alpelisib (Piqray®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO003

Description

Alpelisib (Piqray) is an orally administered kinase inhibitor with predominant activity against PIK3.

Length of Authorization

- Initial: Three months, split fill
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
alpelisib (Piqray)	150 mg tablets (2 x 150 = 300 mg daily dose pack)	PIK3CA mutation, HR+, HER2-, advanced or metastatic breast cancer	56 tablets/28 days	206827
	200 mg tablets (200 mg daily dose pack)		28 tablets/28 days	206829
	200 mg and 50 mg tablets (200 + 50 = 250 mg daily dose pack)		56 tablets/28 days	206828

Initial Evaluation

I. Alpelisib (Piqray) may be considered medically necessary when the following criteria are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. The breast cancer is HR-positive, HER2-negative; **AND**
      2. PIK3CA mutation has been tested and confirmed; **AND**
      3. The provider attests the member is endocrine resistant or refractory; **AND**
      4. The member has not previously progressed on a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]; **AND**
      5. The medication will be used in combination with fulvestrant (Faslodex) only; **AND**

i. Alpelisib (Piqray) will not be used in combination with ANY other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.].

II. Alpelisib (Piqray) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Breast cancer that is not PIK3CA mutated.

III. Alpelisib (Piqray) is considered investigational when used for all other conditions, including but not limited to:
   A. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
   B. Meningioma
   C. Oropharyngeal cancer
   D. Melanoma
   E. Renal cell cancer
   F. Pancreatic cancer
   G. Head and neck cancers
   H. Ovarian cancer

Renewal Evaluation

I. The medication is prescribed by, or in consultation with, an oncologist; **AND**
II. The member will be using in combination with fulvestrant (Faslodex); **AND**
   A. Alpelisib (Piqray) will not be used in combination with ANY other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]; **AND**
III. The member has experienced positive response to treatment, defined by the stabilization of disease or a decrease in tumor size or tumor spread.

Supporting Evidence

I. Alpelisib (Piqray) was evaluated in one double-blind, Phase 3, placebo-controlled randomized trial. Both arms were in combination with fulvestrant. The trial evaluated subjects with and without the PIK3CA mutation; however, those without the mutation did not show favorable outcomes; thus, the efficacy information stated here is specific to those with the PIK3CA mutation. Safety information was pulled from the entirety of the population.
II. Subjects in the pivotal trial had HR+, HER2-, advanced or metastatic breast cancer; 98% of which had received prior endocrine therapy and were deemed to be endocrine resistant. The trial purpose was to focus on the endocrine-refractory population. The primary efficacy outcome was progression free survival (PFS),and secondary outcomes included PFS per a blinded review

committee, overall response (OR) and clinical benefit (CB) (i.e., complete or partial response or stable disease).The primary outcome PFS was 11 months versus 5.7 months for alpelisib (Piqray) plus fulvestrant versus placebo plus fulvestrant (HR 0.65, p<0.001). Overall response was 26.6% versus 12.8% respectively, and CB was 61.5% vs. 45.3% respectively.

III. Of the 169 patients that received alpelisib (Piqray), 9 (5.3%) had history of use of a CDK4/6 inhibitor (e.g., Ibrance, Kisqali, Verzenio). It is unknown whether these patients had progressed on therapy, or, discontinued due to intolerance; however, at this time the evidence for safety and efficacy in the CDK4/6 inhibitor treatment refractory or relapsed population is unknown. Too few patients were included in the trial with this characterization to extrapolate the entirety of the trial results to the patients that have progressed on CDK4/6 inhibitors and it is currently considered experimental and investigational. The population included in the trial is often treated with CDK4/6 inhibitors, so recommendations on optimal sequence of therapy shall be determined upon further clinical evaluation and real-world data. Although it is not uncommon for patients to become resistant to CDK4/6 inhibitors, the available efficacy information on alpelisib (Piqray) as subsequent therapy in this population is lacking. The outcomes described are not correlated with clinically meaningful outcomes such as overall survival or quality of life parameters. This shall be weighed with the very significant safety concerns associated with alpelisib (Piqray).

IV. Alpelisib (Piqray) was evaluated in an open-label, three-cohort, non-comparative phase 2 trial (BYLieve trial), in order to assess efficacy and safety of alpelisib (Piqray) in patients, who previously progressed on CDK 4/6 inhibitors. Cohorts A (N=127) and B (N= not known) included patients, who had prior treatment with CDK 4/6 inhibitor plus aromatase inhibitor, or CDK 4/6 inhibitor plus fulvestrant, respectively. Cohort A received treatment with alpelisib (Piqray) plus fulvestrant, while cohort B received alpelisib (Piqray) plus letrozole. As of 08/2020, efficacy data for cohort A was available. Primary endpoint of proportion of patients alive without disease progression at 6 months was 50.4% (N=61; 95% CI: 41.2,59.6). Secondary outcomes were overall response rate of 17.7% (95% CI: 11.1,25.3), and median progression-free survival of 7.3 months (59.5%, 95% CI: 5.6-8.3). Overall quality of the evidence is considered low given the lack of comparator and open-label trial design. Additionally, this is an ongoing clinical trial, wherein the final results for all cohorts are not available. This may lead to concerns about clinical applicability of the trial outcomes. Based on available results, the efficacy of alpelisib (Piqray) in CDK 4/6 inhibitor refractory population continues to remain uncertain.

V. There is a high risk of serious safety events with alpelisib (Piqray). Serious adverse events occurred in 34.9% vs. 16.7% for the placebo group. Adverse events of serious grade that occurred more often in the alpelisib (Piqray) arm vs. placebo included: hyperglycemia, diarrhea, abdominal pain, acute kidney injury, anemia, nausea, osteonecrosis of the jaw, rash, stomatitis, erythema multiforme, hypokalemia, mucosal inflammation, maculopapular rash, creatinine increased, brain edema, renal failure, bacteremia, Steven's Johnson Syndrome, and many other cases of serious safety concern. Common adverse reactions occurring in more than 20% of subjects included laboratory abnormalities (glucose, creatinine, lymphocyte, GGT, ALT, lipase, calcium, hemoglobin), fatigue, decrease appetite, stomatitis, vomiting, weight loss, aPTT prolongation, and alopecia. Tolerability of alpelisib (Piqray) is of concern; 74% of subjects within

from this trial arm required a dose-interruption and 64% required a dose-reduction vs. 32% and 9% for the placebo group respectively. Permanent discontinuation of drug due to adverse events occurred in 25% of alpelisib (Piqray) subjects vs. 4.2% for placebo.

Investigational or Not Medically Necessary Uses

I. Breast cancer without PIK3CA mutation.
   A. Alpelisib (Piqray) was evaluated in breast cancer patients that did not have the PIK3CA mutation and statistical significance over placebo was not reached.

II. Aleplisib (Piqray) is currently being investigated for safety and efficacy in many oncolytic disease states and potentially other non-oncolytic conditions. Safety and efficacy have not yet been determined in the following:
   A. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
   B. Meningioma
   C. Oropharyngeal cancer
   D. Melanoma
   E. Renal cell cancer
   F. Pancreatic cancer
   G. Head and neck cancers
   H. Ovarian cancer

References

1. Piqray [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. June 2019.
2. National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer V5.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated July 15, 2020.
3. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for -Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380(20):1929-1940.
4. Rugo HS et al. Alpelisib + fulvestrant in patients with PIK3CAmutated hormone-receptor positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results. Oral presentation at: American Society of Clinical Oncology (ASCO); May 29 - May 31, 2020; Chicago, IL. Presentation 1006.

Policy Implementation/Update:

Date Created	July 2019
Date Effective	August 2019
Last Updated	September 2020
Last Reviewed	September 2020

Action and Summary of Changes	Date
Updated supporting evidence section to include data from BYLieve clinical trial	09/2020
Policy created	08/2019