alpelisib (Piqray®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO003

Description

Alpelisib (Piqray, Vijoice) is an orally administered kinase inhibitor with predominant activity against PIK3CA gene.

Length of Authorization

- Initial: Six months; (First three months split fill for alpelisib (Piqray) only)
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
alpelisib (Piqray)	Advanced or metastatic breast cancer, PIK3CA mutation positive, HR+, HER2-,	150 mg tablets (300 mg daily dose pack)	56 tablets/28 days
		200 mg tablets (200 mg daily dose pack)	28 tablets/28 days
		200 mg and 50 mg tablets (250 mg daily dose pack)	56 tablets/28 days
alpelisib (Vijoice)	PIK3CA-Related Overgrowth Spectrum (PROS)[Ŧ, **]	50 mg tablets (50 mg daily dose pack)	28 tablets/28 days
		125 mg tablets (125 mg daily dose pack)	28 tablets/28 days
		200 mg and 50 mg tablets (250 mg daily dose pack)	56 tablets/28 days

***Quantity limit exceptions not allowed, except for dose reductions.**

ŦExperimental/ Investigational indication.

*****Disclaimer: In the event an exception is granted for alpelisib (Vijoice) for any condition, a trial of a comparable, cost-effective formulation of alpelisib will be required [i.e., alpelisib (Piqray)].***

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. A diagnosis of **Advanced or metastatic breast cancer; AND**
      1. The request is for alpelisib (Piqray); **AND**

2. The breast cancer is HR-positive, HER2-negative; **AND**
3. PIK3CA mutation has been tested and confirmed; **AND**
4. Provider attestation that the member is endocrine resistant or refractory; **AND**
5. The member has not previously progressed on a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]; **AND**
6. The medication will be used in combination with fulvestrant (Faslodex) only; **AND**
7. 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 the criteria above are not met and/or when used for:
   A. Breast cancer that is not PIK3CA mutated.

III. Alpelisib (Piqray, Vijoice) is considered investigational when used for all other conditions, including but not limited to:
   A. PIK3CA- Related Overgrowth Spectrum (PROS)
   B. Overgrowth Spectrum disorders without PIK3CA mutation
   C. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
   D. Meningioma
   E. Oropharyngeal cancer
   F. Melanoma
   G. Renal cell cancer
   H. Pancreatic cancer
   I. Head and neck cancers
   J. Ovarian cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Alpelisib (Piqray) will be used 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**

IV. Member has exhibited a positive response to treatment or stability of disease symptoms (e.g., stabilization of disease, a decrease in tumor size or tumor spread)

Supporting Evidence

I. Alpelisib (Piqray, Vijoice) is an orally administered kinase inhibitor with predominant activity against PIK3CA gene. It is FDA-approved for the treatment of advanced or metastatic breast cancer with PIK3CA mutation, and for PIK3CA-Related Overgrowth Spectrum (PROS). The FDA approvals for these indications are specific to the respective formulation of alpelisib as well as recommended dosing. Alpelisib (Piqray) is indicated for the treatment of breast cancer, and alpelisib (Vijoice) is indicated for the treatment of PROS. Of note, use of alpelisib (Vijoice) for the treatment of PROS is considered experimental and investigational (please see the experimental and investigational section below).

II. Given the complexities involved with the diagnosis, treatment approaches and management of therapy for the indicated population, the treatment with alpelisib (Piqray) should be initiated by or in consultation with an oncologist.

III. Alpelisib (Piqray) was evaluated in one double-blind, Phase 3, placebo-controlled randomized trial (SOLAR-1). Both arms were in combination with fulvestrant. The trial evaluated adult 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.

IV. 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 focused 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% versus 45.3% respectively.

V. There is a high risk of serious adverse events with alpelisib (Piqray). Serious adverse events occurred in 34.9% versus 16.7% for the placebo group. Adverse events of serious grade that occurred more often in the alpelisib (Piqray) arm versus 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 concerns. 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 from the treatment arm in SOLAR-1 required a dose-interruption and 64% required a dose-reduction versus 32% and 9% for the placebo arm respectively. Permanent discontinuation of drug due to

adverse events occurred in 25% of alpelisib (Piqray) subjects versus 4.2% for subjects in the placebo group

VI. 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, thus, 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).

VII. 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 were 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 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.

Investigational or Not Medically Necessary Uses

I. PIK3CA-Related Overgrowth Spectrum (PROS):
*** Disclaimer: In the event an exception is granted for alpelisib (Vijoice) for any condition, a trial of a comparable, cost-effective formulation of alpelisib will be required [i.e., alpelisib (Piqray)].*

A. Alpelisib (Vijoice) received accelerated FDA-approval and a breakthrough therapy designation for the treatment of PIK3CA-related overgrowth spectrum (PROS) in patients two years of age and older, who require systemic therapy. This approval was based on the data of an open-label, retrospective chart review study, and continued approval remains contingent upon confirmatory trials.

B. Alpelisib (Vijoice) is available as monthly therapy packs consisting of 50 mg, 125 mg and 200 mg tablets. The recommended dose of alpelisib (Vijoice) is 250 mg once daily for adults. For pediatric patients, the dose is age dependent. For children 2 to 6 years of age: 50 mg once a day; and for children ≥6 years of age and adolescents <18 years of age: initial dose of 50 mg daily for 6 months, followed by dose titration to 125 mg once a day to optimize clinical response.
C. As of September 2022, the monthly cost of alpelisib (Vijoice) remains significantly higher (>2 fold) than that of comparable formulations (therapy packs) of alpelisib (Piqray). In the event an exception is granted for alpelisib (Vijoice) for the treatment of PROS, alpelisib (Piqray) may serve as a comparable cost-effective formulation.
D. According to the prescribing information for alpelisib (Piqray, Vijoice), there is no well-established maximum dose for the approved indications. It is expected that alpelisib (Vijoice) may be utilized at higher doses in order to optimize clinical response. Availability of alpelisib (Piqray) therapy packs consisting of alpelisib (Piqray) 50 mg, 150 mg, and 200 mg tablets, may provide an avenue for dose escalations and optimizations. As an example, for an adult member requiring 250 mg daily dose of alpelisib (Vijoice), a 250 mg daily dose pack of alpelisib (Piqray) may be considered as an alternative. Similarly, a provider outreach may be needed in order to achieve optimized dosing for adolescent members, for whom the recommended daily dose of alpelisib (Vijoice) is 125 mg. It is estimated that these members may see dose escalations to 150 mg or beyond. In absence of concerns regarding drug toxicity, a daily dose of 150 mg may be efficacious alternative to a 125 mg daily dose.
E. PIK3CA-related overgrowth spectrum (PROS) is a heterogeneous group of rare, asymmetric overgrowth disorders caused by postzygotic variants in the PIK3CA gene. One PIK3CA encodes the p110α catalytic subunit of phosphoinositide 3-kinase (PI3K), which transduces activation of tyrosine kinase growth factor and hormone receptors into activation of AKT and mTOR signaling to promote tissue growth.
F. Overgrowth includes adipose tissue, muscle, skin, bone, blood or lymph vessels, or neural tissue, among others. Adipose and vascular components are particularly striking, reflecting the inherent plasticity and postnatal growth potential of these tissues. Complications of PROS depend on the anatomical site and extent of overgrowth, but may include functional impairment (e.g., of walking or swallowing), pain, recurrent superficial infections, thromboembolism, and/or hemorrhage, all of which may be debilitating, and cause early mortality. Based on the organ system involvement and the types of lesions, PROS may present as heterogeneous segmental overgrowth phenotypes - with or without vascular anomalies. Some of the prominent anomalies classified under PROS include CLOVES Syndrome, Klippel-Trenaunay Syndrome (KTS), Fibroadipose Infiltrating Lipomatosis (FIL), and Megalencephaly-Capillary Malformation (MCAP, or M-CM).
G. Current standard of care for PROS involves regular monitoring, debulking surgery, amputation, and/or endovascular occlusive procedures. Regrowth following surgery occurs frequently and repeated surgery is common.

H. Allosteric mTOR inhibitors such as sirolimus, which is approved for posttransplant immunosuppression, have been utilized for PROS treatment. Sirolimus may potently attenuate pathological AKT signaling and reduces cell proliferation in dermal fibroblasts derived from people with PROS, which suggests that it could be an effective treatment of PROS. However, it is important to note that the use of sirolimus may only be applicable to the patient population, whose PROS involves vascular and lymphatic malformations with predominant adipose overgrowth. These lesions are typically seen in CLOVES syndrome, FIL, and MCAP, and manifest as visible lesions on the contralateral limb, truncal region, and/or face. In absence of these anomalies, the use of sirolimus may be deemed inappropriate by the treating provider.

I. A non-randomized, single-arm, open-label clinical trial (N=39) assessed the efficacy and safety of low-dose sirolimus (median target plasma levels of 3.3 ng/mL). Patients aged from three years to 65 years were included. For the primary outcome, tissue volumes at affected and unaffected sites were measured by dual-energy X-ray absorptiometry during 26 weeks of untreated run-in and 26 weeks of sirolimus therapy. Among the 30 participants, who completed the study, sirolimus led to a change in mean percentage total tissue volume of –7.2% (SD 16.0, p 0.04) at affected sites, but not at unaffected sites (+1.7%, SD 11.5, p 0.48) (n = 23 evaluable). No differences were detected in QOL scores before and after sirolimus treatment among adults or children. During run-in, five hospitalizations in five participants and two surgical interventions in two participants were recorded. In the treatment phase 15 hospitalizations in 9 participants and no surgical interventions arose. This difference was not significant (p = 0.24). Twenty-eight of 39 (72%) participants had ≥1 adverse event related to sirolimus of which 37% were grade 3 or 4 in severity and 7/39 (18%) participants were withdrawn consequently.

J. Efficacy of alpelisib (Vijoice) was evaluated using real-world data from EPIK-P1, a single-arm, open-label retrospective chart review study in patients, who received alpelisib (Vijoice) as part of an expanded access program for compassionate use. Eligible patients had clinical manifestations of PROS that were assessed by the treating physicians as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene. The efficacy of alpelisib (Vijoice) was evaluated in a total of 37 patients with at least one target lesion identified on imaging performed within 24 weeks prior to receipt of the first dose. The major efficacy outcome measure was the proportion of patients with a radiological response at week 24 as determined by blinded independent central radiology review, defined as a ≥20% reduction from baseline in the sum of measurable target lesion volume in up to 3 lesions confirmed by at least 1 subsequent imaging assessment. Duration of response was an additional efficacy outcome measure. Of the 37 patients included in the efficacy population, 27% (95% CI: 14, 44) had a radiological response at week 24. The most common (≥10%) adverse reactions occurring in patients were diarrhea, stomatitis, and hyperglycemia. Additionally, improvements in functionality were observed as determined by Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale and Lansky and Karnofsky scales: at baseline, the performance status was recorded for 47 patients: at the 24 weeks follow-up, 30% of

patients showed ECOG PS improvement of at least 1 point and Karnofsky scale at least 20 points.

K. Despite accelerated approval and orphan designation, continued approval of alpelisib (Vijoice) remains contingent upon the verification of clinical benefit in confirmatory trials. Although FDA-approved for the treatment of PROS, efficacy data for alpelisib (Vijoice) is based on a retrospective chart review of a small patient population. The quality of data is considered low and the true clinical value of alpelisib (Vijoice) for the treatment of PROS remains undetermined.

L. Given the lack of curative therapy options and paucity of clinical data supporting the use of currently approved therapies, enrollment in a clinical trial may remain a practical management approach for patients with PROS. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field, while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced diseases with limited or no treatment options. As of September 2022, alpelisib (Vijoice) is available to patients via ongoing clinical trial and an expanded access program across the US and other countries.

II. 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.

III. Aleplisib (Piqray, Vijoice) 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.
5. Canaud G, et al. EPIK-P1: Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum Who Have Received Alpelisib as Part of a Compassionate Use Programme. Presented at the 2021 ESMO Congress; September 17-21, 2021.
6. Alpelisib (Vijoice) prescribing information, Novartis Pharmaceutical Corp.,East Hanover, NJ, USA. April 2022.
7. Alpelisib (Vijoice) clinical trial data (unpublished). https://www.hcp.novartis.com/products/vijoice/pik3ca-related-overgrowth-spectrum/efficacy/.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer, HER2-negative, HR-positive, advanced, or metastatic

Policy Implementation/Update:

Action and Summary of Changes	Date
Inclusion of new indication for PROS in the QL table; added PROS as E/I indication; added supporting evidence for PROS; format changes to align with current policy format	11/2022
Updated supporting evidence section to include data from BYLieve clinical trial	09/2020
Policy created	08/2019