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HEALTH TECHNOLOGY BRIEFING DECEMBER 2020

Treprostinil for chronic thromboembolic pulmonary hypertension

NIHRIO ID	29956	**NICE ID**	10494
Developer/Company	AOP Orphan Pharmaceuticals	**UKPS ID**	657890

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Treprostinil is in clinical development for patients with chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a progressive disease caused by blood clots forming in the lungs that do not dissolve. These clots restrict blood flow through the lungs and cause scar tissue to form on the inside of the pulmonary arteries (arteries that supply the lungs) resulting in pulmonary hypertension. This means the heart has to work harder to pump the blood and can weaken the heart muscles. Some patients may be offered surgery to remove the scar tissue but in patients who are inoperable or who have persistent/recurrent CTEPH after surgery there is a need for additional treatment options.

Treprostinil is given by subcutaneous infusion and works by causing blood vessels to widen to reduce arterial pressure and it also acts to stop platelets sticking together to reduce the formation of blood clots. Treprostinil may offer an additional treatment option for patients with CTEPH who are unsuitable for surgery or who have persistent/recurrent CTEPH following surgery.

PROPOSED INDICATION

Treatment of adult patients with WHO Functional Class (FC) III or IV and: inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent/recurrent CTEPH after surgical treatment to improve exercise capacity.[6]

TECHNOLOGY

DESCRIPTION

Treprostinil (Trepulmix, treprostinil sodium) is a tricyclic prostacyclin analogue that exerts a direct vasodilation effect on the pulmonary and systemic arterial circulation.[1,2] This improves systemic oxygen transport and increases cardiac output with minimal alteration of the heart rate.[2] In addition to treprostinil's direct vasodilatory effects, it also inhibits inflammatory cytokines, which subsequently induces inhibition of platelet aggregation.[3] Trepulmix is a hybrid medicine which means that it is similar to a reference medicine containing the same active substance, but it is used for treating a different form of pulmonary hypertension. The reference medicine for trepulmix is remodulin which contains the active substance treprostinil.[4]

Treprostinil is in clinical development for the treatment of CTEPH. In the phase III clinical trial (NCT01416636) patients in arm 1 are treated subcutaneously with a low-dose of 3 ng/kg/min treprostinil and patients in arm 2 are treated subcutaneously with a high-dose of 30 ng/kg/min treprostinil.[5,6]

INNOVATION AND/OR ADVANTAGES

Currently, patients with CTEPH are offered blood thinners such as warfarin, novel oral anticoagulants or direct oral anticoagulants, in addition to surgery.[7] There is a need for alternative treatments for patients with CTEPH who are either deemed inoperable or who have persistent/recurrent pulmonary hypertension after pulmonary endarterectomy (PEA) surgery.[8]

The clinical effectiveness of treprostinil was demonstrated by improvement in exercise capacity as measured by change in 6-minute walk distance.[5] Subcutaneously administered treprostinil offers advantages such as the ability to titrate the dose to effect (compared to fixed-dose oral therapies).[2] In addition, when compared to central venous catheters, subcutaneous administration reduces the risk of serious blood stream infections.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Treprostinil has Marketing Authorisation for the treatment of idiopathic or heritable pulmonary arterial hypertension (PAH) to improve exercise tolerance and symptoms of the disease in patients classified as New York Heart Association (NYHA) functional class III.[1]
The very common adverse events (occurring in ≥10% of patients) associated with treprostinil are headache, vasodilation, flushing, diarrhoea, nausea, rash, jaw pain, infusion site pain, infusion site reaction bleeding and haematoma.[1]

Treprostinil was granted orphan drug designation by the EMA for the treatment of CTEPH in February 2013.[9]

Treprostinil is also currently in 58 phase II/III clinical studies for other indications such as:[10]

- Interstitial lung disease
- Combined pulmonary fibrosis
- Chronic obstructive pulmonary disease (COPD)
- Ischaemia reperfusion injury
- Congenital heart disease

PATIENT GROUP

DISEASE BACKGROUND

Pulmonary hypertension is high blood pressure in the blood vessels that supply the lungs (pulmonary arteries).[11] CTEPH is a rare and progressive form of pulmonary hypertension caused by blood clots that do not dissolve in the lungs.[12] These clots restrict blood flow through the lungs, which causes a localized increase in blood pressure in the pulmonary arteries and a reduction in the level of oxygen transported to the rest of the body. The increase in blood pressure means the heart must work harder to pump blood, which can weaken the heart muscles. If the condition is left untreated, scar tissue can form due to damage caused by blood clots that are not cleared from the pulmonary arteries. This scar tissue can further narrow the arteries and cause a partial or complete blockage.[13]

CTEPH can occur without any known cause; however, certain factors are known to increase the risk of developing the disease.[13] About 75% of patients diagnosed with CTEPH have had one or more blood clots in the lungs. Other risk factors include; having a high risk of blood clots, chronic inflammatory diseases such as osteomyelitis or inflammatory bowel disease, having the spleen removed, thyroid replacement therapy, cancer, family history of blood clots, and blood clotting disorders.[12,14]

The most common symptoms reported for CTEPH are shortness of breath, fatigue and a low tolerance of exercise. Other symptoms include; chest discomfort, light-headedness, fainting, coughing up blood, swelling in the legs and palpitations.[13] However, CTEPH can be difficult to diagnose because it has symptoms similar to other diseases, including: asthma, emphysema, COPD, obesity and heart failure.[12,14]

The WHO FC describes how severe a patient's pulmonary hypertension symptoms are with class I being the least severe (symptom-free when physically active or resting) and class IV being the most severe (symptoms at rest and severe symptoms with an activity).[15] CTEPH is long-term debilitating due to symptoms such as fatigue and dyspnoea (difficulty breathing), which limit daily activities. If untreated it may also be life threatening due to the development of heart failure.[9]

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2019-20 there were 6,825 finished consultant episodes (FCE) for other secondary pulmonary hypertension (ICD-10 code I27.2) resulting in 5,341 admissions, 3,421 day cases and 13,647 FCE bed days.[16] Currently around 40% of patients with CTEPH are inoperable and with the limited current alternative treatment options, the three year survival rate is only 70% for this group.[17]

In England, in 2018, it was estimated that the overall incidence rate of CTEPH is 3.5 per 1000 person-years, with a peak in the 91 to 182 days following the first venous thromboembolism.

The overall cumulative incidence of CTEPH in the 10 years after the first pulmonary embolism was 3.3% and following a first deep vein thrombosis was 1.3%.[18]

In the NHS's National Audit of Pulmonary Hypertension, 2018-19, there were 2,492 patients in the UK diagnosed with CTEPH.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The goal of treatment is to make everyday living easier and improve a patient's symptoms – ideally to WHO functional class I or II.[15] Patients with CTEPH are managed nationally via specialist NHS designated PAH treatment centres, with the main hub being Papworth in Cambridge, where most of the PEA and BPA is carried out.[20]

Patients are offered anticoagulant medicines to stop more blood clots forming. If the blood clots have caused scar tissue in the patient's pulmonary arteries they may be offered a PEA. This operation removes scar tissue from the inside layer of the pulmonary arteries. This improves the blood flow and removes the pressure inside the arteries.[7] If a PEA is not suitable then patients may be offered a balloon pulmonary angioplasty (BPA) where a tiny balloon is guided into a narrowed lung artery and inflated for a few seconds to widen the artery. This aims to improve blood flow through the lungs and reduce pressure on the heart.[7,21]

CURRENT TREATMENT OPTIONS

The following options are available for the treatment of CTEPH:[20]

- Anticoagulants
  - warfarin
  - heparin
  - fondaparinux
- Riociguat
- Slidenafil

PLACE OF TECHNOLOGY

Treprostinil will offer an additional treatment option for patients with inoperable CTEPH or patients with persistent/recurrent CTEPH following surgery.

CLINICAL TRIAL INFORMATION

Trial	NCT01416636, EudraCT 2008-006441-10; A double-blind controlled clinical study to investigate the efficacy and tolerability of subcutaneous treprostinil sodium in patients with severe non-operable chronic thromboembolic pulmonary hypertension (CTEPH)

	Phase III – Active, not recruiting **Locations:** 4 EU countries (not including UK) **Primary completion date:** November 2016
Trial design	Quadruple-blind, randomized, parallel assignment
Population	N=105; adults aged 18 years to 100 years; current diagnosis of CTEPH; CTEPH classified as severe as defined by an un-encouraged 6 minute walk test (MWT) of between 150 and 400 metres or classification in the WHO/NYHA functional class III or IV; unsuitable to undergo a PEA (non-operable); unsuccessful PEA in the past with residual or recurrent CTEPH
Intervention(s)	Treprostinil (subcutaneous infusion) • Arm 1: low dose treprostinil 3ng/kg/min • Arm 2: high dose treprostinil 30ng/kg/min[5]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Change in 6 MWT distance after 24 weeks. [Time frame: baseline and week 24] See trial record for full list of outcome measures
Results (efficacy)	See trial record
Results (safety)	See trial record

ESTIMATED COST

The estimated cost of treprostinil is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE interventional procedure guidance. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (IPG554). April 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS Clinical Commissioning Policy: Baloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (all ages). April 2018.

OTHER GUIDANCE

- European Society of Cardiology. Pulmonary hypertension (guidelines on diagnosis and treatment of). January 2016.[22]
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ADDITIONAL INFORMATION

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