

Clinical Commissioning Policy: Selexipag for treating pulmonary arterial hypertension (all ages)

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Clinical Commissioning Policy: Selexipag for pulmonary arterial hypertension (all ages)

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Policy Statement

NHS England will not routinely commission selexipag for pulmonary arterial hypertension.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a severe, progressive (that is, worsening) and usually fatal disease with an expected outcome worse than many forms of common cancer. It is caused by changes in the smaller branches of the pulmonary arteries (the arteries that carry blood from the heart to the lungs). The walls of the pulmonary arteries become thick and stiff, narrowing the space for blood to pass through and increasing blood pressure. As the pulmonary arteries are less able to stretch, the heart has to work harder to pump blood to the lungs, which causes damage to the heart, and makes it less efficient at pumping blood around the body and getting oxygen to the muscles.

The starting point in diagnosing PAH is identifying people with increased pulmonary pressure (pulmonary hypertension, or PH). While PH is relatively common, PAH is a rare subgroup. PH is classified into 5 groups by the World Health Organisation (WHO) depending on the underlying cause. Group 1 is PAH (the population covered by this policy) and includes idiopathic PAH (has no known cause), hereditary PAH (passed from parents to children through genes), drug and toxin-induced PAH (caused by drugs or toxins, such as street drugs and certain diet medicines), and PAH caused by several conditions (including connective tissue diseases, HIV infection, liver disease, and congenital heart disease). Groups 2 to 5 cover PH with various underlying causes (these groups are not considered further in this policy).

PAH can affect people regardless of age, ethnicity or other health risk factors. People with PAH experience increasingly debilitating symptoms which severely impact day to day living and quality of life (including breathlessness during exercise and sometimes during rest, extreme tiredness, weakness and chest pain), in addition to increased risk of other illnesses, frequent hospitalisations, and ultimately, right heart failure leading to premature death. There is no cure for PAH. It is a disease with poor prognosis, with 48% of people surviving for only 4 years after diagnosis ([National Audit of Pulmonary Hypertension 8th Annual Report](#)).

See also, section 4 for additional definitions of terms used in this document.

About current treatments

The main treatment for people with PAH is medicines directed at the pulmonary vasculature (blood vessels connecting the heart and the lungs). People with PAH should also be provided with general measures of support, such as advice about general activities and adapting to living with the disease, and psychosocial support (for example counselling). In addition, people with PAH can also be offered adjunctive treatments (that is, treatments given in addition to the main treatment) including anticoagulants (to help prevent blood clots, which people with PAH are at increased risk of) and oxygen therapy.

As PAH is a disease that worsens over time the overall goal of treatment is to treat the underlying changes in the blood vessel to reduce the afterload (strain) on the heart with an aim of improving the function of the heart and symptoms. There are a number of additional treatments which may then be offered. Current treatments include the following, which can be given either alone or in combination:

- Calcium channel blockers (CCBs). CCBs restrict how much calcium can enter cells in the body. Reducing the amount of calcium entering the muscle cells in the blood vessels causes them to relax which allows the arteries to widen and help to lower blood pressure. This treatment is only appropriate for a very small minority of people with PAH. Less than 10% of patients benefit from these drugs and inappropriate use can make patients worse.
- Phosphodiesterase-type 5 (PDE-5) inhibitors. PDE-5 is a type of enzyme found in blood vessel walls that helps control blood flow to the pulmonary arteries. PDE-5 inhibitors stop these enzymes from working properly which helps the blood vessels to relax, increasing blood flow to the lungs, and lowering blood pressure.
- Endothelin receptor antagonists (ERAs). In people with pulmonary hypertension the body produces too much endothelin, which causes the blood vessels to constrict (become narrower), which can increase blood pressure. ERAs reduce the amount of endothelin in the blood.
- Prostaglandins. Prostaglandin is a substance produced in the body that causes the blood vessels in the lungs to dilate (become wider). Artificial prostaglandins can therefore help dilate the blood vessels in lungs, improving

the amount of blood pumped around the body and oxygen in the blood, and can also help slow scarring and cell growth in the blood vessels of the lungs.

- Soluble guanylate cyclase stimulators. Soluble guanylate cyclase is an enzyme that acts as a receptor (that is, it receives chemical signals) for nitric oxide (a gas in the body that helps with pressure in the pulmonary artery). Stimulating this receptor causes blood vessels to relax and widen.

Lung transplantation may be considered for patients who do not benefit from drug therapies.

About the new treatment

Selexipag is an oral treatment thought to activate the prostacyclin receptors in pulmonary arteries in a similar way to the natural substance prostacyclin, which makes the arteries relax and widen. It is licensed for the long-term treatment of adults with PAH that has not been adequately controlled with a medicine known as an ERA, or a PDE-5 inhibitor, or both of these medicines given together. Selexipag works in a similar way to the currently available treatments known as prostaglandins. However, selexipag can be taken as an oral tablet, whereas the current prostaglandins are administered either via a continuous infusion (where the drug is delivered directly into the body over a long period of time), or by inhaling it using a special device.

What we have decided

NHS England has carefully reviewed the evidence to treat PAH with selexipag. NHS England recognises the published evidence identifies that at present, there is sufficient evidence to commission this treatment. However, following the relative prioritisation process undertaken in May 2018 for funding interventions in 2018/19, NHS England has concluded that, balanced against other relative priorities that were also considered during the process, selexipag to treat PAH will not be funded at this time within the resources available. The policy will however be reconsidered in the next prioritisation round, scheduled for November 2018.

1 Introduction

PAH is typically scored on the basis of the severity of PAH-related symptoms into 4 different World Health Organisation (WHO) functional classes (FC I to IV) that reflect clinical outcomes (only functional classes II and III are included in the licence for selexipag):

- Class I: ordinary physical activity does not cause undue breathlessness or fatigue, chest pain or near syncope (fainting).
- Class II: ordinary physical activity causes some undue breathlessness or fatigue, chest pain or near syncope. Comfortable at rest.
- Class III: Less than ordinary activity causes marked undue breathlessness or fatigue, chest pain or near syncope. Comfortable at rest.
- Class IV: Unable to carry out any physical activity without symptoms. Showing signs of right heart failure. Breathlessness and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

In addition, people are also classified according to risk based on the [2015 European Society of Cardiology and the European Respiratory Society \(ESC/ERS\) Guidelines for the diagnosis and treatment of pulmonary hypertension](#).

As PAH is a progressive and usually terminal disease, the overall goal of treatment is to reduce the risk of disease progression and achieve a low risk status (this is an assessment based on clinical features and the results of tests that assess exercise capacity and the function of the right heart). After diagnosis of PAH, people are offered general measures of support, including advice about general activities and adapting to living with the disease and psychosocial support. They can also be offered supportive therapies including anticoagulants and oxygen therapy. There are a number of additional treatments which will almost always be offered. Current PAH-specific treatments can be given alone or in combination and target three key pathways involved in the pathogenesis of PAH – the endothelin pathway (therapies for this pathway are the ERAs ambrisentan, bosentan and macitentan), the nitric oxide pathway (therapies for this pathway are the PDE-5 inhibitors sildenafil and

tadalafil, and the soluble guanylate cyclase stimulator, riociguat) and the prostacyclin pathway (therapies for this pathway are the prostaglandins epoprostenol, iloprost, and treprostinil). Eligibility criteria for some of these drugs are set out in NHS England clinical commissioning policies [Targeted Therapies for Pulmonary Hypertension Functional Class II](#) (for FC II only), [Targeted Therapies for use in Pulmonary Hypertension in Adults](#) (FC III and FC IV), and [Riociguat for Pulmonary Arterial Hypertension](#). If these treatments do not work, surgery may be considered. This may include lung transplantation or balloon atrial septostomy.

Selexipag is an oral prostacyclin receptor agonist. It is thought to activate the prostacyclin receptors in pulmonary arteries in a similar way to the natural substance prostacyclin, which makes arteries relax and widen. It is licensed for “the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO FC II–III, either as combination therapy in patients with disease insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies”. Selexipag, like prostaglandins, targets the prostacyclin pathway. However, there are challenges in the administration of current prostaglandins, which can require high levels of patient training and support, and can be intrusive on patients’ lives, whereas selexipag is administered orally (twice daily). Iloprost is usually inhaled into the lungs using a nebuliser but can also be given intravenously. These treatments may be difficult for some people to administer, for example people with certain mental or physical disabilities, therefore there is an unmet need for this small group of patients as well as for most patients with FCIII. Selexipag offers an alternative route of administration and, as an oral treatment, can be given in the home care setting without requiring hospital attendance, after initial administration is established.

2 Definitions

Balloon atrial septostomy: A procedure that is used to create an opening in the wall between the upper chambers of the heart (atria). This is performed in certain cases to improve blood oxygenation, particularly for congenital heart defects.

Borg dyspnoea index: A numerical scale for assessing shortness of breath, from 0 representing no dyspnoea to 10 as maximal dyspnoea.

Cardiac Index (CI): A system used to measure cardiac output, or the amount of blood pumped out of the left ventricle each minute. The cardiac index is the amount of blood pumped per minute in litres divided by the body surface area of the patient.

Dyspnoea: Sudden shortness of breath or breathing difficulty.

Flushing: A redness of the skin, typically over the cheeks or neck.

N-terminal prohormone of brain natriuretic peptide (NT-proBNP): NT-proBNP levels in the blood are used for screening, diagnosis of acute congestive heart failure (CHF) and may be useful to establish prognosis in heart failure.

Pulmonary arterial pressure (PAP): A measure of the blood pressure found in the pulmonary artery.

Right atrial pressure: The blood pressure in the right atrium of the heart.

Mixed venous oxygen saturation (SvO₂): The percentage of oxygen bound to haemoglobin in blood returning to the right side of the heart. This reflects the amount of oxygen "left over" after the tissues remove what they need.

3 Aims and Objectives

This policy aims to consider the evidence for selexipag for treating people with WHO FC II–III PAH, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in people who cannot take these treatments.

4 Epidemiology and Needs Assessment

Data from previous National Audits of Pulmonary Hypertension estimated that PAH has a diagnosed prevalence of 2,657 patients within an active specialist centre in England ([The 6th Annual National Audit of Pulmonary Hypertension 2015](#)) and a diagnosed incidence of 491 patients following a first referral to a specialised centre in England ([The 5th Annual National Audit of Pulmonary Hypertension 2014](#)).

NHS England estimates that around 530 people could be considered for treatment with selexipag (although based on clinical opinion a third may have a cardiac or respiratory comorbidity which would preclude treatment with selexipag). This is based on the following assumptions:

- 2,657 people have diagnosed PAH in England.
- The licence wording for selexipag states that “efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disease disorders and PAH associated with corrected simple congenital heart disease”. This represents approximately 58.4% (n=1,552) of the total PAH population (based on [the 5th Annual National Audit of Pulmonary Hypertension 2014](#) and data from a specialist pulmonary hypertension centre in England).
- Although the licence for selexipag includes people with FC II and FC III, according to clinical opinion, people with PAH FC III are more likely than those with FC II to receive treatment with selexipag in clinical practice. 73% (n=1,133) of people with PAH have FC III PAH at diagnosis (based on [The 6th Annual National Audit of Pulmonary Hypertension 2015](#)). However, this does not reflect the FC III prevalence in clinical practice, because 30% to 40% of patients may improve with treatment to FC II, and gradually move back to FC III in the longer term at a rate of approximately 10% a year. Therefore the prevalence of FC III in clinical practice may be closer to 50% (n=776). The range of people with FC III in clinical practice is therefore estimated to be 776 to 1,133 people.

- 70% (n=543 to 793) of people with FC III PAH are on dual therapy with an ERA and a PDE-5 inhibitor (estimate from company for selexipag based on clinical opinion).

A maximum of 67% (n=362 to 531) of people with FC III taking an ERA and PDE-5 inhibitor have disease that is not controlled by these treatments (estimate from company for selexipag based on clinical opinion). Currently NHS England commission a prostanoid for these patients ([Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015](#)) although the take up of these treatments is low. Between 2009 and 2016 only 10% of people with FC III PAH received a prostanoid at any point before death ([The 7th Annual National Audit of Pulmonary Hypertension 2017](#)). As a conservative assumption these patients have not been taken into account in eligibility calculations for selexipag.

5 Evidence Base

NHS England considered evidence from 5 studies on the clinical effectiveness and safety of selexipag for treating adults with PAH. These included 2 randomised controlled trials (the main trial by Sitbon et al, 2015, n=1,156, and a trial by Simonneau et al. 2012, n=43); 2 subgroup analyses of the main trial by Sitbon et al. 2015 (Gaine et al 2017, n=334, and Coghlan et al (2018, n=376), and an open label non-comparative trial (Tanabe et al. 2017, n=37). The main study by Sitbon et al. (2015) is the largest trial conducted in people with PAH, however it was not powered for subgroups. This means that the subgroup analyses did not include enough people for the statistical analyses to detect whether there were any statistically significant differences between selexipag and placebo in these subgroups, and therefore they should be interpreted with caution.

The primary outcome in the main study by Sitbon et al. 2015 and its subgroup analyses (Gaine et al 2017, and Coghlan et al. 2018) was a composite outcome of time to either a first morbidity event or death from any cause. The morbidity events included in the primary outcome were hospitalisation for worsening of PAH; worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy; initiation of parenteral prostanoid therapy or chronic oxygen therapy because of worsening of PAH; and disease progression (defined by a decrease in 6-

minute walk distance [6MWD] from baseline combined with worsening of WHO FC for people FC II/III at baseline, or combined with the need for additional PAH-specific treatment for people with FC III/IV at baseline).

The composite morbidity and mortality primary outcome in the main trial by Sitbon et al. (2015) reflects the regulatory suggestion in the European Medicines Agency (EMA) "[Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension](#)" which states that "the investigation of a composite primary endpoint that reflects, in addition to mortality, time to clinical worsening is encouraged in PAH". The European Public Assessment Report (EPAR) noted that the primary outcome is clinically relevant, but it causes issues when assessing the true effect of selexipag on all-cause mortality, because it is a composite, and also because of treatment discontinuation and switching from placebo to selexipag after a primary outcome event. In addition, the study authors stated that the use of this measure was a limitation of the study because it contains a number of subjective components. To address this limitation, the authors stated that the disease progression component was stringently defined and all events were adjudicated by a blinded three-person critical-event committee. The primary outcome in Simonneau and Tanabe was pulmonary vascular resistance (this measures resistance when blood flows through the pulmonary circulatory system). Other outcomes in the studies included quality of life, Borg dyspnoea index (assesses breathlessness) and NTpro-BNP level (used for assessing the risk of acute congestive heart failure).

In the main trial by Sitbon et al. (2015) people received either placebo or selexipag treatment for a median duration of 63.7 and 70.7 weeks respectively. In both groups people had the option to switch to open-label selexipag if they had a first morbidity event described in the primary outcome. People received treatment for up to 4.2 years.

Some participants in the studies were on no background treatments, and others were already on varying mono- and combination therapies (including a PDE-5 inhibitor and an ERA). Selexipag was then added to current treatments, and compared with the addition of placebo, other than in Tanabe et al. (2017), which had no comparator. Selexipag was started at 200µg twice daily, and titrated up until

maximum tolerated dose (maximum total dose 1,600µg). The main study by Sitbon et al. (2015) included people with FC I to IV, although the vast majority of participants (approximately 98%) were FC II to III (selexipag is licensed for people with FC II to FC III PAH only). The subgroup analyses were designed to look at either a specific type of PAH (connective tissue disease associated PAH, Gaine et al. 2017), or for people with FC III disease already on an ERA and a PDE-5 inhibitor (Coghlan et al 2018).

The studies included in the evidence review either had no comparator (Tanabe et al. 2017) or were compared with placebo (all other studies). Also in Sitbon et al. (2015) some participants were not on any background treatments, and others were on varying, locally determined background therapies (either monotherapy or dual therapy) before starting additional treatment with either selexipag or placebo. This means that there is no direct evidence of the addition of selexipag compared with the addition of another active treatment, and the varying background therapies may also disguise the true selexipag treatment effect.

Clinical effectiveness

The primary outcome in the main study by Sitbon et al. (2015) (n=1156) showed that at the end of the study selexipag statistically significantly reduced the risk of first morbidity or mortality event when compared with placebo, with a rate of 27.0% compared with 41.6% (hazard ratio [HR] 0.60, 99% confidence interval [CI]: 0.46 to 0.78, p<0.001). This result was supported by a sub group analysis of people with PAH associated with connective tissue disease (Gaine et al. 2017). Reductions compared with placebo were also shown in subgroup analyses of people taking an ERA and a PDE-5 inhibitor and the following disease classes, however only the result for FC III to IV was statistically significant:

- FC I to IV (HR 0.63, 99% CI: 0.39 to 1.01, reported in the European public assessment report [EPAR]),
- FC III to IV (HR 0.60, 99% CI: 0.43 to 0.83, reported in the EPAR),
- FC III (HR 0.67, 95% CI: 0.45 to 1.01, p=0.056, Coghlan et al. 2018).

The primary outcome in Simonneau et al. (2012) and Tanabe et al. (2017) showed that selexipag statistically significantly improved pulmonary vascular resistance

($p < 0.0022$ both studies) either when compared with placebo (Simonneau et al. 2012), or compared with results at baseline (Tanabe et al. 2017).

Secondary outcome evidence in Sitbon et al. (2015) showed that at the end of the study, selexipag statistically significantly reduced the risk of either hospitalisation because of worsening of PAH or death, with a rate of 17.8% compared with 23.5% for placebo (HR 0.7, 95% CI: 0.54 to 0.91, $p = 0.003$). A reduction was also shown in a subgroup analysis of people with FC III who were taking a PDE-5 inhibitor and an ERA, however this difference was not statistically significant (HR 0.63, 95% CI: 0.38 to 1.05, $p = 0.08$, Coghlan et al. 2018). In Sitbon et al. (2015), there was no statistically significant difference in death from any cause at the end of study when compared with placebo (HR 0.97, 95% CI: 0.74 to 1.28 $p = 0.42$).

Three studies measured 6 minute walking distance (6MWD) as a secondary outcome. Sitbon et al. (2015) and Tanabe et al. (2017) reported statistically significant increases compared with placebo or baseline respectively ($p < 0.0324$ both studies). Simonneau et al. (2012) also reported a mean increase in walking distance at week 17 for people receiving selexipag but this was not statistically significant when compared with placebo. In Sitbon et al. (2015), missing data were imputed by the authors for 21.6% of participants for the outcomes change in function class and 6MWD respectively. This means that some data for these outcomes were derived using patients' data at a previous time point rather than actual patient data observed at the time point in question, which increases the uncertainty of the findings.

Sitbon et al. (2015) and Simonneau et al. (2012) reported no statistically significant difference in change of WHO functional class for people taking selexipag when compared with placebo. In Sitbon et al. (2015), missing data were imputed by the authors for 18.3% of participants for this outcome. Tanabe et al. (2017) showed an improvement in functional class for people receiving selexipag ($n = 4$, 12.1%) with no patients experiencing a deterioration from baseline.

Simonneau et al. (2012), Tanabe et al. (2017) and Sitbon et al. (2015) reported several haemodynamic outcomes (that is, outcomes relating to blood flow) as secondary outcomes. Some results demonstrated statistically significant improvements when compared with baseline (Tanabe et al. 2017) or placebo (Sitbon et al. 2015 and Simonneau et al. 2012), including a statistically significant reduction

in NT-proBNP plasma levels of -123 pg/ml ($p < 0.001$) in Sitbon et al. (2015), and Cardiac Index (Simonneau et al. 2012 and Tanabe et al. 2017). Some results were not statistically significant including plasma NT-proBNP (Simonneau et al. 2012) and SvO₂ (mixed venous oxygen saturation, which is the percentage of oxygen bound to haemoglobin in blood returning to the right side of the heart) (Tanabe et al. 2017).

Quality of life

The main study by Sitbon et al. (2015) used the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) tool to measure quality of life. This is a pulmonary hypertension specific questionnaire which assesses the symptoms, functioning and quality of life for people with pulmonary hypertension. The EPAR for selexipag stated that there was no statistically significant difference when selexipag was compared with placebo for 'overall symptom score' and 'breathlessness'. The EPAR stated that this finding is not fully understood because selexipag had demonstrated a clear benefit on morbidity, which would be expected to be reflected in improved quality of life. It added that although the CAMPHOR questionnaire used in GRIPHON has been validated in mainly small populations with PAH in different regions, it is unclear at present whether it is sensitive to changes in quality of life.

Safety

Sitbon et al. (2015) stated that 252 (43.8%) of the 574 patients receiving selexipag reported one or more serious adverse events and a statistically significant higher proportion of patients discontinued selexipag because of adverse events compared with placebo; 82 (14.3%) and 41 (7.1%) respectively ($p < 0.001$). The most frequent adverse events leading to discontinuation were headache (3.3%), diarrhoea (2.3%) and nausea (1.7%). There were 28 (4.9%) deaths from any cause in the selexipag group and 18 (3.1%) in the placebo group.

The most common adverse events determined from a long term study of 33 patients (Tanabe et al. 2017, $n = 136$ weeks), were headache (73%), diarrhoea (45.9%), jaw pain (45.9%), nausea (37.8%) and flushing (32.4%). Simonneau et al. (2012) reported similar numbers of adverse events in patients receiving either selexipag or placebo with no deaths during the 17 week follow up period.

6 Documents which have informed this Policy

The documents that have informed this policy include a review of the clinical evidence available for selexipag. Additional evidence sources are listed in the table of references below.

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

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