New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Vijoice® (alpelisib) [Novartis Pharmaceuticals Corporation] (vī-jois)**
Dosage Formulations:	Tablets: 50 mg, 125 mg, and 200 mg
FDA Approval Date: **FDB File Date:**	FDA: April 5, 2022 FDB: April 17, 2022
Indication:	• The treatment of adult and pediatric patients 2 years of age and older with severe manifestations of *PIK3CA*-Related Overgrowth Spectrum (PROS) who require systemic therapy • Received 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
Mechanism of Action:	Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominately against PI3Kα • Gain of function variants in the gene encoding the catalytic α-subunit of PI3K (*PIK3CA*) lead to activation of PI3Kα and Akt-signaling, cellular transformation, and the generation of tumors in in vitro and in vivo models. • Activating variants in *PIK3CA* have been found to induce a spectrum of overgrowths and malformations comprising a wide group of clinically recognizable disorders commonly known as PROS. • In an inducible mouse model of CLOVES Syndrome, a phenotype of PROS, alpelisib inhibition of the PI3K pathway resulted in the prevention or improvement of organ abnormalities associated with the disease, depending on when treatment was started. These findings were reversed after withdrawal of alpelisib.

Dose/ Administration:	• Patients aged ≥ 18 years: 250 mg orally once daily with food until disease progression or unacceptable toxicity
	• Patients aged ≥ 2 years and < 18 years:
	  ○ Recommended initial dose is 50 mg orally once daily with food until disease progression or unacceptable toxicity
	  ○ In patients aged ≥ 6 years, a dosage increase to 125 mg once daily may be considered after 24 weeks of therapy at 50 mg once daily
	• Tablets must be swallowed whole; do not split or chew.
	• For patients who have difficulty swallowing tablets, instructions on preparation of an oral suspension are given:
	  ○ Place tablets in 2 to 4 ounces of water and let stand for approximately 5 minutes.
	  ○ Crush the tablets with a spoon and stir until a suspension is obtained.
	  ○ The suspension must be given immediately after preparation. Discard the suspension if not administered within 60 minutes of preparation.
	  ○ After administration, add approximately 2 to 3 tablespoons of water to the same glass. Stir with the same spoon to re-suspend any remaining particles and administer the entire contents. Repeat if particles still remain.
	• Recommended dose reductions for adverse reactions: decrease dose to the next lower dose level. Discontinue in patients who cannot tolerate at least 50 mg daily.

Disease State Clinical Highlights:	• *PIK3CA*-Related Overgrowth Spectrum (PROS) is a spectrum of rare disorders involving variants in the *PIK3CA* gene causing overgrowth in various parts of the body. Variants in the *PIK3CA* gene result in an abnormally active PI3K enzyme, causing affected cells to grow and divide more than they should, and leading to abnormal bone, soft tissue, and blood vessel growth. *PIK3CA* variants may also cause overgrowth by influencing the effects of growth factors and hormones on nearby and distant cells. • The pathogenic variants causing PROS are not passed down from parent to child but result from changes to genes during development in the womb. Often PROS symptoms

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are visible at birth, leading to an early diagnosis, but symptoms may develop later in childhood. Overgrowth may stop in childhood or continue into adulthood.

- Patients with PROS are often treated for symptoms and complications such as bleeding, clotting, pain, and functional impairment. Many patients have surgery to remove lesions, which often must be repeated as the lesions grow back.
- PROS has an estimated prevalence of 14 people per million.
- The pathogenic variants in PROS are mosaic, meaning the variants are only present in certain body cells that affect only certain areas of the body, explaining why overgrowth in PROS appears in only certain body regions or asymmetrically. This also makes genetic testing for diagnosis confirmation difficult as the variant is not present in all cells. A key challenge in genetic testing is to determine which tissue has the greatest likelihood of having a detectable variant. Tissue samples are preferably obtained from dermal biopsy overlying an affected area or from a surgical procedure of the overgrown tissue.
- The spectrum of PROS includes but is not limited to:
  - CLAPO Syndrome:
    - **C**apillary malformation of the lower lip
    - **L**ymphatic malformation of the face and neck
    - **A**symmetry of face and limbs
    - **P**artial **O**vergrowth involving one or more body segments
  - CLOVES Syndrome:
    - **C**ongenital **L**ipomatous **O**vergrowth
    - **V**ascular malformations
    - **E**pidermal nevi
    - **S**coliosis/Skeletal/Spinal anomalies
  - Dysplastic Megalencephaly (DMEG)
  - Fibroadipose Hyperplasia (FAH)/Fibroadipose Overgrowth (FAO)
  - Hemihyperplasia Multiple Lipomatosis (HHML) Syndrome
  - Fibro-Adipose Vascular Anomaly (FAVA)
  - Facial Infiltrating Lipomatosis (FIL)
  - Hemimegalencephaly (HME)
  - Klippel-Trenaunay Syndrome (KTS)
  - Macrodactyly
  - Megalencephaly-Capillary Malformation (MCAP) Syndrome
  - Muscular Hemihyperplasia (HH)
- The National Institutes of Health (NIH) Workshop developed a consensus document for the diagnosis and treatment of patients with PROS in 2013. It was in this workshop that the name "*PIK3CA*-Realted Overgrowth Spectrum (PROS)" was introduced for the group of syndromes related to *PIK3CA* gene variants.
  - NIH Workshop clinical diagnostic criteria for PROS:
    - Presence of somatic *PIK3CA* variant (if no variant is identified, then consider as presumptive PROS)
    - Congenital or early childhood onset
    - Overgrowth sporadic and mosaic
    - Features as described in either Category A or B:
      - Category A: Describes a typically progressive spectrum requiring 2 or more features.
        - Overgrowth: adipose, muscle, nerve, skeletal
        - Vascular malformations: capillary, venous, arteriovenous malformation, lymphatic
        - Epidermal Nevus
      - Category B: Describes isolated features. Individuals may have only one feature, but it must be congenital or early childhood in onset.
        - Large isolated lymphatic malformation
        - Isolated macrodactyly or overgrown splayed feet/hands, overgrown limbs

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	○ Truncal adipose overgrowth ○ Hemimegalencephaly (bilateral)/Dysplastic Megalencephaly/Focal Cortical Dysplasia ○ Epidermal Nevus ○ Seborrheic keratoses ○ Benign lichenoid keratoses
Drug Clinical Highlights:	• Vijoice is the first FDA-approved treatment for PROS. It was 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. • The variants in the PI3K pathway are identical in PROS and cancer, leading to the study of repurposed cancer therapies in PROS treatment. Alpelisib was previously FDA approved in 2019, in combination with fulvestrant, for the treatment of hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, *PIK3CA*-mutated, advanced, or metastatic breast cancer. Alpelisib is marketed as Piqray® for the breast cancer indication. • Contraindications: Hypersensitivity to alpelisib or any of the ingredients • Warnings and Precautions: ○ Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, have occurred in adult patients treated in the oncology setting. Vijoice should be permanently discontinued in the event of severe hypersensitivity. ○ Severe Cutaneous Adverse Reactions (SCARs) ▪ SCARs include Steven-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) ▪ Interrupt therapy with Vijoice for signs and symptoms of SCARs. ▪ Permanently discontinue if SCARs are confirmed. ▪ If SCARs are not confirmed, Vijoice dose reductions along with topical corticosteroids and/or oral antihistamine treatment may be required. ○ Hyperglycemia ▪ Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or fatal cases of ketoacidosis, has occurred in adult patients treated with alpelisib in the oncology setting. ▪ In clinical studies (EPIK-P1), Grade 1 or 2 hyperglycemia was report in 12% of patients treated with Vijoice. ▪ Before initiating treatment, test fasting plasma glucose (FPG), HbA1c, and optimize the patient's blood glucose levels. ▪ After initiation of treatment: • Monitor FPG at least once weekly 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 • Patients with risk factors for hyperglycemia, i.e., obesity, elevated FPG, HbA1c at the upper limit of normal or above, concomitant systemic corticosteroid therapy, or age ≥ 75 years, should be monitored more frequently during the first few weeks of treatment. ▪ If hyperglycemia is experienced, interrupt, reduce the dose, or permanently discontinue Vijoice therapy based on severity. Anti-hyperglycemic treatment may be required. ▪ The safety of Vijoice in patients with Type 1 or Type 2 diabetes has not been established. ○ Pneumonitis ▪ Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, has occurred in adult patients treated in the oncology setting. ▪ In patients with new or worsening respiratory symptoms, interrupt Vijoice therapy immediately and evaluate for pneumonitis. ▪ Permanently discontinue Vijoice if pneumonitis is confirmed.

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- Diarrhea
  - Severe diarrhea, including cases resulting in dehydration and acute kidney injury, has occurred in adult patients treated in the oncology setting.
  - In clinical studies (EPIK-P1), 16% of Vijoice treated patients experienced Grade 1 diarrhea.
  - Interrupt, reduce the dose, or permanently discontinue Vijoice based on severity.
- Embryo-Fetal Toxicity
  - Vijoice can cause fetal harm when administered to a pregnant woman.
  - Verify the pregnancy status in females of reproductive potential prior to initiating therapy.
  - Advise males and females of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.

- Adverse reactions (Grades 1 to 4, incidence ≥ 10%): diarrhea, stomatitis, and hyperglycemia
- Drug Interactions
  - CYP3A Inducers: avoid coadministration
    - Vijoice is metabolized by CYP3A4; concomitant administration may decrease Vijoice concentrations and activity.
  - Breast Cancer Resistance Protein (BCRP) Inhibitors: avoid coadministration
    - Vijoice is transported by BRCP; concomitant administration may increase Vijoice exposure and risk of adverse reactions.
    - If unable to avoid coadministration, closely monitor the patient for increased adverse reactions.
  - CYP2C9 Substrates: closely monitor the patient
    - Vijoice induces CYP2C9; concomitant administration may reduce exposure and activity of the CYP2C9 substrate.
- Clinical Trial: EPIK-P1 (NCT04285723)
  - Single-arm, retrospective chart review study in 57 patients who were treated as part of an expanded access program for compassionate use.
  - Inclusion criteria:
    - Age ≥ 2 years
    - Physician confirmed/documented diagnosis of PROS
    - Documented evidence of a pathogenic variant in the *PIK3CA* gene
    - Patient's condition assessed as severe or life threatening by the treating physician
  - Efficacy was evaluated in 37 patients with at least one target lesion identified on imaging performed within 24 weeks prior to the first dose of Vijoice.
    - Median patient age was 14 years (range 2 to 38 years) with 30% of patients aged ≥ 18 years
    - 92% of patients had congenital overgrowth and 8% had early childhood onset
    - Manifestations of PROS:
      - CLOVES - 81%
      - MCAP - 8%
      - KTS - 2.7%
      - FIL - 8%
      - Other - 5%
      - 5% of patients had concurrent manifestations of CLOVES and MCAP
  - Patients received Vijoice at dosages based on age, ranging from 50 mg to 250 mg once daily.
  - Primary Outcome: proportion of patients with radiological response at Week 24 (+/- 4 weeks) as determined by blinded independent central review, defined as ≥ 20% reduction from baseline in the sum measurable target lesion volume (1 to 3 lesions) confirmed by at least one subsequent assessment, in the absence of a ≥ 20% increase from baseline in any target lesion, progression of non-target lesions, or appearance of new lesions.

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- A 20% volume reduction was selected as it is a commonly accepted threshold in vascular anomalies for the objective assessment of changes of tumor/lesion size and is associated with a clinical benefit in PROS
- Secondary Outcome: duration of response, defined as the time from the first documented response to the date of the first documented disease progression or death due to any cause.
- Efficacy Results at Week 24:

Efficacy parameters	All patients N = 37
Response rate[a,b]	
Responders, n (%)	10 (27)
95% CI	(14, 44)
Duration of response	
Median in months (range)	NR (0.9+, 42.9+)
% ≥ 6 months	70
% ≥ 12 months	60

+ censored observation
[a] Confirmed response as determined by blinded independent central review
[b] Patients without any response assessment at Week 24 were considered non-responders

- Other Secondary Outcomes not presented in the package insert but presented at the 2021 European Society for Medical Oncology (ESMO) Congress:
  - Percent change in lesion volume:
    - 37.5% of the patients with complete cases (n=32) responded (i.e., ≥ 20% reduction in target lesion volume (primary endpoint)
    - 74.2% of patients (23 of 31) experienced reduction in sum of target lesion volume
  - PROS signs and symptoms:
    - Clinically meaningful improvement in PROS signs and symptoms was observed
    - Reductions in the number of Grade 3 & 4 events were observed as early as week 12, confirmed at week 24, and were sustained and/or improved over time
    - No disease-related surgery was required within the first 24 weeks following Vijoice initiation
  - Safety:
    - No patient experienced disease progression or death during the study period
    - No patient discontinued treatment due to adverse events. 91.2% of patients remained on treatment at study end.

Price Per Unit (WAC):

- $32,500 per 28 day supply; $422,500 per year
- Available in daily dose blister packs:
  - 50 mg daily dose blister pack (28 of the 50 mg tablets)
  - 125 mg daily dose blister pack (28 of the 125mg tablets)
  - 250 mg daily dose blister pack (28 of the 200 mg tablets & 28 of the 50 mg tablets)

Therapeutic Alternatives:

- Prior to the approval of Vijoice, the only treatment options for PROS were surgery or interventional radiology. These are rarely curative with risks of complications and recurrence.
- Activation of the PI3K/AKT/mTOR pathway is a major cause of overgrowth syndromes.
  - Sirolimus, a direct inhibitor of mTORC1 which is found at the end of the PI3K/AKT pathway, has been shown in prospective studies to improve pain and functional limitation in patients with lymphatic, venous, or combined malformations (including PROS). While not FDA approved for PROS, it has been approved for related disease states including tuberous sclerosis and lymphangioleiomyomatosis.
  - Vijoice's inhibition of PI3K occurs at the top of the PI3K/AKT/mTOR pathway, making it more likely to correct and control the overgrowth seen in PROS.

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	• Alpelisib is also marketed as Piqray for the treatment of breast cancer. Piqray, like Vijoice, is also available in 28 day blister packs:
	  ○ 200 mg daily dose blister pack (28 of the 200 mg tablets)
	  ○ 250 mg daily dose blister pack (28 of the 200 mg tablets & 28 of the 50 mg tablets)
	  ○ 300 mg daily dose blister pack (56 of the 150 mg tablets)
	• The adult dose of 250 mg per day is in similar blister packaging for both Vijoice and Piqray. Piqray 250 mg per day blister pack has a WAC cost of $18,721 compared to the Vijoice 250 mg per day blister pack WAC cost of $32,500.

Prior Authorization Approval Criteria:	**Must meet the following criteria:**
	
	<u>Initial Therapy:</u>
	• Prescribed by or in consultation with an appropriate specialist in the treated disease state **AND**
	• Participant is aged ≥ 2 years **AND**
	• Documented diagnosis of PROS as verified by genetic testing or signs and symptoms of disease (see NIH Workshop diagnostic guidelines) **AND**
	• Documentation of at least one target lesion identified on imaging with baseline measurement of target lesion volume **AND**
	• Participant is not currently pregnant **AND**
	• Participant (male or female of appropriate age) is utilizing concurrent effective contraception methods **AND**
	• Participants aged ≥ 18 years: therapeutic reason why Piqray 250 mg daily dose pack cannot be utilized
	• Initial approval for 6 months
	
	<u>Continuation of Therapy:</u>
	• Documentation of benefit of therapy by one of the following:
	  ○ ≥ 20% reduction in measurement of target lesion volume
	  ○ Reduction in sum of lesion volume
	  ○ Clinically meaningful improvement in signs and symptoms of disease (i.e., vascular malformation, functional improvement, limb asymmetry, pain)
	• Continued approval for 1 year
	
	Additional Provider Diagnostic/Monitoring Criteria, if desired:
	• Optimization of the participant's blood glucose levels prior to initiation of therapy.
	• After initiation of therapy, monitoring of blood glucose levels at least once weekly for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated
	• HbA1c should be monitored every 3 months and as clinically indicated

Implication to State Medicaid Program:	• LOE: TBD
	• There is not currently a specific ICD10 code for PROS. PROS spectrum disorders may fall under one of the following non-specific codes:
	  ○ Q87.2 – Congenital malformation syndromes predominantly involving limbs
	  ○ Q87.3 – Congenital malformation syndromes involving early overgrowth
	• Other Clinical Trials:
	  ○ EPIK-P2 (NCT04589650) - Prospective Phase 2 multicenter study with a randomized, double-blind, upfront 16-week placebo-controlled period, and an extension period to evaluate the safety, efficacy, and pharmacokinetics of Vijoice in treating pediatric and adult patients with PROS. Estimated study completion is March 2023.
	  ○ EPIK-P3 (NCT04980833) - Phase 2 study to assess long-term safety and efficacy of Vijoice in patients with PROS who participated in EPIK-P1. Estimated study completion is July 2027.

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