Clinical Policy: Alpelisib (Piqray, Vijoice)

Reference Number: CP.PHAR.430
Effective Date: 07.09.19
Last Review Date: 08.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Alpelisib (Piqray®, Vijoice®) is a phosphoinositide 3-kinase (PI3K) inhibitor.

FDA Approved Indication(s)

Piqray is indicated in combination with fulvestrant for the treatment of adults 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.

Vijoice is indicated for the treatment of adult and pediatric patients 2 years of age or older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.*

**This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Piqray and Vijoice are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Breast Cancer (must meet all)**:**

1. Request is for Piqray;
2. Diagnosis of breast cancer;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Disease has all of the following characteristics (a, b, c, and d):
   a. HR-positive (i.e., estrogen or progesterone receptor [ER/PR]-positive);
   b. HER2-negative;
   c. Advanced (locally recurrent) or metastatic;
   d. Positive for PIK3CA mutation;
6. Piqray is prescribed in combination with fulvestrant;
7. Disease has progressed on or after an endocrine-based therapy regimen (*see Appendix B*);

8. For Piqray requests, member must use alpelisib, if available, unless contraindicated or clinically significant adverse effects are experienced;
9. Request meets one of the following (a or b):*
   a. Dose does not exceed 300 mg (two 150 mg tablets) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. PIK3CA Related Overgrowth Spectrum (must meet all)**:**
1. Request is for Vijoice;
2. Diagnosis of PROS;
3. Age ≥ 2 years;
4. Member meets one of the following (a or b):
   a. Documented evidence for PIK3CA gene mutation;
   b. If unable to perform biopsy to confirm PIK3CA gene mutation, member meets all of the following (i, ii, and iii):
      i. Congenital or early childhood onset (birth to the age of eight);
      ii. Overgrowth that is sporadic and mosaic (other terms: patchy, irregular);
      iii. Either of any two clinical spectrum features from Category A or any one isolated feature from Category B (see *Appendix E*);
5. Member's condition is severe or life-threatening requiring systemic therapy as determined by treating physician;
6. For non-cutaneous lesions, member has at least one target lesion identified on imaging within the last 6 months;
7. Dose does not exceed any of the following (a, b, or c):
   a. Age 2-5 years: 50 mg (1 tablet or oral granules packet) per day;
   b. Age 6-17 years: 125 mg (1 tablet) per day;
   c. Age ≥ 18 years: 250 mg (two 125 mg tablets) per day.

Approval duration: 6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Breast Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Piqray for breast cancer and has received this medication for at least 30 days;
2. Request is for Piqray;
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed 300 mg (two 150 mg tablets) per day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. PIK3CA Related Overgrowth Spectrum (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Request is for Vijoice;
3. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> of the following:
   a. Reduction in size, volume, and/or total number of measurable lesions from baseline via subsequent imaging scan;
   b. Improvement in at least one sign, symptom, or complication of PROS (e.g., pain, fatigue, vascular malformation, limb asymmetry, disseminated intravascular coagulation);
   c. Improvement in functional status (e.g., mobility, performance, work/school attendance);
4. If request is for a dose increase, new dose does not exceed any of the following (a, b, or c):
   a. Age 2-5 years: 50 mg (1 tablet or oral granules packet) per day;
   b. Age 6-17 years: 125 mg (1 tablet) per day;
   c. Age ≥ 18 years: 250 mg (two 125 mg tablets) per day.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ER: estrogen receptor
FDA: Food and Drug Administration
HER2: human epidermal growth factor receptor 2
HR: hormone receptor
NCCN: National Comprehensive Cancer Network
PR: progesterone receptor
PROS: PIK3CA-related overgrowth spectrum

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Endocrine Therapy		
anastrozole (Arimidex®)	1 mg PO QD	1 mg/day
exemestane (Aromasin®)	25 mg PO QD	25 mg/day
Fareston® (toremifene)	60 mg PO QD	60 mg/day
fulvestrant (Faslodex®)	500 mg IM into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter	500 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Endocrine Therapy		
letrozole (Femara®)	2.5 mg PO QD	2.5 mg/day
tamoxifen (Nolvadex®, Soltamox®)	20 to 40 mg PO QD	40 mg/day
megestrol acetate	40 mg PO QID	160 mg/day
NCCN-recommended CDK4/6 inhibitors to be used in combination with aromatase inhibitors as first-line therapy		
Kisqali® (ribociclib)* Verzenio® (abemaciclib) Ibrance® (palbociclib)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**NCCN category 1 recommendation*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): severe hypersensitivity to Piqray or Vijoice or to any of its components
- Boxed warning(s): none reported

Appendix D: General Information

Subdivisions of PROS

- CLAPO syndrome: capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry, and partial/generalized overgrowth
- CLOVES syndrome: congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal
- Diffuse capillary malformation with overgrowth
- Dysplastic megalencephaly
- Fibroadipose hyperplasia/fibroadipose overgrowth/hemihyperplasia-multiple lipomatosis syndrome
- Fibroadipose vascular anomaly
- Facial infiltrating lipomatosis
- Hemimegalencephaly
- Klippel-Trenaunay syndrome
- Lipomatosis of nerve
- Macodactyly
- Megalencephaly-capillary malformation syndrome
- Muscular hemihyperplasia

Appendix E: National Institutes of Health (NIH) Workshop Recommended Clinical Features of PROS

Category A (spectrum) - 2 or more features	Category B (isolated features) – any 1 feature
• Overgrowth: adipose, muscle, nerve, skeletal • Vascular malformations: capillary, venous, arteriovenous malformation, lymphatic • Epidermal nevus	• Large, isolated lymphatic malformation • Isolated macrodactyly or overgrown, splayed feed/hands, overgrown limbs • Truncal adipose overgrowth • Hemimegaloencephaly (bilateral), dysplastic megalencephaly, focal cortical dysplasia • Epidermal nevus • Seborrheic keratoses • Benign lichenoid keratoses

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Piqray	Breast cancer	In combination with fulvestrant: 300 mg PO daily with food	300 mg/day
Vijoice	PROS	Pediatric patients (2 to < 18 years of age): 50 mg* PO daily with food. Consider a dose increase to 125 mg PO daily in pediatric patients ≥ 6 years old for response optimization after 24 weeks of treatment with Vijoice at 50 mg once daily Adult patients: 250 mg PO daily with food *Oral granules may be used to administer a 50 mg daily dose only. Do not use multiple 50 mg packets or a partial packet of oral granules for patients prescribed a 125 mg or a 250 mg dose. Do not combine oral granules and tablets to achieve the prescribed dose.	• Age 2 – 5: 50 mg/day • Age 6-17: 125 mg/day • Age ≥ 18: 250 mg/day

VI. Product Availability

Drug Name	Availability
Piqray	Tablets: 50 mg, 150 mg, 200 mg
Vijoice	Tablets: 50 mg, 125 mg, 200 mg Oral granules single-use packet: 50 mg

VII. References

1. Piqray Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2024. Available at: https://www.us.piqray.com/. Accessed May 6, 2024.

2. Vijoice Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2024. Available at: https://www.novartis.us/sites/www.novartis.us/files/vijoice.pdf. Accessed May 6, 2024.
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4. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org. Accessed May 23, 2024.
5. National Comprehensive Cancer Network. Breast Cancer Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed May 23, 2024.
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7. Canaud G, Lopez Gutierrez JC, Irvine A, et al. EPIK-P1: Retrospective chart review study of patients (pts) with PIK3CA-related overgrowth spectrum (PROS) who have received alpelisib (ALP) as part of a compassionate use programme. Annals of Oncology. 2021; 32(S5):S127.
8. Canaud G, Hammill AM, Adams D, Vikkula M, and Keppler-Noreuil KM. A review of mechanisms of disease across PIK3CA-related disorders with vascular manifestations. Orphanet J Rare Dis. 2021;16:306.
9. PIK3CA-related overgrowth spectrum. National Organization for Rare Disorders (NORD). 2022. Available at: https://rarediseases.org/rare-diseases/pik3ca-related-overgrowth-spectrum/. Accessed May 23, 2024.
10. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet A. 2015;167A:287-95.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2020 annual review: no significant changes; references reviewed and updated.	04.30.20	08.20
3Q 2021 annual review: no significant changes; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	05.05.21	08.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
3Q 2022 annual review: no significant changes; added oral oncology generic redirection language; references reviewed and updated. RT4: Newly approved agent Vijoice for PROS added to policy.	05.17.22	05.22 (ad hoc)
For PROS, for initiation of therapy added option for diagnosis of PROS if PIK3CA gene mutation is not identified, for continuation of therapy added option to demonstrate positive response that includes improvement in PROS related signs, symptoms or complications and functional status, for imaging requirement added	08.30.22	11.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
must be obtained within the last 6 months. Template changes applied to other diagnoses/indications and continued therapy section.		
3Q 2023 annual review: no significant changes; for Piqray added examples of CDK4/6 inhibitors to be used with aromatase inhibitors as first-line therapy to Appendix B; references reviewed and updated.	04.20.23	08.23
RT4: Revised FDA-approved indication description for Piqray to include all adults regardless of gender and postmenopausal status; no change to criteria.	02.01.24	
3Q 2024 annual review: no significant changes; RT4: added oral granules dosage form per updated prescribing information; references reviewed and updated.	05.23.24	08.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.