22 May 2026
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Vijoice (alpelisib)
Treatment of PIK3CA related overgrowth spectrum
EU/3/21/2420

Sponsor: Novartis Europharm Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance(s)	Alpelisib
Other name(s)	-
International Non-Proprietary Name	Alpelisib
Tradename	Vijoice
Orphan condition	Treatment of PIK3CA related overgrowth spectrum
Sponsor's details:	Novartis Europharm Limited Vista Building Elmpark Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion	18 February 2021
EC decision	26 March 2021
EC registration number	EU/3/21/2420
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Nicolas Beix / Carolina Prieto Fernandez
Applicant	Novartis Europharm Limited
Application submission	5 May 2025
Procedure start	22 May 2025
Procedure number	EMA/H/C/006539
Invented name	Vijoice
Proposed therapeutic indication	Vijoice is indicated for the treatment of adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Vijoice
CHMP opinion	21 May 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Sine Buhl Naess-Schmidt
Sponsor's report submission	29 January 2026
COMP discussion	14-16 April 2026
COMP opinion (adoption via written procedure)	22 May 2026

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing alpelisib was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in tumour size and preliminary clinical data in patients with the condition showing a reduction in benign tumour size, oedema and a recovery of normal cardiac and musculoskeletal function;
- the condition is life-threatening and chronically debilitating due to functional impairment (e.g., of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infections due to the overgrowth of benign tumors and can include impaired neurological development, seizures, thromboembolisms, pulmonary hypertension, and hemorrhages;
- the condition was estimated to be affecting approximately 1.25 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing alpelisib as an orphan medicinal product for the orphan condition: treatment of PIK3CA related overgrowth spectrum".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA)-related overgrowth spectrum (PROS) is an umbrella term for a group of rare overgrowth disorders with diverse phenotypes that results from somatic mosaic gain-of-function mutations on the PIK3CA gene, activating the PI3K pathway (Keppler-Nureuil et al., 2015; Luks et al., 2015). PIK3CA encodes p110a, a component of the

PI3-kinase enzyme, which is involved in cellular proliferation, survival, and growth pathways (Hughes et al., 2020).

The clinical characteristics of PROS can be diverse and depend on the timing of the mutation during embryogenesis (Gazzin et al., 2023). PROS are characterised by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. Segmental overgrowth is often congenital in onset, but it is usually noted by one year of age with progressive overgrowth of tissues persisting in some cases into adulthood (Keppler-Noreuil et al., 2016). It is a highly anatomically variable condition admixture of overgrown tissues; capillaries, veins, and lymphatics, in addition to adipose tissue is often most affected, although organs can also be affected (Madsen et al., 2018).

PROS includes multiple conditions which can be classified as in table 1 below.

Table 1. PROS Classification

Localised or tissue-specific	**Multisystemic and with possible brain involvement**
Macrodactyly	Fibroadipose Overgrowth/Hemihyperplasia-Multiple Lipomatosis (FAO/HHML)
Epidermal Nevi	Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal Abnormalities syndrome (CLOVES)
Seborrheic Keratosis	Capillary malformation of the lower lip, Lymphatic malformation of face and neck, Asymmetry of face and limbs, and Partial/generalised Overgrowth syndrome (CLAPO)
PIK3CA-related muscular overgrowth with ectopic accessory muscles	Megalencephaly-Capillary Malformation-Polymicrogyria syndrome (MCAP)
Hemiorofacial asymmetry with peripheral nerve enlargement ad perineuriomatous pseudo-onion bulb proliferations	
Facial infiltrating lipomatosis (FIL)	
Lymphatic malformations (LM)	
Klippel-Trenaunay Syndrome (KTS)	

Source: Table adapted from Douzgou et al., 2022

PROS is primarily diagnosed molecularly, using genetic testing, optimised for the detection of low-level mosaic variants (usually Next Generation Sequencing or digital droplet polymerase chain reaction testing) (Douzgou et al., 2022).

Clinical diagnostic criteria have been proposed by Keppler-Nureuil et al. (2015):

- Required:
    - Presence of somatic *PIK3CA* mutation
    - Congenital or early childhood onset

    - Overgrowth sporadic and mosaic
    - Features as described in Spectrum or Isolated Features categories below.
- Spectrum (two or more features that are typically progressive):
    - Overgrowth: adipose, muscle, nerve, skeletal
    - Vascular malformations: capillary, venous, arteriovenous malformation, lymphatic
    - Epidermal nevus
- Isolated features
    - Large isolated lymphatic malformation
    - Isolated macrodactyly or overgrown splayed feet/hands, overgrown limbs
    - Truncal adipose overgrowth
    - Hemimegalencephaly (bilateral)/dysplastic megalencephaly/focal cortical dysplasia 2
    - Epidermal nevus
    - Seborrheic keratoses
    - Benign lichenoid keratoses

The approved therapeutic indication "Vijoice is indicated for the treatment of adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy" falls within the scope of the designated orphan condition "treatment of PIK3CA related overgrowth spectrum".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

PROS is characterized by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. Segmental overgrowth is often congenital at onset, but it is usually noted by 1 year of age with progressive overgrowth of tissues persisting in some cases into adulthood. Though some genotype–phenotype correlation in PROS has been suggested (Mirzaa et al, 2016; Keppler-Noreuil et al, 2014), the main determinant of phenotype is the timing and location of the pathogenic mutation. Consequently, PROS is characterized by a high degree of inter individual phenotypic heterogeneity. The overgrowth features vary greatly for reasons which are unknown; some lesions exhibit excess growth, which is limited to childhood, while other individuals have progressive soft tissue overgrowth during adult life. Functional impairment (e.g., of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infections can be a consequence of the overgrowth and can include impaired neurological development, seizures, thromboembolisms, pulmonary hypertension, and haemorrhages, amongst other manifestations all of which may be debilitating (particularly in the paediatric population) and may cause early mortality.

The condition can be accepted as chronically debilitating and life-threatening.

Number of people affected or at risk

The sponsor's strategy to estimate the prevalence of PIK3CA-related overgrowth spectrum (PROS) in the targeted European region is developed to support orphan maintenance for alpelisib in the PROS indication and incorporates literature and other data sources identified since the 2021 initial orphan designation submission.

The sponsor frames PROS as a recently consolidated clinical entity, recognised as a single condition composed of separates phenotypic manifestations that share a common molecular basis, namely postzygotic activating mutations in PIK3CA leading to mosaic overgrowth through hyperactivation of the PI3K/AKT/mTOR pathway (De Santis et al., 2017; Keppler-Noreuil et al., 2015). This recent nosological consolidation, together with marked phenotypic heterogeneity, mosaicism, and evolving diagnostic criteria, is presented as the main reason why robust prevalence data are scarce.

To address this limitation, the sponsor used a multi-source strategy aligned with EMA and COMP guidance on orphan prevalence estimation. The targeted region was defined as the 27 European Union Member States plus Iceland, Liechtenstein, and Norway, while studies from the United Kingdom were also retained for consistency with previous submissions as supportive data. A targeted literature search was conducted in 2025 using the same overall strategy as in the initial orphan designation report. Because few studies refer specifically to PROS as a unified condition, the search was broadened to include the individual component phenotypes subsumed under PROS. The literature search yielded 69 unique records, 19 full-text articles were reviewed, and 6 new publications were considered relevant to the updated report. The approach followed reflects an attempt to prioritise population-based evidence, although the sponsor acknowledges that such data remain very limited.

The sponsor supplemented the review with data from rare disease databases like Orphanet. Other sources, such as registries and patient organisations, were considered only supportive since they are voluntary, non-population-based, and incomplete.

The key new epidemiological evidence identified by the sponsor is a population-based study from the Piedmont region of Italy (Reynolds et al., 2023), which the sponsor presents as the main basis for prevalence estimation. This study identified 37 PROS cases among 825,593 live births between 1998 and 2021. Of these, 30 cases, corresponding to 81%, had a detected PIK3CA variant. Because no deaths occurred among the identified patients during the study period, the sponsor considered incidence and prevalence to be equivalent within this cohort. Using the EMA denominator convention, the study estimated a 25-year prevalence of PROS of 0.45 per 10,000 live births and a prevalence of molecularly confirmed PROS of 0.36 per 10,000 live births. The sponsor relies heavily on this study because it is the only identified population-based European study providing direct estimates for PROS as a whole.

In addition to this principal study, the sponsor reviewed the epidemiology of individual PROS-related phenotypes reported in older literature and Orphanet. However, most of these data were found to be of limited utility for prevalence estimation. Earlier literature cited prevalence or incidence values for certain component disorders, but the sponsor notes that the original bases for several of these estimates could not be verified and that many of them likely included both PROS-related and non-PROS-related cases. Accordingly, the sponsor treats these figures as likely overestimates if applied to PROS. However, the sponsor highlights that even the highest Orphanet prevalence estimate for a PROS-related phenotype remains far below the orphan threshold and that the frequencies of most other phenotypes are orders of magnitude lower. This is used to reinforce the conclusion drawn from the Piedmont study that the overall prevalence of PROS is very low.

Similarly, case series from referral centres and institutional cohorts, while useful for characterising the disease spectrum and confirming rarity, were not considered suitable for deriving population prevalence. For this reason, they were used as descriptive support only and not as a denominator-based basis for prevalence calculations.

Conclusion

Overall, given the uncertainty inherent in the available data, including variation in case ascertainment, diagnostic confirmation, phenotype definition, and the limitations of supportive database and registry sources, the sponsor's hierarchical and conservative approach provides a reasonable basis for prevalence estimation. The available evidence supports the conclusion that PROS prevalence in the targeted European region is approximately 1 per 10,000 population or less, and below the orphan designation threshold of 5 per 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no authorised products currently specifically for the condition.

The sponsor cites guidelines for diagnosis and treatment of PROS (Douzgou et al., 2022). Standard of care treatment options include debulking surgery, sclerotherapy, and laser therapy (Gazzin et al., 2023; Canaud et al., 2021). For treatment of overgrowth/fibro-lipomatous masses, debulking surgery is usually the first method, especially in cases of functional limitations and/or pain. Surgery is also considered to treat other symptoms such as macrodactyly and leg length discrepancy. For vascular malformations, sclerotherapy, laser therapy and oral medications are available which are often used off label (Gazzin et al., 2023).

Medicines under investigation for the condition include sirolimus which is currently used off label to treat PROS (Mirzaa et al., 2023). In 2022, the product discussed in this orphan maintenance report (Vijoice) received Food and Drug Administration approval under accelerated approval for the treatment of adult and paediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy (VIJOICE USPI, 2025).

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 22 May 2026

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of PIK3CA related overgrowth spectrum (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to functional impairment (for example impaired walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infections due to the overgrowth of benign tumours and can include impaired neurological development, seizures, thromboembolisms, pulmonary hypertension, and haemorrhages;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Vijoice, alpelisib for treatment of PIK3CA related overgrowth spectrum (EU/3/21/2420) is not removed from the Community Register of Orphan Medicinal Products.