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe.

Contraindications

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

Common Adverse Reactions

Nasopharyngitis, upper respiratory tract infection, headache, and fatigue.

Warnings & Precautions

- Infections
- Theorical Risk for Particular Infections
- Tuberculosis (TB)
- Malignancies
- Hypersensitivity Reactions
- Posterior Reversible Encephalopathy
- Immunizations
- Noninfectious Pneumonia

Clinical Studies

The FDA approval of Selarsdi was based on data from a phase 3 study that compared the efficacy and safety of Selarsdi to the reference product Stelara in patients with moderate to severe plaque psoriasis. Results showed the products were therapeutically equivalent, meeting the primary endpoint for psoriasis area and severity index percent improvement from baseline to week 12. A phase 1 study showed bioequivalence between Selsardi and the reference product.

Place in Therapy

Ustekinumab products are used to treat moderate to severe plaque psoriasis, psoriatic arthritis, Crohn disease, and ulcerative colitis. The first ustekinumab biosimilar (Wezlana; ustekinumab-auub) was approved last year. Wezlana was also approved with interchangeability.

New FDA-Approved Drug Products

New Biosimilar Product

Hercessi™ (trastuzumab-strf) lyophilized powder, for intravenous use

Specialty

FDA-Approved Indication

- For the treatment of HER-2 overexpressing breast cancer.
- For the treatment of HER-2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Dosage & Administration

Adjuvant treatment of HER2-Overexpressing Breast Cancer:

- Initial dose of 4 mg/kg over 90-minute IV infusion, then 2 mg/kg over 30-minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of Hercessi, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy.
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer:

- Initial dose of 4 mg/kg as a 90-minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30-minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer:

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

Dosage Forms & Strengths

For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution

Contraindications

None

Common Adverse Reactions

Headache, fever, infections, insomnia, cough, congestive heart failure, rash, stomatitis, neutropenia, diarrhea, nausea, and chills.

Warnings & Precautions

- ***BBW***: Cardiomyopathy, Infusion Reactions, Embryo-Fetal Toxicity and Pulmonary Toxicity.
- Exacerbation of Chemotherapy- Induced Neutropenia.

Clinical Studies

FDA approval was granted based on comprehensive analytical, pre-clinical, and clinical data, which showed Hercessi and its reference product, Herceptin (trastuzumab) are highly similar in terms of efficacy, safety, and quality. The study was able to demonstrate pharmacokinetic (PK) comparability and clinical efficacy/safety similarity between Hercessi and its reference product.

Place in Therapy

Hercessi (trastuzumab-strf) is the sixth biosimilar to Herceptin. Despite its aggressive nature, HER2-positive cancer shows a more favorable response to treatments that specifically target HER2 proteins in cancer therapy. As a biosimilar, Hercessi provides additional treatment options that may be more affordable.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Xromi™ (hydroxyurea) oral solution

Specialty | Orphan Drug

FDA-Approved Indication

To reduce the frequency of painful crises and reduce the need for blood transfusions in pediatric patients aged 6 months of age to less than 2 years with sickle cell anemia with recurrent moderate to severe painful crises.

Dosage & Administration

Initial dose: 15 mg/kg orally once daily. Monitor the patient's blood count every two weeks. The dose may be increased by 5 mg/kg/day every 8 to12 weeks until a maximum tolerated dose or 35 mg/kg/day is reached if blood counts are in an acceptable range. The dose is not increased if blood counts are below the acceptable range and toxic. Discontinue Xromi until hematologic recovery if blood counts are considered toxic. Renal impairment: Reduce the dose of Xromi by 50% in patients with creatinine clearance less than 60 mL/min.

Dosage Forms & Strengths

Oral Solution: 100 mg/mL in a 150 mL multiple-dose bottle

Contraindications

In patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

Warnings & Precautions

- ***BBW:*** Myelosuppression and Malignancies
- Hemolytic anemia
- Embryo-Fetal toxicity
- Vasculitic toxicities
- Live Vaccinations
- Risk with concomitant use of antiretroviral drugs.

Common Adverse Reactions

Neutropenia and thrombocytopenia.

Drug Interaction

- Antiretroviral drug.
- Laboratory Test Interference.

Clinical Studies

The effectiveness of Xromi was established based on an adequate and well-controlled study of hydroxyurea capsules in adult patients that had sickle cell anemia with recurrent moderate to severe pain crises and additional pharmacokinetic data from a single-arm, open-label study of Xromi in pediatric patients aged 10 months to less than 2 years with sickle cell anemia, who were treatment naïve or had not received hydroxyurea in the 6 months prior to enrollment.

Place in Therapy

Sickle cell anemia, a type of sickle cell disease (SCD), is an inherited blood disorder that affects hemoglobin (Hb). Patients with SCD frequently experience severe pain related to vaso-occlusive crises (VOCs), resulting in significantly higher hospitalization rates and emergency department (ED) utilization rates compared with the general population. SCD affects about 100,000 people in the United States. Hydroxyurea is considered the gold standard and is usually a first-line therapy in individuals with SCD who have frequent VOCs, including infants, children, and adults. Generic hydroxyurea, although not FDA-approved for SCD, is frequently used off-label in adults due to its documented clinical efficacy in SCD and low cost compared to other SCD agents. Its use in pediatric patients is limited; its availability as only a 500-mg capsule proves challenging in children due to lack of dosing flexibility and difficulty swallowing. However, the capsules may be used in compounding oral liquid formulations of hydroxyurea for use in the infant and young pediatric population.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Rezenopy™ (naloxone hydrochloride) nasal spray

FDA-Approved Indication

For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adult and pediatric patient.

Dosage & Administration

For intranasal use only (seek emergency medical care immediately after use). Administration of a single spray of Rezenopy nasal spray intranasally into one nostril in adult and pediatric patients. If the patient does not respond within 2 to 3 minutes or responds and then relapses into respiratory depression, an additional dose of Rezenopy nasal spray may be given into the other nostril with a new device. Do not administer more than 2 sprays per day.

Dosage Forms & Strengths

Nasal spray: 10 mg of naloxone hydrochloride in 0.11 mL.

Contraindications

Hypersensitivity to naloxone hydrochloride.

Warnings & Precautions

- Risk of recurrent respiratory and CNS depression
- Risk of limited efficacy with partial agonist or mixed agonist/ antagonist
- Precipitation of severe opioid withdrawal
- Risk of cardiovascular (CV) effects

Common Adverse Reactions

Abdominal pain upper, nasopharyngitis, and dysgeusia.

Clinical Studies

The approval was supported by pharmacokinetic data, which established the safety and efficacy of the product.

Place in Therapy

The United States Centers for Disease Control and Prevention's National Center for Health Statistics estimated that there were almost 107,000 individuals that died from a drug overdose in 2021. Other formulations of naloxone are available as a nasal spray and injection for opioid overdose. This includes over-the-counter (OTC) formulations (e.g., Narcan).

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Retevmo™ (selpercatinib) tablets, for oral use

Specialty | Orphan Drug

FDA-Approved Indication

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA approved test.
- Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy.
- Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).
- Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

Dosage & Administration

Dosage is based on weight. Less than 50 kg: 120 mg orally twice daily. 50 kg or greater: 160 mg orally twice daily.

Dosage Forms & Strengths

Capsules: 40 mg, 80 mg
Tablets: 40 mg, 80 mg, 120 mg, 160 mg

Contraindications

None

Common Adverse Reactions

Edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, headache, decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium.

Warnings & Precautions

- Hepatotoxicity
- Interstitial Lung Disease (ILD)/ Pneumonitis
- Hypertension
- QT interval Prolongation
- Hemorrhagic events
- Hypersensitivity
- Tumor Lysis Syndrome
- Risk of Impaired Wound Healing
- Hypothyroidism
- Embryo-Fetal toxicity

Drug Interactions

- Acid Reducing Agents
- Strong and Moderate CYP3A Inhibitors
- Strong and Moderate CYP 3A Inducers
- CYP2C8 and CYP3A Substrates
- Certain P-gp Substrates

Use in Specific Population

- Lactation: Advise not to breastfeed.
- Pediatric Use: Monitor open growth plates in adolescent patients.

Place in Therapy

Retevmo is a selective RET kinase inhibitor, and it is approved specifically for patients with cancer who have RET gene alterations. There are two products for RET-mutated cancers: Retevmo and Gavreto.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Entresto™ sprinkle (sacubitril and valsartan) oral pellets

FDA-Approved Indication

To reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

Dosage & Administration

Orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient. If less than 40kg: 1.6 mg/kg to 3.1mg/kg. If 40kg but less than 50kg: 24 mg/kg to 72 mg/kg. If at least 50kg: 49 mg/kg to 97 mg/kg.

Dosage Forms & Strengths

Film-coated oral pellets within capsules: 6 mg/6 mg; 15 mg/16 mg.

Contraindications

- Hypersensitivity to any component.
- History of angioedema related to previous ACEi or ARB therapy.
- Concomitant use with ACE inhibitors.
- Concomitant use with aliskiren in patients with diabetes.

Warnings & Precautions

- Observe for signs and symptoms of angioedema and hypotension.
- Monitor renal function and potassium in susceptible patients.

Common Adverse Reactions

Hypotension, hyperkalemia, cough, dizziness, and renal failure.

Drug Interactions

- Avoid concomitant use with aliskiren in patients with estimated glomerular filtration rate less than 60
- Potassium-sparing diuretics
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- Lithium

Use in Specific Population

- Lactation: Breastfeeding not recommended
- Severe Hepatic Impairment: Use not recommended.

Place in Therapy

Current standard of care treatments for heart failure includes ARNI (ARB+neprolysin inhibitor; Entresto). Entresto is preferred instead of an ACEi or ARB when possible because it prevents hospitalization or CV death in about 1 in 21 patients versus an ACEi alone in patients with HFrEF, per 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Ingrezza™ Sprinkle (valbenazine) capsules, for oral use

Specialty | Orphan Drug

FDA-Approved Indication

- Tardive dyskinesia
- Chorea associated with Huntington's disease

Dosage & Administration

For tardive dyskinesia: The initial dosage is 40 mg once daily. After one week, increase the dose to the recommended dosage of 80 mg once daily. For chorea associated with Huntington's disease: The initial dosage is 40 mg once daily. Increase the dose in 20 mg increments every two weeks to the recommended dosage of 80 mg once daily. Ingrezza Sprinkle may be opened and sprinkled over soft food (do not use milk or drinking water) and may be swallowed whole with water. Do not crush or chew.

Dosage Forms & Strengths

Ingrezza Sprinkle capsules: 40 mg, 60 mg, and 80 mg

Contraindications

Known hypersensitivity to valbenazine or any components of Ingrezza or Ingrezza Sprinkle.

Warnings & Precautions

- ***BBW:*** Depression and suicidal ideation and behavior in patients with Huntington's disease.
- Hypersensitivity, including angioedema may occur.
- Somnolence/sedation
- QT Prolongation
- Neuroleptic Malignant Syndrome (NMS)
- Parkinsonism

Common Adverse Reactions

Somnolence, urticaria, rash, and insomnia.

Use in Specific Population

- Pregnancy: May cause fetal harm.
- Lactation: Advise not to breastfeed

Drug Interactions

- MAOIs
- Strong CYP3A4 Inducers/Inhibitors
- Strong CYP2D6 Inhibitors

Clinical Studies

The FDA based its approval on data showing bioequivalence and tolerability of Ingrezza Sprinkle as compared with Ingrezza capsules.

Place in Therapy

First-line treatment options for TD include specific movement disorder medications, such as Ingrezza and Austedo. Ingrezza Sprinkle to make administration easier for patients who have difficulty swallowing or prefer not to take a capsule. Ingrezza Sprinkle offers the same dosage strengths as Ingrezza, and the contents of the capsules can be sprinkled on soft food for oral administration.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Specialty | Orphan Drug

Rinvoq™ LQ (upadacitinib) solution, for oral use

FDA-Approved Indication

- For the treatment of adults and pediatric patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers
- For the treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

Dosage & Administration

Rinvoq LQ oral solution is not substitutable with Rinvoq extended-release tablets.

- *Psoriatic Arthritis*: Pediatric Patients 2 to less than 18 Years of Age Weighing at Least 10 kg: The recommended dosage is based on body weight.
- *Polyarticular Juvenile Idiopathic Arthritis*: The recommended dosage is based on body weight.

Dosage Forms & Strengths

Oral solution: 1 mg/mL

Contraindications

Known hypersensitivity to upadacitinib or any of the excipients in Rinvoq/ Rinvoq LQ

Warnings & Precautions

- ***BBW:*** Serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis.
- Hypersensitivity
- Gastrointestinal (GI) Perforations
- Laboratory Abnormalities
- Vaccinations
- Medication residue stools

Common Adverse Reactions

Upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, and headache.

Drug Interactions

- Strong CYP3A4 Inhibitors/Inducers

Use in Specific Population

- Hepatic Impairment: Not recommended in patients with severe hepatic impairment.

Place in Therapy

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, manifesting most commonly with peripheral arthritis, dactylitis, enthesitis, and spondylitis. It is to be used in PsA after the use of TNF blockers due to safety concerns with the JAK inhibitor class. Xeljanz and Rinvoq are the only JAK inhibitors approved to treat PsA, but only Rinvoq LQ is indicated for pediatric patients. Xeljanz oral solution will compete with Rinvoq LQ for the indication of polyarticular idiopathic arthritis.

New FDA-Approved Drug Products

New Formulations, Combinations, and Line Extensions

Vijoice™ (alpelisib) oral granules

Specialty | Orphan Drug

FDA-Approved Indication

For the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CARelated Overgrowth Spectrum (PROS) who require systemic therapy.

Dosage & Administration

The recommended dosage of Vijoice in adult patients is 250 mg orally, once daily, administered as recommended until disease progression or unacceptable toxicity. The recommended initial dosage of Vijoice in pediatric patients is 50 mg orally, once daily, administered as recommended until disease progression or unacceptable toxicity.

Dosage Forms & Strengths

Oral Granules: 50 mg

Contraindications

Severe hypersensitivity to Vijoice or to any of its ingredients.

Warnings & Precautions

- Severe Hypersensitivity
- Severe Cutaneous Adverse Reactions (SCAR's)
- Hyperglycemia
- Pneumonitis
- Diarrhea or Colitis
- Embryo-Fetal Toxicity

Common Adverse Reactions

Diarrhea, stomatitis, and hyperglycemia.

Use in Specific Population

- Lactation: Advise not to breastfeed.

Clinical Studies

The FDA approval of Vijoice was based on real-world data from the EPIK-P1 clinical trial, a retrospective chart review study that evaluated the efficacy of alpelisib in 37 patients 2 years of age and older with PROS. Patients in the study had received alpelisib as part of an expanded access program for compassionate use. The primary efficacy outcome measure was the proportion of patients with a radiological response at Week 24, defined as a ≥20% reduction from baseline in the sum of measurable target lesion volume. Of the 37 patients included in the efficacy population, 27% had a radiological response at Week 24, and 60% had a response lasting 12 months or longer.

Place in Therapy

Vijoice is a kinase inhibitor that works by inhibiting the PI3K pathway and is the first FDA-approved treatment for PROS. Vijoice was previously available as an oral tablet for this indication.

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)
Valbenazine Tosylate Capsules 40mg and 80mg	Lupin Pharmaceuticals, Inc.	Ingrezza	Psychotherapeutic and Neurological Agents- Misc.	[1] Huntington's Disease; [2] Tardive Dyskenia
Erbulin Mesylate Intravenous Solution 1mg/ 2mL (0.5 mg/mL)	Gland Pharma Limited	Halaven	Antineoplastic and Adjunctive Therapies	[1] Breast Cancer; [2] Liposarcoma
Doxycycline (Anhydrous) Immediate / Delayed Release Capsules 40 mg	Dr. Reddys Laboratories Inc; Lupin Pharmaceuticals, Inc.	Oracea	Dermatologicals	Rosacea
Estradiol Transdermal Gel (Metered) 0.06% (1.25 g / activation)	Solaris Pharma Corporation	EstroGel	Estrogens	Menopausal Symptoms
Deflazacort Oral Suspension 22.75 mg/mL	Tris Pharma Inc.	Emflanza Suspension	Corticosteroids	Duchenne Muscular Dystrophy
Midostaurin Capsules 25mg	Teva Pharmaceuticals USA, Inc.	Rydapt	Antineoplastic and Adjunctive Therapies	[1] Acute Myeloid Leukemia; [2] Systemic Mastocytosis.
Mirabegron extended-release tablets 25mg	Lupin Pharmaceuticals, Inc.; Zydus Pharmaceuticals	Myrbetriq	Urinary Antispasmodics	Overactive bladder

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
Fanapt (iloperidone) From: Vanda Pharms, Inc	For the treatment of schizophrenia in adults	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults
Abecma (idecabtagene vicleucel) From: Bristol Myers Squibb	For the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an Anti-CD38 monoclonal antibody.	For the treatment of adult patients with relapsed or refractory multiple myeloma after two or more prior lines of therapy including an immunomodulatory agent (IMID), a proteasome inhibitor (PI), and an Anti-CD38 monoclonal antibody
Fasenra (benralizumab) From: Astrazeneca	For the maintenance treatment of patients with severe asthma aged 12 years or older with eosinophilic phenotype.	For the treatment of children aged 6 to 11 with severe asthma.
Dovato (dolutegravir and lamivudine) From: VIIV Hlthcare	For the treatment of HIV-1 infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato™	For the treatment of HIV-1 infection in adults and adolescents 12 years of age and older with weighting at least 25kg with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Dovato™
Carvykti (ciltacabtagene autoleucel) From: Janssen Pharmaceuticals, Inc.	For the treatment of adults with Relapsed or Refractory Multiple Myeloma (RRMM) after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an Anti-CD38 monoclonal antibody	For the treatment of adult patients with Relapsed or Refractory Multiple Myeloma who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

Enhertu (fam-trastuzumab deruxtacan-nxki) From: Alexion Pharm	[1] For adult patients with unresectable or metastatic her-2 positive (IHC 3+ or ISH positive) breast cancer who have received a prior Anti-HER2-based regimen [2] For adult patients with unresectable or metastatic her2-low (IHC 1+ or ICH 2+/ISH-) breast cancer, [3] For adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations [4] For adult patients with locally advanced or metastatic her2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.	For adult patients with unresectable or metastatic her2-positive (IHC 3+) solid tumors who have received a prior systemic treatment and have no satisfactory alternative options.
Alecensa (alectinib) From: Hoffmann-La Roche	For the treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test.	For the adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥ 4 cm or node positive) as detected by an FDA approved test.
Lutathera (lutetium Lu 177 dotatate) From: Novartis	For the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.	For the treatment of pediatric patients 12 years and older with somatostatin receptor-positive (SSTR+) gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut NETs.
Ingrezza (valbenazine) From: Neurocrine	For the treatment of adults with Tardive Dyskinesia.	For the treatment of Chorea associated with Huntington's disease.
Otezla (apremilast) From: Amgen Inc.	For treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy.	For the treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

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
Datopotamab deruxtecan From: AstraZeneca; Daiichi Sankyo	Non-Small Cell Lung Cancer	BLA accepted	High
Elamipretide From: *Stealth Bio Therapeutics Inc.*	Barth Syndrome	NDA accepted	High High