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Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

Hyftor (Sirolimus)
Treatment of tuberous sclerosis
EU/3/17/1910

Sponsor: Plusultra pharma GmbH

**Note**

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

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# 1. Product and administrative information

| | |
|---|---|
| **Product** | |
| Designated active substance | Sirolimus |
| Other names | Hyftor, Sirolimus, |
| International Non-Proprietary Name | Sirolimus |
| Tradename | Hyftor |
| Orphan condition | Treatment of tuberous sclerosis |
| Sponsor's details: | Plusultra Pharma GmbH<br>Fritz-Vomfelde-Strasse 36<br>40547 Duesseldorf<br>North Rhine-Westphalia<br>Germany |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | Best Regulatory Consulting Ltd |
| COMP opinion | 13 July 2017 |
| EC decision | 23 August 2017 |
| EC registration number | EU/3/17/1910 |
| **Post-designation procedural history** | |
| Transfer of sponsorship | Transfer from Best Regulatory Consulting Ltd to FGK Representative Service GmbH – EC decision of 25 March 2019<br><br>Transfer from FGK Representative Service GmbH to Plusultra Pharma GmbH – EC decision of 26 November 2021 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | Martina Weise / Blanca Garcia-Ochoa |
| Applicant | Plusultra Pharma GmbH |
| Application submission | 26 November 2021 |
| Procedure start | 24 December 2021 |
| Procedure number | EMA/H/C/005896/0000 |
| Invented name | Hyftor |
| Proposed therapeutic indication | Treatment of angiofibroma associated with the tuberous sclerosis in adults and children<br><br>Further information on Hyftor can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Hyftor |
| CHMP opinion | 23 February 2023 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteurs | Joao Rocha / Elisabeth Johanne Rook |
| Sponsor's report submission | 09 September 2022 |
| COMP discussion | 14-16 February 2023 |
| COMP opinion (adoption via written procedure) | 27 February 2023 |

# 2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing sirolimus was considered justified based on preliminary clinical data form the published literature demonstrating that a topical formulation of sirolimus is able to improve angiofibroma symptoms in patients affected by the condition;
- the condition is chronically debilitating due to facial disfigurement and severe neurological symptoms and life threatening due to the formation of multiple tumours;
- the condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sirolimus will be of significant benefit to those affected by the condition. The sponsor has provided evidence of improved formulation characteristics, which might lead to improved clinical efficacy compared to current available topical magistral/officinal formulations of sirolimus. The Committee considered that this constitutes a clinically relevant advantage.

# 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**

Tuberous sclerosis or tuberous sclerosis complex (TSC) is an autosomal dominant inherited neurocutaneous disorder that is characterised by the development of multi-organ benign tumour-like growths, most usually observed in the skin, brain, kidney, heart and lungs that could potentially lead to organ dysfunction.

TSC is caused by mutations in two genes: The TSC1 gene is located on chromosome 9 and produces a protein called hamartin and the TSC2 gene is located on chromosome 16 and produces the protein tuberin. These two proteins create a complex that regulates the mammalian target of rapamycin (mTOR).

Due to the pathophysiology of TSC, the progression and appearance of its signs and symptoms are slow and subtle thus, patients are usually misdiagnosed or diagnosed at later stages in life. Focal cortical malformations (FCMs) are the most common cause of medically intractable epilepsy (resistant to antiepileptic drug polytherapy) in the paediatric patient population.

The definition and description of the condition has not changed since the initial orphan designation.

The approved therapeutic indication "Hyftor is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older'' falls within the scope of the designated orphan condition "treatment of tuberous sclerosis".

**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**

Tuberous sclerosis complex (TSC) is a chronical debilitating condition, and many organ systems can be affected by the disease, with potential serious consequences.

Skin manifestations, such as angiofibroma, are observed in nearly all patients, and can be extensive. In particular, facial angiofibroma may have a considerable psychological impact on patients as these cannot be covered by clothing [Knoepfel 2014], causing emotional distress and social isolation/marginalisation [Biondo 2014], as well as physiological impact in many patients.

Epilepsy is the most common clinical manifestation. Other neurological manifestations comprise cortical tubes, subendymal nodules, and Subependymal giant cell astrocytomas (SEGA). Neuropsychiatric manifestations affect almost all TSC patients at some point in their life. This includes intellectual disability, autism, speech difficulties, disruptive behaviour, depression, and sleep problems. Angiomyolipoma as a renal manifestation may lead to renal function impairment and acute complications such as retroperitoneal haemorrhage with massive blood loss that may be fatal. Lymphangioleiomyomatosis as a pulmonary manifestation can be silent but it can also lead to progressive lung function impairment. Cardiac rhabdomyomas could lead to heart failure in foetus or during the first year of life or to arrhythmia later in life.

TSC is a life-threatening condition with a fivefold higher mortality rate than that in the age- and gender-matched general population [Eijkemans 2015]. In this study, within 15.8 years, 29 of 351 individuals with TSC died (standardized mortality ratio: 4.8; 95% confidence interval: 3.4–6.9). A Swedish study found that 7.8% of individuals with TSC died during the study period (mean duration of observation: 8.82 years) [Welin 2017]. In 50%, death was directly related to TSC. In one study the median age of death was 33 years [Amin 2017]. Most TSC related deaths occur as a result of complications from seizures as well as renal complications [Amin 2017; Zöllner 2019].

The condition remains chronically debilitating and life threatening.

**Number of people affected or at risk**

The sponsor identified two studies reporting the prevalence of TSC in the EU:

- Germany: In a retrospective analysis of health insurance data patients with TSC (based on the ICD-10 code Q85.1) were identified for the 10-year period January 2007 – December 2016 [Strzelczyk 2021]. Based on these data a prevalence of 0.79 per 10,000 was estimated.
- Sweden: TSC data (based on the ICD-10 code Q85.1) from a national register were analysed for the time period 2004-2014 [Welin 2017]. From information on 551 patients a prevalence of 0.54 per 10,000 was estimated. In an older Study from Western Sweden only individuals aged up to 20 years were evaluated. In this population prevalence of TSC was 0.78 per 10,000 [Ahlsén 1994].

The sponsor claimed that the figure 0.79 is in line with the prevalence of the initial orphan designation where a prevalence of "approximately 1 in 10,000 people in the EU" was estimated. The COMP considered that the values provided above, and the estimate given at the time of initial designation would support a final estimate of "approximately 1 in 10,000", also to be in line with recent applications. The estimate and the range of values submitted by the sponsor are acceptable.

## 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**

The sponsor claimed that no treatment is available addressing TSC in general. The disease can affect various organ systems and hence its management is a multidisciplinary approach with involvement of different medical experts [Krueger 2013]:

- Systemic mTOR inhibitors are used for the treatment of systemic manifestations of TSC.
- Seizures and epilepsy may be treated with cannabidiol as authorized specifically in TSC (see below) or with other anti-seizure medications commonly used in this setting such as vigabatrin, a GABA transaminase inhibitor used for treatment of infantile spasms.
- Tumours in the different organ systems may be treated surgically, including acute subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma, and cardiac rhabdomyoamas [Bissler 2016; Sugalska 2021].
- Angiomyolipoma many also be treated with embolytic/ablative therapies
- Patients with severe LAM (Lymphangioleiomyomatosis) may be candidates for lung transplantation.

Currently, two products are authorized in the EU for the treatment of TSC, Votubia and Epidyolex (Table 1).

**Table 1: EU orphan medicinal products for the treatment of tuberous sclerosis**

| **Product** | **Votubia** | **Epidyolex** |
|---|---|---|
| Active Substance | Everolimus | Cannabidiol |
| Authorisation Number (Date) | EU/1/11/710 (6 September 2011) | EU/1/19/1389 (20 April 2021) |

| Product | Votubia | Epidyolex |
|---|---|---|
| Approved Therapeutic Indication | *Renal angiomyolipoma associated with tuberous sclerosis complex (TSC)*<br>Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.<br>The evidence is based on analysis of change in sum of angiomyolipoma volume.<br>*Subependymal giant cell astrocytoma (SEGA) associated with TSC*<br>Votubia is indicated for the treatment of adult and paediatric patients with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery.<br>The evidence is based on analysis of change in SEGA volume.<br>Further clinical benefit, such as improvement in disease related symptoms, has not been demonstrated. | Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older. |

The proposed indication for Hyftor is: ''Treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older'.

Votubia is indicated for renal angiomyolipoma associated with TSC and SEGA associated with TSC, while the indication for Hyftor is for the treatment of facial angiofibroma associated with TSC. As mentioned in the SmPC, Votubia also had a significant meaningful improvement in skin lesion response, in the trials in patients with renal angiomyolipoma (AML) and/or SEGA associated with TSC. However, since the use of Votubia is restricted to patients with systemic manifestations of the disease (renal AML or SEGA), it forms no suitable option for the totality of the target population of Hyftor, i.e. patients with facial angiofibroma, which may occur without renal angiomyolipoma /SEGA. Therefore, it is not considered a satisfactory method from a regulatory perspective and does not need to be taken into account in the significant benefit assessment of Hyftor.

Epidyolex is indicated for use as adjunctive therapy of seizures associated with TSC, and it has no effects on facial angiofibroma. Therefore, it is not considered a satisfactory method from a regulatory perspective and does not need to be taken into account in the significant benefit assessment of Hyftor.

**Significant benefit**

Not applicable.

# 4. COMP position adopted on 27 February 2023

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 tuberous sclerosis (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 chronically debilitating due to disfiguring tumours and severe neurological symptoms including treatment-resistant seizures that can lead to cognitive disability and life threatening due to the formation of multiple tumours;
- at present no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Hyftor.

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 Hyftor, sirolimus, for treatment of tuberous sclerosis (EU/3/17/1910) is not removed from the Community Register of Orphan Medicinal Products.