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THE PROS PERSPECTIVE

PROS Management With VIJOICE® (alpelisib)

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The perspectives provided within this newsletter by Dr Richter are his own and not reflective of his affiliation. The medical expert in this newsletter was compensated by Novartis Pharmaceuticals Corporation to provide their perspectives.

ISSVA, International Society for the Study of Vascular Anomalies; PROS, PIK3CA-related overgrowth spectrum.

INDICATION

VIJOICE® (alpelisib) tablets is indicated for 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.

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 confirmatory trials.

IMPORTANT SAFETY INFORMATION

VIJOICE is contraindicated in patients with severe hypersensitivity to alpelisib or any of its ingredients.

Severe Hypersensitivity. Severe hypersensitivity reactions, including anaphylaxis, angioedema, and anaphylactic shock, have occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with VIJOICE. VIJOICE is not approved for use in the oncology setting. Permanently discontinue VIJOICE in the event of severe hypersensitivity.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

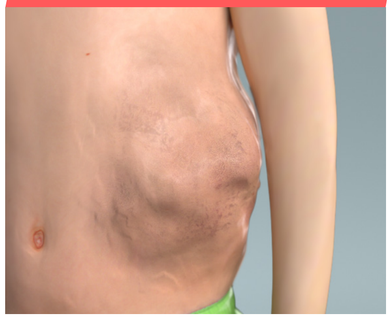
What are daily challenges presented to patients with PROS?

The impact depends on the part of the body affected. For the limbs, activity is often reduced due to intermittent pain, instability, and asymmetry. PROS causes gradual functional decline and can lead to social isolation in some patients.

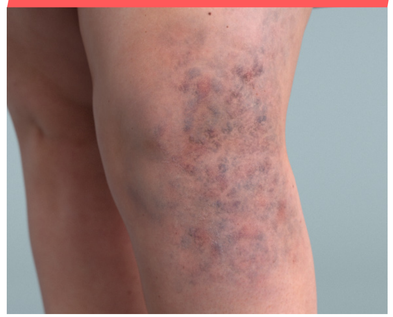
PROS is a spectrum of diverse overgrowth disorders caused by a PIK3CA mutation[1]

Features of PROS disorders broadly include the following types of overgrowth:

Lipomatous overgrowth



Vascular malformations



Skeletal overgrowth

Lymphatic malformations

A variety of signs and symptoms are associated with PROS disorders that can cause severe medical complications, disfigurements, and functional complications that interfere with daily living[2-5]

- **Bone abnormalities,** including leg asymmetry and scoliosis
- **Pain**
- **Hypertrophy**
- **Vascular complications,** including disseminated intravascular coagulation
- **Fatigue**

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IMPORTANT SAFETY INFORMATION (cont)

Severe Cutaneous Adverse Reactions (SCARs). SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with VIJOICE. If signs or symptoms of SCARs occur, interrupt VIJOICE until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, permanently discontinue VIJOICE. If a SCAR is not confirmed, VIJOICE may require dose modifications, topical corticosteroids, or oral antihistamine treatment.

Hyperglycemia. Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar nonketotic syndrome (HHNKS) or fatal cases of ketoacidosis, has occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with VIJOICE.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

How does VIJOICE work in the treatment of PROS?

VIJOICE targets the underlying cause of PROS by inhibiting the PI3Kα enzyme.

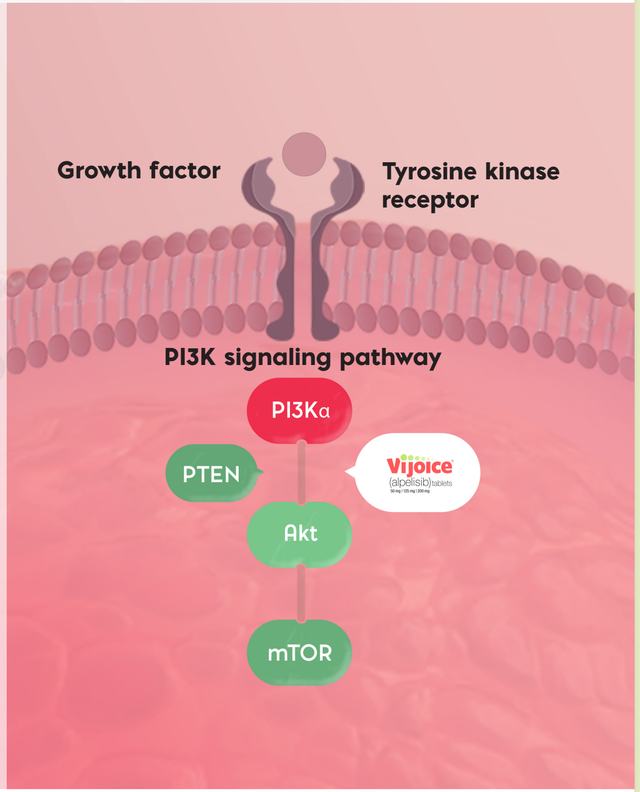
Other treatment options for PROS do not address the underlying cause of the disease[6,7]

Other treatment options for PROS

- Surgery
- Oral immunosuppressants
- Radiologic embolization

VIJOICE targets the underlying cause of PROS[1,6,7]

- VIJOICE works by selectively inhibiting PI3Kα, a key upstream component of the PI3K pathway[6,8]
- The inhibition of this pathway interrupts various downstream signaling, including Akt/mTOR and Akt-independent cascades[6,9]



PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin homolog; Akt, kinase B; mTOR, mammalian target of rapamycin.

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IMPORTANT SAFETY INFORMATION (cont)

Hyperglycemia (cont). In the EPIK-P1 study, grade 1 or 2 hyperglycemia was reported in 12% of patients treated with VIJOICE.

Before initiating treatment with VIJOICE, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment with VIJOICE, monitor fasting glucose (FPG or fasting blood glucose) at least once every week 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. Monitor fasting glucose more frequently for the first few weeks during treatment with VIJOICE in patients with risk factors for hyperglycemia, such as obesity (body mass index ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

How do the longer-term data from EPIK-P1 together with EPIK-P3 support your decision to use VIJOICE in your patients with PROS?

> *The longer-term data supporting VIJOICE align with what I've seen in practice. The data, which include patients with large, volumetrically significant lesions, underscore the drug's potential effectiveness in reducing the overgrowth.*

The clinical evidence of VIJOICE across a median of 3.5 years and up to 6 years of treatment[6,10]

EPIK-P1 and EPIK-P3 Study Overview

- **EPIK-P1:** Retrospective medical chart review of 57 pediatric and adult patients with PROS who were treated with VIJOICE in a compassionate use program[6,8]
  - Population included patients who received at least 1 dose of VIJOICE for at least 24 weeks before the data cut-off date for the study analysis[6,8]
  - **43.9%** of patients had been **treated with sirolimus and 87.7% of patients had at least 1 surgery** prior to treatment with VIJOICE[8]
- **EPIK-P3:** An ongoing clinical study with retrospective and prospective phases that enrolled a subset of patients from EPIK-P1. At completion of the retrospective chart review phase of EPIK-P3, patients had received VIJOICE for at least 2 years and up to 6 years after starting EPIK-P1[10]

VIJOICE Overgrowth Response (EPIK-P1)[6]

27% **of patients experienced a response at Week 24*,†**

Response was determined by BICR.

(10/37) (95% CI, 14-44)

VIJOICE reduced the signs and symptoms of PROS[10]

Patients experienced improvements in the most common PROS signs and symptoms, including **fatigue, vascular malformations, DIC, limb asymmetry, and pain**. Some improvements were seen as early **as Week 12, and also, some were maintained for more than 3 years‡**

BICR, blinded independent central review; CI, confidence interval; DIC, disseminated intravascular coagulation; CTCAE, Common Terminology Criteria for Adverse Events.
*Confirmed response as determined by BICR. Response was defined as the proportion of patients achieving ≥20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions) confirmed by at least 1 subsequent imaging assessment, provided that none of the individual target lesions had a ≥20% increase from baseline, nontarget lesions had not progressed, and there were no new lesions as determined by BICR.[6]
†Patients without any response assessment at Week 24 were considered nonresponders.[6]
‡Improvement was defined based on CTCAE version 4.03 grade reduction or resolution of the event. Percentages were calculated based on the number of patients who reported the event at baseline.[10]

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IMPORTANT SAFETY INFORMATION (cont)

Hyperglycemia (cont). If a patient experiences hyperglycemia after initiating treatment with VIJOICE, monitor fasting glucose as clinically indicated and at least twice weekly until fasting glucose decreases to normal levels. During treatment with antihyperglycemic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and as clinically indicated. Consider consultation with a health care provider with expertise in the treatment of hyperglycemia, and counsel patients on lifestyle changes.

The safety of VIJOICE in patients with type 1 and uncontrolled type 2 diabetes has not been established. Patients with a history of diabetes mellitus may require intensified hyperglycemic treatment. Closely monitor patients with diabetes.

Interrupt, reduce the dose of, or permanently discontinue VIJOICE based on severity.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

What do the combined EPIK-P1 and EPIK-P3 data for functionality and for number of surgeries, as measured in the studies, mean to you as a clinician?

"Patients want improved functionality to do the things they've always wanted to do. Seeing them become more functional is truly impactful."

Functionality Assessment through the longer-term assessment[10]*

In EPIK-P1, at least[8†]

50% of patients **experienced improved or stable function** at Week 24

(24/47)

In EPIK-P1 + EPIK-P3

~81% of patients had an **improved score by at least 20 points** at the last available post-index assessment[10‡]

(38/47)

VIJOICE and surgeries in most patients[10]

No adult patients required any PROS-related surgery during the longer-term evaluation.
Three pediatric patients required progression-related surgery during the longer-term evaluation

ECOG, Eastern Cooperative Oncology Group.
*No other scales were reported for change in score. Change in score is only applicable if both index and post-index date information are available. Patients may have started with Lansky at index and switched to Karnofsky at a later time.[8,10] ECOG scales assess level of functioning by measuring a patient's daily activity, physical ability, and ability to care for oneself.[11] Lansky and Karnofsky scales assess a patient's ability to perform normal activities of daily living and functional status.[11,12] For the ECOG scale, improvement is defined as a decrease by at least 1 point and worsening is defined as an increase by at least 1 point. For the Karnofsky and Lansky scales, improvement is defined as an increase by at least 20 points, worsening is defined as a decrease by at least 20 points, and stable is defined as a change in score between -20 and 20 points.[8,10]
†The performance status score was not reported for 23 of 47 patients at Week 24.[8]
‡The median score at the index date was 70.0 (range: 20-100).[10]

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IMPORTANT SAFETY INFORMATION (cont)

Pneumonitis. Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, has occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with VIJOICE.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt VIJOICE immediately and evaluate the patient for pneumonitis. Consider a diagnosis of noninfectious pneumonitis in patients presenting with nonspecific respiratory signs and symptoms, such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic examinations and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue VIJOICE in all patients with confirmed pneumonitis.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

How do you approach adjusting a patient's VIJOICE treatment if there are concerning side effects?

Our team has typically encountered rash and dry skin with our patients. One developed hyperglycemia, so we started metformin and reduced the dose of VIJOICE. We made a shared decision with the patient and family to continue treatment, as the hyperglycemia was manageable, and she continued to experience clinical benefits.

Safety profile

- Longer-term follow-up from EPIK-P3 did not show any new safety signals[10]
- In EPIK-P1, the most commonly reported ARs were diarrhea (16%), stomatitis (16%), and hyperglycemia (12%)[6]
- No patients permanently discontinued treatment due to ARs[8]

ARs suspected to be related to study treatment in either pediatric (<18 years of age) or adult patients (EPIK-P1+EPIK-P3)

AR	All grades (%)		Grades 3/4 (%)	
	Pediatric (N=39)	Adult (N=18)	Pediatric (N=39)	Adult (N=18)
Gastrointestinal disorders	20.5	27.8	0	0
Aphthous ulcer	12.8	16.7	0	0
Stomatitis	7.7	0	0	0
Infections and infestations	0	11.1	0	5.6
Cellulitis	0	5.6	0	5.6
Metabolism and nutrition disorders	5.1	27.8	0	0
Hyperglycemia	5.1	27.8	0	0
Skin and subcutaneous tissue disorders	2.6	22.2	0	0
Alopecia	0	16.7	0	0

Grading according to CTCAE version 4.03.

AR, adverse reaction.

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IMPORTANT SAFETY INFORMATION (cont)

Diarrhea or Colitis. Severe diarrhea, resulting in dehydration, and, in some cases, acute kidney injury and colitis, has occurred in adult patients treated with alpelisib in the oncology setting and may occur in patients treated with VIJOICE. In the EPIK-P1 study, 16% of patients experienced grade 1 diarrhea during treatment with VIJOICE. Monitor patients for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in the stool. Interrupt, reduce the dose of, or permanently discontinue VIJOICE based on the severity of diarrhea or colitis.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

What aspects of VIJOICE dosing and administration stand out to you as an HCP?

“There is less maintenance and in-person follow-up required with VIJOICE. With other treatment options, we need frequent follow-ups, blood draws for WBC checks, and antibiotics. When starting patients on VIJOICE, we can stay in touch with some patients through phone calls or telehealth.”

VIJOICE is taken orally, once daily in patients with PROS

HCP, health care professional; WBC, white blood cell.

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IMPORTANT SAFETY INFORMATION (cont)

Embryo-Fetal Toxicity. Based on findings in animals and its mechanism of action, VIJOICE can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VIJOICE and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with VIJOICE and for 1 week after the last dose.

Please see additional Important Safety Information throughout this newsletter. Please click here for full Prescribing Information.

Targeted therapy for vascular anomalies from a PROS condition represents a significant option in treatment. For many patients who may not be ideal surgical candidates, VIJOICE has helped reduce the number of required interventions. By addressing the disease systemically with targeted therapy, we have observed reductions in malformation size, a decreased need for surgeries, and an overall reduction in burden of disease.

The **FIRST** and **ONLY** FDA-approved treatment for pediatric and adult patients with PROS

FDA, US Food and Drug Administration.

References: **1.** Keppler-Noreuil KM, Rios JJ, Parker VER, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A*. 2015;167A(2):287-295. **2.** Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. *Am J Med Genet A*. 2014;164A(7):1713-1733. **3.** Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trénaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998;73(1):28-36. **4.** van der Ploeg HM, van der Ploeg MN, van der Ploeg-Stapert JD. Psychological aspects of the Klippel-Trenaunay syndrome. *J Psychosom Res*. 1995;39(2):183-191. **5.** Zhang J, Wang K, Mei J. Late puerperal hemorrhage of a patient with Klippel-Trenaunay syndrome: a case report. *Medicine (Baltimore)*. 2019;98(50):e18378. **6.** Vijoice. Prescribing information. Novartis Pharmaceuticals Corp. **7.** Guimarães IS, Tessarollo NG, Lyra-Júnior PCM, et al. Targeting the PI3K/AKT/mTOR pathway in cancer cells. In: Rangel LBA, Silva IV, eds. *Updates on Cancer Treatment. Intech Open*. 2015:1-36. **8.** Data on file. Study CBYL719F12002. Novartis Pharmaceuticals Corp; 2021. **9.** Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature*. 2018;558(7711):540-546. **10.** Data on file. Studies CBYL719F12002 and CBYL719F12401. Novartis Pharmaceuticals Corp; 2023. **11.** Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655. **12.** Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. *Cancer*. 1987;60(7):1651-1656.

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IMPORTANT SAFETY INFORMATION (cont)

The most common adverse reactions (all grades, incidence ≥10%) were diarrhea (16%), stomatitis (16%), and hyperglycemia (12%).

The most common laboratory abnormalities (all grades, incidence ≥20%) were decreased calcium (corrected) (60%), decreased phosphate (59%), increased glucose (56%), increased HbA1c (38%), increased creatinine (31%), increased bilirubin (29%), increased potassium (24%), decreased leukocyte (22%), decreased lymphocyte (20%), and decreased hemoglobin (20%).

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