EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 April 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Trepulmix (treprostinil sodium)
Treatment of chronic thromboembolic pulmonary hypertension
EU/3/13/1103
Sponsor: SciPharm S.a.r.l.

Note

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

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Table of contents

1. Product and administrative information

Product	
Active substances at the time of orphan designation	Treprostinil sodium
Other name	-
International Non-Proprietary Name	-
Tradename	Trepulmix
Initial orphan condition	Treatment of chronic thromboembolic pulmonary hypertension
Sponsor's details:	SciPharm S.a.r.l. 26-28 Rue Edward Steichen L-2540 Luxembourg Luxembourg
Orphan medicinal product designation procedural history	
Sponsor/applicant	SciPharm S.a.r.l.
COMP opinion date	09 January 2013
EC decision date	08 February 2013
EC registration number	EU/3/13/1103
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege/Ewa Balkowiec Iskra
Applicant	SciPharm S.a.r.l.
Application submission date	08 February 2019
Procedure start date	28 February 2019
Procedure number	EMA/H/C/005207
Invented name	Trepulmix
Proposed therapeutic indication	Treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (severity classified WHO Functional Class (FC) II, III or IV), to improve exercise capacity and symptoms of the disease Further information on Trepulmix can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/trepulmix
CHMP opinion date	30 January 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Eva Malikova
Sponsor's report submission date	06 January 2020
COMP opinion date	20 February 2020

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2013, designation was based on the following grounds:

- For the purpose of orphan designation, the COMP considered that the indication should be renamed as "treatment of chronic thromboembolic pulmonary hypertension" (hereinafter referred to as "the condition"). The Committee considered that the condition is a distinct medical entity based on the "Guidelines for the diagnosis and treatment of pulmonary hypertension" published in 2009 by the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT);
- the intention to treat the proposed condition with the product as applied for designation was considered justified in the basis of published clinical data in patients with the proposed condition that showed improved survival and physical activity for treated patients;
- based on literature data the condition was estimated to be affecting between 0.1 and 0.52 in 10,000 people in the European Union, at the time the application;
- the condition is life-threatening and chronically debilitating due to impairment of physical ability with symptoms including dyspnoea and fatigue and a 5-year survival rate as low as 16% for untreated patients with CTEPH;
- Although satisfactory methods of treatment of the condition exist in the European Union, sufficient justifications have been provided that the treprostinil sodium might be of significant benefit to those affected by the condition. This appears justified on the grounds of the clinically relevant advantage of improved efficacy. This is based on clinical data in inoperable patients with the proposed condition who were treated with the proposed product and showed improved survival and physical activity.

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

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension which is considered a long-term complication of pulmonary embolism, although the underlying processes are poorly understood and likely to be multifactorial. Symptoms are non-specific and mainly related to progressive right ventricular dysfunction. The COMP considered that the orphan condition is still a well described distinct medical entity, acceptable for the purpose of orphan designation.

The proposed therapeutic indication: "Trepulmix is indicated for the treatment of adult patients with WHO Functional Class (FC) III or IV and:

- inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity"

falls within the scope of the designated orphan condition "Treatment of chronic thromboembolic pulmonary hypertension".

Intention to diagnose, prevent or treat

The intention to treat was considered acceptable based on the positive benefit/risk assessment of the CHMP, please see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor noted survival rates at 1, 2, 3 and 5 years of 67%, 43%, 37% and 16%, respectively in untreated patients (Skoro-Sajer et al. J Thromb Haemost 2007; 5:483-9).

The COMP considered that the treatment options have recently evolved with the availability of balloon pulmonary angioplasty and pulmonary vasodilators (Taniguchi et al, J Heart Lung Transplant. 2019 Aug;38(8):833-842); the 1- and 3-year survival rates of patients diagnosed since 2013 have improved but still remain at levels of approximately 91.6% and 85.0%.

The seriousness of the condition was acknowledged on the grounds of impairment of physical ability caused by the right heart dysfunction and associated mortality as describe above.

Number of people affected or at risk

At the time of the designation, it was estimated, based on published medical literature, that the condition affected between 0.1 and 0.52 in 10,000 people in the European Union. A higher estimate is proposed at the time of review based on the following assumptions:

- Point prevalence estimates were derived from incidence by multiplying with an assumed median duration of approximately 10 years; this duration was assumed from published survival curves pointing high survival rates at 1 and 3 years with the available treatment (Taniguchi et al, J Heart Lung Transplant. 2019 Aug;38(8):833-842)
- Incidence rates for diagnosed CTEPH cases were derived in turn from a review article by Gall et al, (Eur Respir Rev 2017; 26: 160121); this article included data for five European countries in 2015 and a projection for 2025, and the sponsor interpolated the data and proposed an incidence of approximately 0.1 per 10,000 for the time of application.
- By using the formula of incidence x duration, an estimate of 1 per 10,000 was proposed for the purpose of this maintenance procedure.

It is also of note that in addition to the established diagnosed cases, an additional figure including undiagnosed cases was also proposed, the latter stemming from the assumption that up to approximately 4% of pulmonary embolism patients may develop CTEPH. This was then considered in addition to cases without PE history (Gall et al, above). The sponsor using this alternative methodology estimated a prevalence of 4.4 per 10,000.

While both estimates remain below the threshold, with 1 and 4.4 per 10,000 respectively, it was considered by the COMP that inclusion of undiagnosed cases would be a conservative and assumptive approach which may overestimate the burden of the condition. The COMP therefore considered the conclusion of approximately 1 per 10,000 for the purpose of this maintenance procedure.

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

Riociguat, is authorised for the treatment of CTEPH in the EU and is indicated for the treatment of adult patients with WHO Functional Class II to III with a) inoperable CTEPH and b) persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity.

Current guidelines on CTEPH (Kim, 2019, Eur Respir J. 2019 Jan 24;53(1)) stress the importance of potential surgical treatments for the affected patients: " In addition to chronic anticoagulation therapy, each patient with CTEPH should receive treatment assessment starting with evaluation for pulmonary endarterectomy, which is the guideline recommended treatment. For technically inoperable cases, PH-targeted medical therapy is recommended (currently riociguat based on the CHEST studies), and balloon pulmonary angioplasty should be considered at a centre experienced with this challenging but potentially effective and complementary intervention".

Significant benefit

The sponsor's main argument for significant benefit is a clinically relevant advantage stemming from including CTEPH patients with poor NYHA/WHO functional class III and IV, while riociguat is authorised only for CTEPH patients with functional class II and III.

The pivotal study (CTREPH) in support of the marketing authorisation was a 24-week, randomised, double-blind controlled trial, in patients in WHO functional class III or IV with a 6-min walk distance of 150-400 m at baseline, who were assigned to continuous SC treprostinil low or high dose. The low dose was expected to provide a subtherapeutic effect and was used for blinding purposes of the smell and local effects during infusion. The primary endpoint was the change from baseline in 6-min walk distance at week 24.

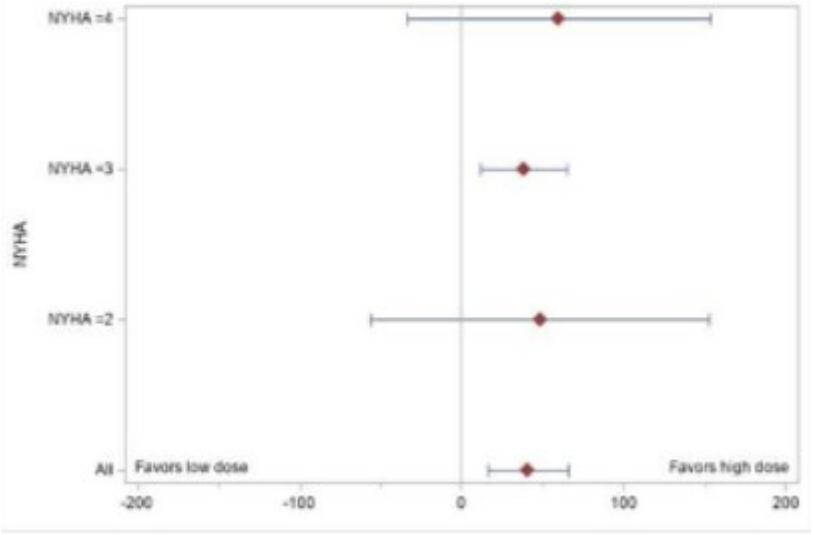
It was reported that 8 patients (low dose: 5; high dose: 3) with class IV at baseline were included in the CTREPH study. One patient died following a septic appendicitis. Seven patients survived the 6 months blinded study phase. Four entered the follow-up phase. One patient died after 41 months of treprostinil treatment. One patient participated 12.6 months before lost to follow-up. Two patients were still on treatment within the follow-up phase with a time of survival till October 2018 of 39.6 and 42.5 months.

The sponsor presented an analysis of the effects in study CTREPH as per functional class at baseline, with regard to the 6MWD change. Albeit not statistically favouring the high dose group, there was a trend which was consistent with the effects in other functional classes (figure 1). Other arguments presented by the applicant, such as an indirect comparison of the CTREPH results versus the CHEST study with the effects of riociguat, were not considered acceptable as the comparability of the juxtaposed studies was not justified.

It was also discussed that the included patients with Fc IV in the trial, who could walk more than 150 m within 6 minutes at baseline in accordance of the inclusion criteria, are not fully representative of the total target population of FcIV patients, who are typically bed-bound. The COMP took into consideration that there are no other pharmacological treatments authorised for the use in FcIV CTEPH patients, and this supports the significant benefit of Trepulmix. Post-hoc subgroup analyses of five patients of the CTREPH study with a prior non satisfactory response to riociguat, also supported efficacy of SC treprostinil by showing an adequate response.

Furthermore, it was also reported that that in a prospective registry with another treprostinil containing product, evaluating the efficacy and safety of long-term treatment of SC treprostinil in severe PH, showed overall survival rates in CTEPH patients (N=42; 22 subjects started in NYHA IV) of 79%, 60% and 42% after 1, 5 and 9 years respectively (Sadushi-Kolici et al; Journal of Heart and Lung Transplantation, 2012). The effects in functional class IV patients were also supported by further literature, where treprostinil improved exercise capacity, hemodynamics and survival in severe inoperable disease (Skoro-Sajer, et al. J. Thromb. Haemost. 5(3), 483 – 489)

Figure1: adopted from the sponsor's application documents



Overall it was considered that the addition of functional class IV patients in the authorised indication represents a broadening of the population compared to the authorised riociguat, which is only authorised for class II and III patients. A clinically relevant advantage of improved efficacy was therefore considered justified, taking into consideration the authorised indication.

4. COMP position adopted on 20 February 2020

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 chronic thromboembolic pulmonary hypertension (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 impairment of physical ability with symptoms including dyspnoea and fatigue and 5-year survival rates as low as 16% for untreated patients with CTEPH;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that treprostinil sodium may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has submitted clinical data supporting improvements in functional class IV patients, for whom no authorised products exist. The Committee considered that this constitutes a clinically relevant advantage.

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 Trepulmix, treprostinil sodium, for treatment of chronic thromboembolic pulmonary hypertension (EU/3/13/1103) is not removed from the Community Register of Orphan Medicinal Products.