NHS England

Clinical Commissioning Policy Proposition:

Selexipag in the treatment of Pulmonary Arterial Hypertension

Reference: NHS England A11X04/01

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Plain Language Summary

This policy proposition aims to confirm NHS England's commissioning approach to selexipag in the treatment of Pulmonary Arterial Hypertension (PAH) as part of the wider commissioning policy for targeted therapies for use in pulmonary hypertension in adults.

Pulmonary hypertension (often shortened to PH) is a serious condition where the blood pressure in the pulmonary arteries is high. This causes progressive damage to the heart and lungs. PAH is a type of PH that is caused by problems with the small branches of the pulmonary arteries. The national audit for pulmonary hypertension reports 8,431 patients seen by designated UK pulmonary hypertension specialists in 2013/2014.

There are many different treatments available for PH. These treatments can improve the symptoms of PH and therefore improve quality of life. Some can slow the progression of PH and can also help reverse damage to the heart and lungs. Treatment for PH can be split into three categories, conventional therapy such as diuretics, targeted therapy and surgery. Many people with PH are treated with both conventional and targeted therapies, although this can be different for different people. Some people with PH may need surgery. How PH is treated will depend on a number of things, for example how severe the PH is or what type of PH the patient has.

NHS England has designated six centres to provide pulmonary hypertension services for adults and has a policy for targeted therapies. Selixipag is a new oral therapy and there has been clinical interest in the inclusion of this therapy within the current policy.

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of selexipag in the treatment of PAH.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission selexipag in the treatment of Pulmonary Arterial Hypertension (PAH).

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether selexipag in the treatment of Pulmonary Arterial Hypertension (PAH) will not be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Pulmonary arterial hypertension (PAH) is a rare and debilitating chronic disease of the pulmonary vasculature, characterised by vascular proliferation and remodelling of the small pulmonary arteries. This results in a progressive increase in pulmonary vascular resistance (PVR) which can ultimately lead to right heart failure and premature death. PAH is a progressive illness; if not diagnosed early and/or left untreated, the patient condition will deteriorate rapidly, leading to premature mortality in all aetiologies.

PAH can be classified into five etiological subgroups including; idiopathic, heritable, drug and toxin induced, associated, and persistent pulmonary hypertension of the newborn. In addition, PAH is typically scored on the basis of the severity of PAH-specific symptoms into four different World Health Organisation (WHO) functional classes. This system allows clinicians to make accurate differential diagnoses among diseases that demonstrate similarities in clinical presentation and pathophysiology, and helps to guide their decisions regarding appropriate treatment.

PAH has been shown to respond to targeted therapy and there are a number of different treatments available for PAH as set out in the clinical commissioning policies for pulmonary hypertension (see Section 12: Documents which have informed this policy).

This policy proposition considers the role of selexipag, an orally available prostacyclin receptor agonist, in the treatment of PAH in the context of the existing policy.

3. Definitions

Pulmonary hypertension (PH) is a rare disorder of the blood vessels in the lung, characterised by raised pressure in the pulmonary artery, which results in a range of symptoms and may be life threatening.

Selexipag is an orally available prostacyclin receptor agonist.

A receptor agonist is a type of drug provoking a biological response itself upon binding to a receptor.

A prostacyclin receptor (or prostaglandin I2 receptor, IP1) is a receptor for prostacyclin, a compound of the prostaglandin type produced in arterial walls, which functions as an anticoagulant and vasodilator. Prostacyclin also has an antiproliferative effect on smooth muscle cells, thus antagonizing an important contributor to the vascular narrowing seen in PAH.

4. Aim and objectives

The policy aims to define NHS England's commissioning position for Selexipag in the treatment of Pulmonary Arterial Hypertension (PAH) in the context of the existing NHS England policy for tageted therapies for use in pulmonary hypertension in adults.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with PAH.

5. Epidemiology and needs assessment

The estimated annual incidence of diagnosed PAH in the general population ranges from 0.9 to 7.6 cases per million persons, while the prevalence of diagnosed PAH in the general population is between 6.6 and 26 cases per million persons (Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015). The national audit for pulmonary hypertension reports 6,491 patients had a consultation with a UK PAH specialist in 2014/15.

6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of selexipag in the treatment of Pulmonary Arterial Hypertension (PAH).

This evidence review was undertaken to answer the following questions:

1. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) clinically effective compared with no intervention or with other standardised treatments?
2. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) safe to use in the treatment of worsening PAH?
3. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor) cost effective in patients with pulmonary arterial hypertension? Are there any papers including a risk-benefit analysis?

Summary:
The current body of evidence for selexipag use in Pulmonary Arterial Hypertension (PAH) is based on one large, industry-sponsored Phase III trial and another small non-

independent, randomised, proof of concept Phase II trial. While both studies appear to indicate some improvement with selexipag for 6 minutes walking distance, the functional significance of this improvement is not clear. The large, randomised Phase III trial also shows reduction in death or hospitalisation due to PAH. The same study also indicates lack of significant impact on preventing further deterioration of symptoms and all-cause mortality. Although some of the study participants were on alternate therapeutic interventions for PAH, there was no data on comparative clinical effectiveness amongst various drugs. There were no studies on cost effectiveness of selexipag. Further studies with clearly defined clinical endpoints and longer follow-up will be beneficial in providing conclusive evidence for the use of selexipag.

1. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) clinically effective compared with no intervention or with other standardised treatments?

The recently published finding from the Prostacyclin Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) trial, a randomised, double blind, placebo controlled study is the most pivotal evidence available for selexipag use in PAH (Sitbon et al, 2015). This is a large industry-sponsored trial involving 1156 patients in 39 countries. The primary endpoint was defined as a composite index comprising of events of death from any cause or complications related to pulmonary arterial hypertension. This primary endpoint occurred in 397 patients, with significantly less events among patients in the selexipag group (27%), compared to placebo (41.6%) group (selexipag vs the placebo: hazard ratio 0.60; 99% confidence interval 0.46 - 0.78; P<0.001). This was in line with the higher death or hospitalisation due to worsening of PAH occurring in fewer patients in the selexipag group (102 patients, 17.8%, hazard ratio 0.70; 95% CI, 0.54 to 0.91; P = 0.003), compared to the placebo group (137 patients, 23.5%) during the study.

However, there was no difference in the all-cause mortality or reduction in deterioration of symptoms (no worsening WHO class) between the two groups. The all-cause mortality and worsening of WHO class formed part of the primary end point composite index and were also considered individually as secondary end points. The composite index contained a number of subjective components, as pointed out by the authors as a limitation of the study, and remains to be validated as a summary measure for clinical effectiveness.

As part of the primary endpoint composite index and as a secondary endpoint, the 6-minute walk distance was reported to be decreased by a median of 9.0 m from baseline in the placebo group and had increased by 4.0 m from baseline in the selexipag group at 26 weeks of treatment (treatment effect, 12.0 m; 99% CI, 1 to 24; P = 0.003). The functional significance of this magnitude of improvement and comparison with other therapeutic alternatives is not clear.

Preceding evidence for GRIPHON trial came from a 17 week, proof-of-concept, Phase 2, randomised, double-blind, placebo-controlled trial of 43 patients (Simonneau et al, 2012). Based on this study the intervention group has a statistically significant fall in

pulmonary vascular resistance at week 17. Although there was a positive trend for some secondary outcome measures the difference was not statistically significant. The secondary outcome measures included 6-minute walk distance, aggravation of PAH, exploratory endpoints including Borg dyspnoea score, WHO Functional Class, and N-terminal pro brain natriuretic peptide.

2. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor or both ERA and PDE-5) safe to use in the treatment of worsening PAH?

Evidence so far indicates that selexipag is generally well tolerated. In the small patient population, Simonneau et al (2012) reported similar adverse event rates between selexipag and placebo groups and there were no deaths at a relatively short follow-up of 17 weeks. In GRIPHON Phase III, 41 patients (7.1%) in the placebo group and 82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely because of an adverse event. The most frequent adverse events leading to discontinuation in the selexipag group were headache (in 3.3% of the patients), diarrhoea (in 2.3%), and nausea (in 1.7%). Hyperthyroidism occurred in 8 patients in the selexipag group and led to treatment discontinuation in 1 patient. No serious adverse events were reported more frequently (i.e., at a rate >1% higher than placebo group) in the selexipag group (Sitbon et al, 2015).

During the GRIPHON trial, selexipag was administered orally in individualized doses with a maximum allowable dose of 1600 µg twice daily. In the initial dose adjustment phase (12 weeks), the drug was initiated at a dose of 200 µg twice daily and increased weekly in twice-daily increments of 200 µg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed . The dose was then decreased by 200 µg in both daily doses, and this reduced dose was considered to be the maximum tolerated dose for that patient. Adverse events associated with the drug occurred more frequently during the dose-adjustment phase.

Simonneau et al (2012) noted that as selexipag is orally available with a relatively long elimination half-life of 7.9 hrs it could help in improving pharmacokinetics, safety and ease of administration compared to need for IV administration of available prostacyclin agonists. This aspect was not specifically tested in the two studies.

3. Is selexipag (monotherapy or combined with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor) cost effective in patients with pulmonary arterial hypertension? Are there any papers including a risk-benefit analysis?

Currently, there is no evidence comparing effectiveness and cost effectiveness of selexipag with other drugs used in the management of pulmonary hypertension. Although GRIPHON Phase III study enrolled participants on stable dosage of endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both, there

was no analysis of comparative clinical impact of selexipag with these drugs.

7. Documents which have informed this policy

Clinical Commissioning Policy: Targeted Therapies for Pulmonary Hypertension Functional Class II. April 2013. Reference: NHSCB/A11/P/a.
Clinical Commissioning Policy: National policy for targeted therapies for the treatment of pulmonary hypertension in adults. May 2014. Reference: NHS England/A11/P/b.
Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. July 2015. Reference: NHS England A11/P/c.
National Audit of Pulmonary Hypertension 2014. Health and Social Care Information Centre.
Simonneau, G., et a,l 2009. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol, 54, S43-54.

8. Date of review

This document will lapse upon publication by NHS England of a commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).