PDL DRUG REVIEW

Proprietary Name: Piqray®
Common Name: alpelisib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Alpelisib, the active ingredient of Piqray®, is a kinase inhibitor. It is an inhibitor of phosphatidylinositol-3 kinase (PI3K) with inhibitory activity predominantly against PI3Kα. In vivo, alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer.

Indication: In combination with fulvestrant 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on animal data and its mechanism of action, Piqray® can cause fetal harm when given to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risks to a fetus. Prior to starting treatment, verify the pregnancy status of females of reproductive potential and use effective contraception during treatment and for 1 week after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 50mg, 150mg, 200mg. Do not chew, crush, or split tablets prior to swallowing.

Recommended Dosage: Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with Piqray® based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests for the detection of PIK3CA mutations in breast cancer is available at http://www.fda.gov/companiondiagnostics.

Take 300mg PO QD with food until disease progression or unacceptable toxicity. When given with Piqray®, the recommended dose of fulvestrant is 500mg administered on days 1, 15, and 29, and once monthly thereafter. Dose modifications may be required for adverse reactions, such as hyperglycemia, rash, diarrhea, or other toxicities. Refer to the prescribing information for further details. Dose adjustments are not required with hepatic impairment or mild to moderate renal impairment; however, the effect of severe renal impairment on alpelisib pharmacokinetics is not known.

Drug Interactions: As the concomitant use of Piqray® with a strong CYP3A4 inducer may decrease alpelisib concentrations, avoid the concomitant use of Piqray® with strong CYP3A4 inducers. The concomitant use of Piqray® with a BCRP inhibitor may increase alpelisib concentration. Thus, avoid the use of BCRP inhibitors in

patients treated with Piqray®. If unable to use alternative drugs, when Piqray® is used in combination with BCRP inhibitors, closely monitor for increased adverse reactions.

Coadministration of Piqray® with CYP2C9 substrates (e.g. warfarin) may reduce plasma levels of these drugs. Monitor when Piqray® is used concomitantly with CYP2C9 substrates.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Piqray® plus fulvestrant) minus reported % incidence for placebo plus fulvestrant for all grades. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The reported adverse events included diarrhea (42%), nausea (23%), stomatitis (24%), vomiting (17%), abdominal pain (6%), dyspepsia (5%), fatigue (13%), mucosal inflammation (18%), edema peripheral (10%), pyrexia (9.1%), mucosal dryness (7.8%), urinary tract infections (5%), weight decreased (24.9%), decreased appetite (26%), dysgeusia (14.5%), headache (5%), rash (45%), alopecia (17.6%), pruritus (12%), and dry skin (14.2%). Laboratory abnormalities included lymphocyte count decreased (12%), hemoglobin decreased (13%), activated partial thromboplastin time (aPTT) prolonged (5%), platelet count decreased (8%), glucose increased (45%), creatinine increased (42%), gamma glutamyl transferase (GGT) increased (8%), alanine aminotransferase (ALT) increased (10%), lipase increased (17%), calcium (corrected) decreased (7%), glucose decreased (12%), potassium decreased (11.2%), albumin decreased (6%), and magnesium decreased (6.8%).

Severe hypersensitivity and severe cutaneous reactions, including Stevens-Johnson Syndrome (SJS) and Erythema Multiforme (EM) were reported in patients treated with Piqray®. SJS and EM were reported in 0.4% and 1.1% of patients, respectively. Do not start Piqray® treatment in patients with a history of SJS, EM or Toxic Epidermal Necrolysis (TEN). If SJS, TEN, or EM is confirmed, permanently discontinue treatment. Advise patients of the signs and symptoms of severe hypersensitivity reactions or severe cutaneous reactions.

Severe hyperglycemia, including ketoacidosis, has been reported in patients treated with Piqray® (65%). Among patients who experienced Grade ≥2 hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range 5 to 517 days). Before starting treatment with Piqray®, test fasting plasma glucose, HbA1c, and optimize blood glucose. After treatment has been started, monitor blood glucose and/or fasting plasma glucose at least once every week for the first 2 weeks, then at least once every 4 weeks and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. The safety of Piqray® in patients with type 1 DM and uncontrolled type 2 DM has not been established as these patients were excluded from the clinical trials. Patients with a medical history of type 2 DM were included. Closely monitor patients with diabetes.

Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, has been reported in patients treated with Piqray®. Permanently discontinue Piqray® in all patients with confirmed pneumonitis and advise patients to report new or worsening respiratory symptoms.

Severe diarrhea, including dehydration and acute kidney injury, occurred in patients treated with Piqray®. Most patients (58%) experienced diarrhea during treatment with Piqray®. Grade 3 diarrhea occurred in 7% of patients. Among patients with Grade 2 or 3 diarrhea, the median time to onset was 46 days (range 1 to 442 days). Dose reductions were required in 6% of patients and 2.8% of patients permanently discontinued Piqray® due to diarrhea. In the 164 patients that experienced diarrhea, anti-diarrheal medications (e.g. loperamide) were required to manage symptoms in 63% of these patients. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs while taking Piqray®.

Contraindications: Severe hypersensitivity to alpelisib or any of its components

Manufacturer: Novartis Pharmaceuticals

Analysis: The safety and efficacy of Piqray® plus fulvestrant were assessed in a randomized, double-blind, placebo-controlled study (SOLAR-1) that included patients (N=572) with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients received treatment until radiographic disease

progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks for the first 18 months and every 12 weeks thereafter.

There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. The median age of included patients was 63 years, while most were women (99.8%) and most were white (66%). Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (68%) or 1 (32%). The median duration of exposure to Piqray® plus fulvestrant was 8.2 months, with 59% of patients exposed for >6 months. Most patients (98%) received prior hormonal therapy as the last treatment.

The main efficacy outcome was investigator-assessed progression-free survival (PFS) in the cohort with a PIK3CA mutation per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Other outcomes assessed included overall response rate (ORR) and overall survival (OS) in the cohort with a PIK3CA mutation. Results can be seen in the table below, which was adapted from the prescribing information. At the time of the final PFS analysis, 27% (N=92/341) of patients had died and overall survival follow-up was immature. No PFS benefit was observed in patients whose tumors did not have a PIK3CA tissue mutation (HR 0.85).

Response	Piqray® + fulvestrant	Placebo + fulvestrant
Progression Free Survival (PS)	N=169	N=172
Number of PFS events	103 (61%)	129 (75%)
Median PFS, months	11.0	5.7
HR; p-value	0.65; p=0.0013	
Overall Response Rate (ORR)	N=126	N=136
ORR	35.7%	16.2%

Place in Therapy: Piqray® is indicated in combination with fulvestrant 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. Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with Piqray® based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens. If no mutation is detected in a plasma specimen, test tumor tissue. In a clinical trial compared with placebo plus fulvestrant, Piqray® plus fulvestrant had a significantly improved progression-free survival in a cohort with a PIK3CA mutation.

It is recommended that Piqray® should be Non-Recommended with Conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Piqray [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corp; 2019.