**Pharmaceutical Approval Update**

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**Olumiant (baricitinib) tablets**

**Manufacturer:** Eli Lilly, Indianapolis, IN  
**Date of Approval:** May 31, 2018  
**Indication:** Olumiant is indicated for treating adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

**Drug Class:** A Janus kinase (JAK) inhibitor  
**Uniqueness of Drug:** Baricitinib is the second oral JAK inhibitor to be approved by the FDA for the treatment of RA. It is, however, the first JAK inhibitor that has greater inhibitory potency at JAK1, JAK2, and TYK2, compared to JAK3. The first oral JAK inhibitor, tofacitinib, is a specific inhibitor of only JAK3. The relevance of inhibiting the 4 known JAK enzymes (JAK1, JAK2, JAK3, and TYK2) to therapeutic effect is not currently known. Baricitinib is approved for use in more than 30 countries worldwide.

**Warnings and Precautions:**

**Boxed Warning:** for the risk of serious infections, malignancies, and thrombosis.

**Serious infections.** Serious and sometimes fatal bacterial, mycobacterial, invasive viral, fungal, or other opportunistic infections have been reported in Olumiant-treated patients with RA. The use of Olumiant should be avoided in patients with active, serious infection. If a serious infection develops while receiving Olumiant, interrupt therapy until the infection is controlled. Do not give Olumiant to patients with active tuberculosis. Viral reactivation, including cases of herpes virus reactivation, occurred in Olumiant clinical trials. If a patient develops herpes zoster, Olumiant therapy should be stopped until resolution of the infection. Patients should be tested for latent tuberculosis prior to Olumiant initiation.

**Non-melanoma skin cancers (NMSCs).** NMSCs have been reported in Olumiant-treated patients. Therefore, periodic skin examinations are recommended for patients at an increased risk for skin cancer development.

**Thrombosis.** Olumiant should be used with caution in patients who may be at increased risk for thrombosis. Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), were observed at an increased incidence in Olumiant-treated patients compared to placebo-treated patients. In addition, arterial thrombosis events in the extremities have been reported in Olumiant clinical trials. Many of these adverse events were serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. If clinical features suggestive of arterial thrombosis occur, patients should be evaluated promptly and treated appropriately.

**Gastrointestinal (GI) perforation.** Olumiant should be used with caution in patients who may be at increased risk for GI perforation (e.g., history of diverticulitis) since these were reported in clinical studies. Patients who have new-onset abdominal symptoms should be evaluated promptly for the potential for GI perforation.

**Laboratory assessment.** Laboratory assessment is recommended due to the potential for changes in the neutrophil count, lymphocyte count, hemoglobin level, liver enzymes, and lipid profile.

**Vaccinations.** Avoid the use of Olumiant with live vaccines.

**Use in special populations.** Olumiant is not recommended in patients with severe hepatic impairment, or in patients with moderate or severe renal impairment.

**Dosing and Administration:** The recommended dose of Olumiant is one 2-mg tablet daily, taken orally without regard to food. It may be given as monotherapy or in combination with methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs). Olumiant should not be started in patients with an absolute lymphocyte count (ALC) < 500 cells/mm³, an absolute neutrophil count (ANC) < 1,000 cells/mm³, or a hemoglobin level < 8 g/dL. Olumiant doses should be modified in cases of lymphopenia, neutropenia, or anemia, following the label guidelines.

**Commentary:** The efficacy and safety of Olumiant were based on results from RA-BEACON, a randomized, double-blind, placebo-controlled study whereby patients (n = 527) were assigned to treatment with either baricitinib 2 mg or 4 mg, or placebo, along with any conventional DMARDs they were already receiving. Study enrollees had an inadequate response or were intolerant to 1 or more TNF inhibitor therapies. The study showed a statistically higher American College of Rheumatology score of ≥ 20% improvement (ACR20) for baricitinib-treated patients, and early symptom relief at Week 1. ACR20 responses were 49% for baricitinib-treated patients and 27% for placebo-treated patients. At Week 12, improvements in all ACR20 component scores occurred in baricitinib-treated patients compared to placebo-treated patients. Baricitinib-treated patients also described clinical improvements in physical function based on the Health Assessment Questionnaire Disability Index (HAQ-DI) compared to placebo patients. The most common adverse reactions were upper respiratory infections, nausea, herpes simplex, and herpes zoster infections.

**Source:** Eli Lilly and Company, Olumiant prescribing information.

**Zemdri (plazomicin) injection, for intravenous (IV) use**

**Manufacturer:** Achaogen, Inc., South San Francisco, CA  
**Date of Approval:** June 25, 2018  
**Indication:** Plazomicin is indicated for patients 18 years of age or older with complicated urinary tract infections (cUTIs), including pyelonephritis. Since limited clinical safety and efficacy data are available, plazomicin should be reserved for patients who have limited or no alternative treatment options.
Drug Class: An aminoglycoside antibacterial agent

Uniqueness of Drug: Plazomicin is the only once-daily aminoglycoside approved for use in cUTIs, including pyelonephritis. Plazomicin has microbiological activity against pathogens designated by the Centers for Disease Control and Prevention (CDC) as urgent and serious public health threats, including carbapenem-resistant Enterobacteriaceae (CRE) and extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae.

Contraindications: Plazomicin is contraindicated in patients with known hypersensitivity to any aminoglycoside.

Warnings and Precautions:
- **Boxed warning.** Nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm. Similar to other aminoglycosides, nephrotoxicity has been reported with plazomicin. The risk of nephrotoxicity is greater in patients with impaired renal function, the elderly, and in those receiving concomitant nephrotoxic medications. Ototoxicity, manifesting as hearing loss, tinnitus, and/or vertigo, has been reported with plazomicin treatment. Symptoms of aminoglycoside-associated ototoxicity may be irreversible and may not clear up until after therapy completion. Aminoglycosides have been associated with neuromuscular blockade. Patients, particularly those who are considered high-risk, should be monitored for adverse reactions associated with neuromuscular blockade. Aminoglycosides can cause fetal harm when administered to pregnant women.

- Hypersensitivity reactions, including anaphylaxis. These reactions have been reported with aminoglycosides. If an allergic reaction occurs, discontinue plazomicin therapy.

- **Clostridium difficile-associated diarrhea (CDAD).** CDAD has been reported with nearly all systemic antibacterial drugs. If diarrhea occurs, evaluate the patient for CDAD.

Availability and stability. Plazomicin injection 500 mg/10 mL (50 mg/mL) is available as a single-dose vial. After dilution, plazomicin solution for administration is stable for 24 hours at room temperature at concentrations of 2.5 mg/mL to 45 mg/mL in 0.9% Sodium Chloride Injection, USP, and in Lactated Ringer’s Injection, USP. In addition, there is already some published data on the physical compatibility of plazomicin during simulated Y-site administration with some IV drugs (N = 92).

Dosage and Administration: The recommended dose of plazomicin is 15 mg/kg every 24 hours by IV infusion over 30 minutes to patients 18 years of age or older with creatinine clearance (CrCl) ≥ 90 mL/min. The recommended duration of plazomicin therapy is 4 to 7 days for cUTIs, including pyelonephritis. If diarrhea occurs, evaluate the patient for CDAD.

- The recommended dose of plazomicin is 15 mg/kg every 24 hours by IV infusion over 30 minutes to patients 18 years of age or older with creatinine clearance (CrCl) ≥ 90 mL/min. The recommended duration of plazomicin therapy is 4 to 7 days for cUTIs, including pyelonephritis. Plazomicin should be assessed in all patients prior to initiating plazomicin therapy, and daily throughout therapy. For patients with an estimated CrCl (Cockcroft-Gault) ≥ 60 mL/min to < 90 mL/min, the recommended plazomicin dose is 15 mg/kg every 24 hours (using total body weight [TBW]). For patients with TBW > IBW (ideal body weight) by 25% or more, use the adjusted body weight. For estimated CrCl ≥ 30 mL/min to < 60 mL/min, dose 10 mg/kg every 24 hours. For estimated CrCl ≥ 15 mL/min to < 30 mL/min, dose 10 mg/kg every 48 hours.

- **Therapeutic Drug Monitoring (TDM):** It is recommended to perform TDM in cUTI patients with renal impairment. For patients with a CrCl ≥ 15 mL/min and < 90 mL/min, TDM is recommended to maintain plasma trough concentrations below 3 mcg/mL. Plazomicin serum trough concentrations should be measured within about 30 minutes prior to administration of the second plazomicin dose. Adjustment of plazomicin dosing based on TDM involves extending the dosing interval by 1.5-fold (e.g., from every 24 hours to every 36 hours), if the trough concentration is ≥ 3 mcg/mL.

**Commentary:** Efficacy was determined in the microbiological modified intent-to-treat (mMITT; N=388) population (all patients who received study medication and had at least one baseline uropathogen). Included were 42% (n = 162) with pyelonephritis. Baseline characteristics were similar between the 2 treatment groups. Patients were randomized in a double-blind manner in this noninferiority trial to receive plazomicin 15 mg/kg IV once daily over 30 minutes or meropenem 1 gram every 8 hours as an IV infusion. Switching to an oral antibacterial agent was allowed after a minimum of 4 days and a maximum of 7 days of IV therapy, for a total treatment duration of 7-10 days. The median patient age in the trial was 64 years; 53% were female. Co-primary efficacy endpoints were: composite cure (clinical cure and microbiological eradication) in the mMITT population at Day 5; and test-of-cure (TOC) visit (Day 17±2 from the first study drug dose). Composite cure rates at Day 5 were 88% for plazomicin-treated patients compared to 91% of meropenem-treated patients. Composite cure was defined as resolution or improvement of clinical cUTI symptoms and a microbiological outcome of eradication. Composite cure rates at TOC were 82% for plazomicin-treated patients compared to 70% of meropenem-treated patients. The most common adverse reactions were decreased renal function, diarrhea, headache, hypertension, hypotension, nausea, and vomiting.


**Epidiolex (cannabidiol [CBD]) oral solution**

**Manufacturer:** GW Research Ltd, Marketed by Greenwich Biosciences, Inc., Carlsbad, CA

**Date of Approval:** June 25, 2018

**Indication:** Epidiolex (cannabidiol [CBD]) is indicated for treating seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

**Drug Class:** Cannabinoid

**Uniqueness of Drug:** Cannabidiol (CBD) is a chemical component within the Cannabis sativa plant, but it does not cause euphoria. This is the first FDA-approved drug that contains a purified drug component derived from marijuana. It is also the first FDA-approved drug to treat patients with Dravet syndrome. Dravet syndrome is a rare genetic condition occurring in the first year of life, identified with frequent febrile seizures. Later on, different seizure types typically occur, such as myoclonic seizures and, potentially, status epilepticus. Children with Dravet syndrome typically experience poor language and motor skill development, hyperactivity, and difficulty relating to others.

**Contraindications:** Epidiolex is contraindicated in those patients with a prior hypersensitivity reaction to CBD or any of the ingredients in the product, which includes sesame seed oil.

Warnings and Precautions:

**Hepatocellular Injury.** Epidiolex can cause transaminase elevations. Dose-related transaminase elevations occurred in clinical trials. Concomitant use of valproate and higher Epidiolex doses increases the risk of transaminase elevations. Patients with elevated baseline transaminase levels of more than 3 times the upper limit of normal (ULN) (3 x ULN), along with bilirubin elevations of more than 2 x ULN, should be evaluated prior to Epidiolex initiation. Prior to starting Epidiolex treatment, serum transaminases (ALT and AST) and total bilirubin levels should be obtained. These levels should be obtained at Months 1, 3, and 6 after Epidiolex initiation, and periodically thereafter, or as clinically indicated. These levels should also be obtained within one month of Epidiolex dosage changes, and other medication changes (e.g., those with hepatic effects). Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.

**Somnolence and Sedation.** Patients should be monitored for somnolence and sedation. Patients should be advised not to drive or operate machinery until they have gained sufficient experience with taking Epidiolex.

**Suicidal Behavior and Ideation.** Antiepileptic drugs (AEDs), including Epidiolex, increase the risk of suicidal thoughts or behavior. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

**Hypersensitivity Reactions.** Advise patients to seek immediate medical care if they experience a hypersensitivity reaction. Epidiolex should be discontinued and not restarted.

**Drug Interactions.** Epidiolex is metabolized by CYP3A4 and CYP2C19; therefore, coadministration with moderate or strong CYP3A4 or CYP2C19 inhibitors will increase cannabidiol plasma concentrations. Consider reducing the Epidiolex dose when co-administered with these agents. Co-administration of Epidiolex with strong CYP3A4 or CYP2C19 inducers will decrease cannabidiol plasma concentrations, potentially lowering Epidiolex efficacy. Therefore, consider increasing the Epidiolex dose when co-administered with these agents. Consider a dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 (e.g., clobazam) when given with Epidiolex.

**Availability, Dosage, and Administration:** Epidiolex is available as a 100-mg/mL, strawberry-flavored, clear to yellow liquid (100-mL bottle). A calibrated measuring device will be provided for dosing and is recommended to measure and deliver the prescribed dose accurately. Household spoons should not be used. After the bottle is opened, discard any unused Epidiolex after 12 weeks of first opening the bottle. Epidiolex is administered orally starting with a dose of 2.5 mg/kg twice daily. After Week 1, the dose can be increased to a maintenance dosage of 5 mg/kg twice daily. Patients who tolerate this dose and need further seizure reduction may benefit from a dose increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily. This should be done in weekly increments of 2.5 mg/kg twice daily, as tolerated. For patients who require rapid titration from 10 mg/kg/day to 20 mg/kg/day, the dose may be increased every other day. This higher dose was associated with an increase in adverse reactions.

Commentary: The effectiveness of Epidiolex was evaluated in 3 randomized, double-blind, placebo-controlled clinical trials involving 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome. Epidiolex, taken along with other medications, was shown to be effective in reducing the frequency of seizures when compared with placebo. The most common adverse reactions that occurred in Epidiolex-treated patients in these trials were: decreased appetite, diarrhea, elevated liver enzymes, infections, insomnia, lethargy, malaise and weakness, rash, sleep disorder, and poor sleep quality. Epidiolex must be dispensed with a patient Medication Guide that describes important information about the drug’s uses and risks.