NEW DRUG APPROVAL

Brand Name	Vijoice®
Generic Name	alpelisib
Drug Manufacturer	Novartis Pharmaceuticals Corporation

New Drug Approval

FDA approval date: April 5, 2022

Review designation: Priority; Orphan

Type of review: New Drug Application (NDA): 215039

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

PIK3CA-related overgrowth spectrum (PROS) includes a group of genetic disorders that leads to overgrowth of various body parts due to changes (mutations) in the gene *PIK3CA*. This gene is involved in making a protein that helps regulate cell growth, division and survival. A broad array of disorders falls within this spectrum, with some overlap of symptoms between the different disorders. Syndromes within the spectrum may also overlap genetically, meaning they may share specific *PIK3CA* gene mutations in cells in the areas of the body that are affected. Since *PIK3CA* mutations in these disorders are not present in all cells, only certain areas of the body are overgrown, ranging from isolated digits to whole limbs, trunk, or brain. Different tissues may be involved individually or in combination such as fat, muscle, bone, nerve, brain and blood vessels. Genetic mutations that cause these disorders are not passed down from parent to child but instead result from changes to genes during development in the womb. Symptoms associated with these disorders can be present at birth (congenital) or appear later in early childhood. Overgrowth may stop in childhood or continue into adulthood.

Different subtypes within PROS include: CLAPO syndrome, CLOVES syndrome, DCMO, DMEG, FAH/FAO/HHML, FAVA, FIL, HMEG, Klippel-Trenaunay syndrome (KTS), LON, macrodactyly, MCAP and muscular hemihyperplasia (HH).

Because PROS includes several different syndromes, the exact incidence and prevalence rates are not known. These syndromes are typically diagnosed at birth or in early childhood. Many syndromes such as MCAP, CLOVES and KTS affect males and females in equal numbers.

Although reported rates of individual PROS disorders are low or unknown, the spectrum collectively could represent a more significant patient number, with an estimated prevalence of 14 people per million.

Efficacy

The efficacy of Vijoice® was assessed in EPIK-P1 (NCT04285723), a single-arm clinical study in patients who were treated as part of an expanded access program for compassionate use which enrolled patients across seven sites in five countries (France, Spain, US, Ireland and Australia). Eligible patients 2 years of age and older with PIK3CA-Related Overgrowth Spectrum (PROS) who received Vijoice® had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene. Patients received Vijoice® at dosages based on age ranging from 50 mg to 250 mg orally once daily. The efficacy of 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 of Vijoice®. The median age of patients was 14 years (range: 2 to 38); 22% of patients were 2 to 5 years, 22% were 6 to 11 years, 27% were 12 to less than 18 years of age, and 30% were ≥ 18 years; 57% were female, 11% were White and race was not reported for 89%. Ninety-two percent of patients had congenital overgrowth and 8% had early childhood-onset. Patients had heterogeneous manifestations of PROS, including CLOVES, (81%), Megalencephaly-Capillary Malformation Polymicrogyria (MCAP; 8%), Klippel-Trenaunay Syndrome (KTS; 2.7%), Facial Infiltrating Lipomatosis (FIL; 8%), and Other (5%). Five percent (5%) of patients had concurrent manifestations of CLOVES and MCAP. The major efficacy outcome measure for the study was the proportion of patients with radiological response at Week 24 as determined by blinded independent central review (BICR), defined as a ≥ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions) confirmed by at least one subsequent imaging assessment, in the absence of a ≥ 20% increase from baseline in any target lesion, progression of non-target lesions, or appearance of a new lesion. An additional efficacy outcome measure was 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 are presented in below Table:

Table 1: Efficacy Results at Week 24 in EPIK-P1

Efficacy parameters	**All patients N = 37**
Response rate[a,b]	
Responders, n (%) 95% CI	10 (27) (14, 44)
Duration of response (DOR)	
Median in months (range)	NR (0.9+, 42.9+)
% ≥ 6 months	70
% ≥ 12 months	60
Abbreviation: +: censored observation. [a]Confirmed response as determined by blinded independent central review (BICR). [b]Patients without any response assessment at Week 24 were considered non-responders.	

Safety

ADVERSE EVENTS

Most common adverse reactions (Grades 1 to 4, incidence ≥ 10%) were diarrhea, stomatitis, and hyperglycemia.

WARNINGS & PRECAUTIONS

Severe Hypersensitivity:
Permanently discontinue Vijoice®. Promptly initiate appropriate treatment.

Severe Cutaneous Adverse Reactions (SCARs):
Vijoice® can cause SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Interrupt Vijoice® for signs or symptoms of SCARs. Permanently discontinue Vijoice® if SCARs are confirmed.

Hyperglycemia:
Vijoice® can cause severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis. The safety of Vijoice® in patients with Type 1 or uncontrolled Type 2 diabetes has not been established. Before initiating treatment with Vijoice®, test fasting plasma glucose (FPG), HbA1c, and

optimize blood glucose. After initiating treatment, monitor periodically. Initiate or optimize anti-hyperglycemic medications as clinically indicated. Interrupt, reduce dose, or discontinue Vijoice® if severe hyperglycemia occurs.

Pneumonitis:
Vijoice® can cause severe pneumonitis and interstitial lung disease. Monitor for clinical symptoms or radiological changes. Permanently discontinue Vijoice® if pneumonitis occurs.

Diarrhea:
Vijoice® can cause severe diarrhea, dehydration, and acute kidney injury. Interrupt, reduce dose, or permanently discontinue Vijoice® based on severity.

Embryo-Fetal Toxicity:
Vijoice® can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

Severe hypersensitivity to Vijoice® or to any of its ingredients.

Clinical Pharmacology

MECHANISMS OF ACTION

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations 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 mutations 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 Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal syndrome (CLOVES), 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 alpelisib treatment was started. These findings were reversed after withdrawal of alpelisib.

Dose & Administration

ADULTS

250 mg taken orally once daily with food.

PEDIATRICS

2 to less than 18 years of age: 50 mg taken orally once daily with food.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 50 mg, 125 mg, and 200 mg

Table 2: Prescribing information

Daily Dose	Each Carton Contains	Each Blister Pack Contains
50 mg	One 28-day supply blister pack	28 tablets
125 mg	One 28-day supply blister pack	28 tablets
250 mg	Two 14-day supply blister packs (56 tablets total)	14 tablets: 200 mg tablets 14 tablets: 50 mg tablets

Source: Vijoice Prescribing Information.