Alpelisib (Piqray) tablets

**Manufacturer:** Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

**Date of Approval:** May 24, 2019

**Indication:** Alpelisib is a kinase inhibitor indicated in combination with fulvestrant (Faslodex) for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

**Drug Class:** PIK3CA inhibitor

**Uniqueness of Drug:** Alpelisib is the first and only treatment specifically used for patients with a PIK3CA mutation in HR-positive/HER2-negative advanced breast cancer. It is the first drug to be approved under the FDA's Real-Time Oncology Review pilot program, which allows manufacturers to start the review process before an application is officially submitted. The FDA also granted this application a priority review designation.

**Warnings and Precautions:**

**Severe hypersensitivity reactions.** Discontinue alpelisib permanently and promptly initiate appropriate treatment.

**Severe cutaneous reactions.** There have been reported cases of severe cutaneous reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme (EM). Do not initiate treatment in patients with a history of SJS, EM, or toxic epidermal necrolysis (TEN). Interrupt alpelisib if signs or symptoms of severe cutaneous reactions are present, until the etiology of the reaction has been determined. Consider consultation with a dermatologist. Permanently discontinue alpelisib if there is confirmation of SJS, EM, or TEN.

**Hyperglycemia.** Severe hyperglycemia, including ketoacidosis, was reported in patients. The safety of alpelisib in patients with type-1 or uncontrolled type-2 diabetes has not been established. Before initiating treatment with alpelisib, test fasting plasma glucose and hemoglobin Alc (HbA1c) and optimize blood glucose. After initiating treatment, monitor patient periodically. Initiate or optimize antihyperglycemic medications as clinically indicated. Interrupt, reduce dose, or discontinue alpelisib if severe hyperglycemia occurs.

**Pneumonitis.** Severe cases of pneumonitis and interstitial lung disease have been reported in patients. Monitor for clinical symptoms or radiological changes. Interrupt or discontinue treatment if severe pneumonitis occurs.

**Diarrhea.** Severe cases of diarrhea, including dehydration and acute kidney injury, have been reported in patients. Most patients experience diarrhea (grade ≤ 2) during treatment with alpelisib. Advise patients to start anti-diarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs. Interrupt, reduce dose, or discontinue treatment if severe diarrhea occurs.

**Embryo-fetal toxicity.** Advise patients of the potential risk to a fetus. Advise patients to use effective contraception.

**Dosing and Administration:** The recommended dose is 300 mg (two 150-mg tablets) taken orally, once daily, with food. Continue treatment until the disease progresses or unacceptable toxicity occurs. If a dose is missed, it can be taken with food within nine hours after the time it is usually taken. After more than nine hours, the dose should be skipped for that day. The next day, alpelisib should be taken at the usual time.

If vomiting occurs after taking the dose, advise the patient not to take an additional dose that day and to resume the dosing schedule the next day at the usual time.

When given with alpelisib, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter.

**Commentary:** The FDA based its approval on findings from SOLAR-1, a phase 3, randomized, double-blind, placebo-controlled trial of alpelisib plus fulvestrant compared with placebo plus fulvestrant in 572 women and men with HR-positive, HER2-negative, advanced breast cancer that grew or spread while or after they were being treated with an aromatase inhibitor (such as anastrozole, letrozole, or exemestane). The study showed improvement in progression-free survival (PFS) for participants whose tumors had a PIK3CA mutation and who received alpelisib and fulvestrant. Participants with the mutation who received alpelisib had a PFS averaging 11 months, compared with an average of 5.7 months for participants with the mutation who did not receive alpelisib. The most common adverse reactions (≥ 20%) were increased glucose, increased creatinine, diarrhea, rash, decreased lymphocyte count, increased gamma glutamyl transferase, nausea, increased alanine aminotransferase, fatigue, decreased hemoglobin, increased lipase, decreased appetite, stomatitis, vomiting, decreased weight, decreased calcium, decreased glucose, prolonged activated partial thromboplastin time, and alopecia.

**Source:** Novartis Pharmaceuticals Corporation, Piqray prescribing information

**Polatuzumab vedotin-piiq (Polivy) for injection**

**Manufacturer:** Genentech Inc., South San Francisco, California

**Date of Approval:** June 10, 2019

**Indication:** Polatuzumab in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.
Drug Class: Anti-CD79b antibody-drug conjugate

Uniqueness of Drug: Polatuzumab is the first FDA-approved chemotherapy regimen for patients with relapsed or refractory diffuse large B-cell lymphoma. It is a first-in-class antibody-drug conjugate targeting CD79b, a protein expressed in most of the B cells. The antibody-drug conjugate combines a monoclonal antibody (mAb) and a potent cytotoxic agent with a linker system. The mAb of polatuzumab binds to the CD79b protein and destroys the B cells by delivering a cytotoxic agent into them. The FDA granted an accelerated approval for this indication based on the complete response rate seen in clinical trials. Continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Warnings and Precautions:

Peripheral neuropathy. Polatuzumab can cause peripheral neuropathy, including severe cases. Peripheral neuropathy occurs as early as the first cycle of treatment and is cumulative. Polatuzumab may also exacerbate pre-existing peripheral neuropathy. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, dysesthesia, neuropathic pain, burning sensation, weakness, or gait disturbance. Patients who experience new or worsening peripheral neuropathy may require a delay in receiving polatuzumab, a dose reduction, or its discontinuation.

Infusion-related reactions. Polatuzumab can cause infusion-related reactions, sometimes severe. Delayed infusion-related reactions have occurred in patients as late as 24 hours after receiving the drug. Administer an antihistamine and antipyretic prior to the administration of polatuzumab, and monitor patients closely throughout the infusion. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management.

Myelosuppression. Treatment with polatuzumab can cause serious or severe myelosuppression including neutropenia, thrombocytopenia, and anemia. Monitor complete blood counts throughout treatment. Cytopenias may require a delay, dose reduction, or discontinuation of polatuzumab. Consider the administration of prophylactic granulocyte colony stimulating factor.

Serious and opportunistic infections. Serious or fatal infections, including opportunistic infections such as sepsis, pneumonia (e.g., Pneumocystis jiroveci and other fungal pneumonia), herpes virus infection, and cytomegalovirus infection, have occurred in patients treated with polatuzumab. Closely monitor patients during treatment for signs of infection. Administer prophylaxis for P. jiroveci pneumonia and herpes virus.

Progressive multifocal leukoencephalopathy (PML). PML has been reported after treatment with polatuzumab. Monitor patients for new or worsening neurological, cognitive, or behavioral changes. Hold polatuzumab and any concomitant chemotherapy if PML is suspected, and permanently discontinue if the diagnosis is confirmed.

Tumor lysis syndrome. Polatuzumab may cause tumor lysis syndrome (TLS). Patients with a high tumor burden and rapidly proliferative tumor may be at increased risk of TLS. Monitor closely and take appropriate measures, including TLS prophylaxis.

Hepatotoxicity. Serious cases of hepatotoxicity consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with polatuzumab. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications can increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level.

Embryo-fetal toxicity. Advise pregnant women of the potential risk to a fetus. Advise female patients to use effective contraception during treatment with polatuzumab and for at least three months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with polatuzumab and for at least five months after the last dose.

Dosing and Administration: The recommended dose is 1.8 mg/kg as an intravenous infusion over 90 minutes every 21 days, for 6 cycles, in combination with bendamustine and a rituximab product. Administer polatuzumab, bendamustine, and the rituximab product in any order on Day 1 of each cycle. The recommended dose of bendamustine is 90 mg/m²/day on Days 1 and 2 when administered with polatuzumab and a rituximab product. The recommended dose of rituximab product is 375 mg/m² intravenously on Day 1 of each cycle.

Administer an antihistamine and antipyretic at least 30 minutes prior to polatuzumab. Administer the initial dose of polatuzumab over 90 minutes. Monitor patients for infusion-related reactions during the infusion and for a minimum of 90 minutes following completion of the initial dose. If the previous infusion was well tolerated, the subsequent dose of polatuzumab may be administered as a 30-minute infusion. Patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion.

If a planned dose of polatuzumab is missed, administer it as soon as possible. Adjust the schedule of administration to maintain a 21-day interval between doses.

Administration:

- Administer polatuzumab as an intravenous infusion only.
- Polatuzumab must be administered using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2- or 0.22-micron pore size) and catheter.
- Do not mix polatuzumab with or administer as an infusion with other drugs.

Commentary: FDA approval of polatuzumab was based on the positive outcomes of the second phase of an ongoing, global phase 1b/2, multicenter, open-label clinical study. A total of 80 patients were randomized to receive either polatuzumab with bendamustine/rituximab (BR) or BR alone for six 21-day cycles. The primary endpoint of the study was the complete response rate at the end of the treatment: 40% of patients treated with polatuzumab plus BR achieved a complete response, compared with 18% of patients treated with BR alone. The most common adverse reactions (≥ 20%) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

Source: Genentech Inc., Polivy prescribing information
Eculizumab (Soliris) concentrated solution for intravenous infusion

**Manufacturer:** Alexion Pharmaceuticals, Inc., Boston, Massachusetts

**Date of Approval:** June 27, 2019

**Indication:** Eculizumab is a complement inhibitor indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

**Drug Class:** Monoclonal antibodies

**Uniqueness of Drug:** The FDA approved eculizumab injection as a first-line treatment for NMOSD, a rare autoimmune disease of the central nervous system that mainly affects the optic nerves and spinal cord.

**Warnings and Precautions:**

**Boxed warning:**
- Life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab and can become rapidly life-threatening or fatal if not recognized and treated early.
- Comply with the most current recommendations from the Advisory Committee on Immunization Practices for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least two weeks prior to administering the first dose of eculizumab, unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection.
- Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.
- Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Prescribers must enroll in the REMS program.

**Dosing and Administration:** The recommended dose of eculizumab is 900 mg weekly for the first four weeks, followed by 1,200 mg for the fifth dose one week later, then 1,200 mg every two weeks thereafter. Administer eculizumab at the recommended dosage-regimen time points, or within two days of those time points.

**Administration:**
- Administer only as an intravenous (IV) infusion. Do not administer as an IV push or bolus injection.
- Administer the eculizumab admixture by IV infusion over 35 minutes in adults and over one to four hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of eculizumab are stable for 24 hours at 2°–8° C (36°–46° F) and at room temperature.
- If an adverse reaction occurs during the administration of eculizumab, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

**Commentary:** The effectiveness of eculizumab for the treatment of NMOSD was demonstrated in a clinical study of 143 patients with NMOSD and AQP4 antibodies, who were randomized to receive either eculizumab or placebo. Compared with placebo, eculizumab reduced the number of NMOSD relapses by 94% over the 48-week trial. Eculizumab also reduced the number of hospitalizations and treatment of acute attacks with corticosteroids and plasma exchange. The most common adverse reactions (≥ 10%) are upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and confusion.

**Source:** Alexion Pharmaceuticals, Inc., Soliris prescribing information.