NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Treprostinil sodium for treating symptomatic chronic thromboembolic pulmonary hypertension

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of treprostinil sodium within its marketing authorisation for treating chronic thromboembolic pulmonary hypertension.

Background

Pulmonary hypertension is characterised by high blood pressure in the pulmonary arteries, the blood vessels that supply the lungs. Chronic thromboembolic pulmonary hypertension is a rare and progressive form of pulmonary hypertension caused by blood clots which cluster and remain in the pulmonary arteries restricting blood flow through the lungs. This causes a localised 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. Damage caused by blood clots which are not cleared from the pulmonary arteries can form scar tissue which can further narrow the arteries and cause a complete or partial blockage. The most common symptoms of chronic thromboembolic pulmonary hypertension include shortness of breath, fatigue and a low tolerance of exercise.

The World Health Organisation (WHO) Functional Class and the New York Heart Association (NYHA) Functional Classification are 2 similar assessments used to describe the severity of the symptoms of pulmonary hypertension. The WHO Functional Class defines symptom severity into 4 classes:

- Class 1: symptom free when resting or when physically active;
- Class 2: no symptoms at rest, but normal activities cause discomfort and shortness of breath;
- Class 3: symptom free when resting but normal activities are greatly limited because of shortness of breath and tiredness;
- Class 4: symptoms experienced when resting and severe symptoms experienced when physically active.

Chronic thromboembolic pulmonary hypertension can occur without any known cause. However, 75% of people with chronic thromboembolic pulmonary hypertension have had one or more blood clot in the lung.[1] Both men and women are equally affected by chronic thromboembolic pulmonary hypertension.[2] The overall incidence rate of chronic thromboembolic pulmonary hypertension in England is 3.5 per 1,000 person years.[3] An estimated 393 people were diagnosed with chronic thromboembolic pulmonary hypertension in the UK in 2019 to 2020.[2]

There are a range of treatments that can help to improve symptoms and manage chronic thromboembolic pulmonary hypertension. People are initially offered anticoagulant medicines to stop blood clots forming. A pulmonary thromboendarterectomy (PTE) may be offered to remove the clots and scar tissue

from inside the arteries. PTE can be curative and most people's symptoms improve after surgery. However, an estimated 20 to 40% of people are not eligible for surgery because of comorbidities or the location of the clot.[4] In addition, the disease persists in around a third of people who do have surgery.[5]

Treatment options for people with inoperable disease or disease which is persistent, or returns, following surgery are limited. People may be offered riociguat, which has a marketing authorisation in the UK for treating inoperable or persistent, or recurrent, chronic thromboembolic pulmonary hypertension. Other treatment options may include prostacyclin analogues (epoprostenol, beraprost, iloprost), endothelin receptor antagonists (bosentan, ambrisentan, macitentan) and phosphodiesterase-5 inhibitors (sildenafil, tadalafil) which are currently used for pulmonary arterial hypertension, a specific sub-type of pulmonary hypertension. Selexipag is also currently used for pulmonary arterial hypertension. It may be offered to people either as a combination therapy in people whose disease is not controlled with endothelin receptor antagonists and/or phosphodiesterase-5 inhibitors, or as a monotherapy in people for whom these treatments are unsuitable. If the presence of narrow or blocked vessels are identified a balloon pulmonary angioplasty (BPA) may be offered for people who are ineligible for PTE. BPA involves widening the artery to improve blood flow through the lungs and reduce pressure on the heart. If symptoms persist following targeted medical therapy or BPA a lung transplant may be considered.

The technology

Treprostinil sodium (Trepulmix, AOP Orphan) is a tricyclic prostacyclin, which widens the blood vessels and stops platelets from sticking to each other to form blood clots. It is administered by subcutaneous infusion.

Treprostinil sodium has a UK marketing authorisation for treating people with WHO Functional Class III or IV and inoperable chronic thromboembolic pulmonary hypertension, or persistent or recurrent chronic thromboembolic pulmonary hypertension after surgical treatment to improve exercise capacity.

Intervention(s)	Treprostinil sodium
Population(s)	Adults with WHO Functional Class III or IV chronic thromboembolic pulmonary hypertension which is inoperable or persistent, or recurrent, after surgical treatment

Comparators	• riociguat • prostacyclin analogues: epoprostenol, beraprost and iloprost (these do not currently have a marketing authorisation in the UK for this indication and beraprost does not have a marketing authorisation in the UK for any indication) • endothelin receptor antagonists: bosentan, ambrisentan and macitentan (these do not currently have a marketing authorisation in the UK for this indication) • phosphodiesterase-5 inhibitors: sildenafil and tadalafil (these do not currently have a marketing authorisation in the UK for this indication) • selexipag (does not currently have a marketing authorisation in the UK for this indication).
Outcomes	The outcome measures to be considered include: • overall survival • exercise capacity • symptomatic improvements, as measured by the WHO Functional Class or NYHA Functional Classification • frequency of hospitalisation and GP visits • lung or heart-lung transplantation • haemodynamic assessment (e.g. cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Discontinued appraisals:** 'Pulmonary arterial hypertension (adults) – drugs' (discontinued appraisal) (2005). NICE technology appraisals guidance [ID12]. **Related Guidelines:** 'Hypertension in adults: diagnosis and management' (2019). NICE guideline 136. Review in progress. Publication expected April 2023. **Related Quality Standards:** 'Hypertension in adults' (2015). NICE quality standard 28. **Related NICE Pathways:** Hypertension (2019) NICE pathway
Related National Policy	NHS England (2015) Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults NHS England (2018) Clinical Commissioning Policy: Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (all ages) NHS England (2018) Clinical Commissioning Policy Selexipag for treating pulmonary arterial hypertension (adults) NHS England (2017) Clinical Commissioning Policy: iociguat for pulmonary arterial hypertension The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 2 and 3. Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1 to 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for treprostinil sodium been included in the scope? In particular:

- Which treatments are considered to be established clinical practice in the NHS for symptomatic chronic thromboembolic pulmonary hypertension?

- Are other formulations of treprostinil used outside of their marketing authorisations in clinical practice in the NHS for symptomatic chronic thromboembolic pulmonary hypertension?

- Are there any other treatments used outside of their marketing authorisations in clinical practice in the NHS for symptomatic chronic thromboembolic pulmonary hypertension?

- Would exercise training as an add-on treatment option to pulmonary arterial hypertension targeted therapy be used in clinical practice in the NHS for symptomatic chronic thromboembolic pulmonary hypertension?

- Is BPA offered concurrently with targeted medical therapy or after targeted medical therapy in clinical practice in the NHS?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom treprostinil sodium is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider treprostinil sodium will fit into the existing NICE pathway, hypertension?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which treprostinil is licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider treprostinil to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?

Do you consider that the use of treprostinil sodium can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Chest Foundation (2020) Chronic Thromboembolic Pulmonary Hypertension (CTEPH): Symptoms. Accessed September 2021.

2 NHS Digital (2021) National Audit of Pulmonary Hypertension Great Britain, 2019-20. Accessed September 2021.

3 Martinez C, Wallenhorst C, Teal S et al. (2018) Incidence and risk factors of chronic thromboembolic pulmonary hypertension following venous thromboembolism, a population-based cohort study in England. Pulmonary Circulation 8(3).

4 NHS England (2018) Clinical Commissioning Policy: Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (all ages). Accessed September 2021.

5 Freed D.H, Thomson B.M, Berman M et al. (2011) Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. The Journal of Thoracic and Cardiovascular Surgery 141(2):383–87.