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

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

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Contents

Policy Statement

NHS England will commission selexipag for pulmonary arterial hypertension in adults in accordance with the criteria outlined in this document.

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.

This policy document outlines the arrangements for funding of this treatment for the population in England.

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 through drug misuse 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 activities and adapting to living with a progressively deteriorating ability to walk, 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 vessels to reduce the strain on the heart with an aim of improving the function of the heart and symptoms. There are a number of additional treatments which address the underlying pathology more directly. Current treatments include the following, which can be given either alone or in combination:

- Calcium channel blockers (CCBs). CCBs reduce the amount of calcium entering the muscle cells in the blood vessels causing them to relax which allows the arteries to widen and help to lower blood pressure. This treatment is only effective in a very small minority of people with PAH. Around 5% of patients benefit from these drugs.
- 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 become narrower, which can increase blood pressure. ERAs reduce the amount of endothelin in the blood.
- 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. These

agents work on the same pathway as PDE5 inhibitors, these treatments cannot be combined as together these agents causes low blood pressure.

- Prostaglandins. Prostaglandin is a substance produced in the body that causes the blood vessels in the lungs to become wider, levels of prostaglandin are severely reduced in patients with PAH. Artificial prostaglandins are one of the most effective established treatments for PAH. They dilate the blood vessels in the lungs, improve 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. Prostaglandin therapies have been shown to reduce mortality in isolation or in combination with other treatments for PAH.

  Prostanoids have a very short half-life (around 6 minutes) and fatal rebound pulmonary hypertension can occur with interruption of treatment, so intravenous (IV) therapy is psychologically challenging and requires significant dexterity and familiarity with the required technology. These treatments are difficult to manage. Some patients - particularly those with certain mental or physical disabilities - simply cannot access prostanoid therapy at present.
- Lung transplantation is considered in all patients who progress to end stage despite optimal use of available drug therapies. However, the demand for organs significantly exceeds the supply of organs, so only small numbers of patients are likely to receive a transplant.

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 other prostaglandins are currently prescribed to around 10% of all patients so the majority of patients with functional class (FC) III status (for more information on WHO functional class statuses see the Introduction section of this policy) do not

access this treatment. Selexipag can be taken as an oral tablet, whereas as noted above, there are challenges in the administration of current prostaglandins, because these require high levels of patient training and support and either need to be given as a continuous infusion delivered directly into the body over a long period of time, or by breathing it in through a mask. Selexipag offers a new treatment to patients with FCIII disease status deteriorating on current therapies. As an oral treatment it can be given in the home care setting without requiring hospital attendance, after initial administration is established.

What we have decided

NHS England has carefully reviewed the evidence to treat pulmonary arterial hypertension with selexipag. We have concluded that there is enough evidence to make the treatment available.

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 some functional classes 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 disease with a poor prognosis, the overall goal of treatment is to reduce disease progression and achieve a low risk status (this is an evidence-based assessment, utilising multiple parameters – when achieved the mortality is reduced to less than 5% per year). After diagnosis of PAH, people are offered general advice and support, psychosocial support. They can also be offered supportive therapies including anticoagulants and oxygen therapy. 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).

Only about 9% of patients currently receive prostanoid therapies. Eligibility criteria for 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. In high risk patients or where deterioration occurs despite available medical therapy, lung transplantation is considered, though most patients are either not suitable, or die before a suitable organ is found.

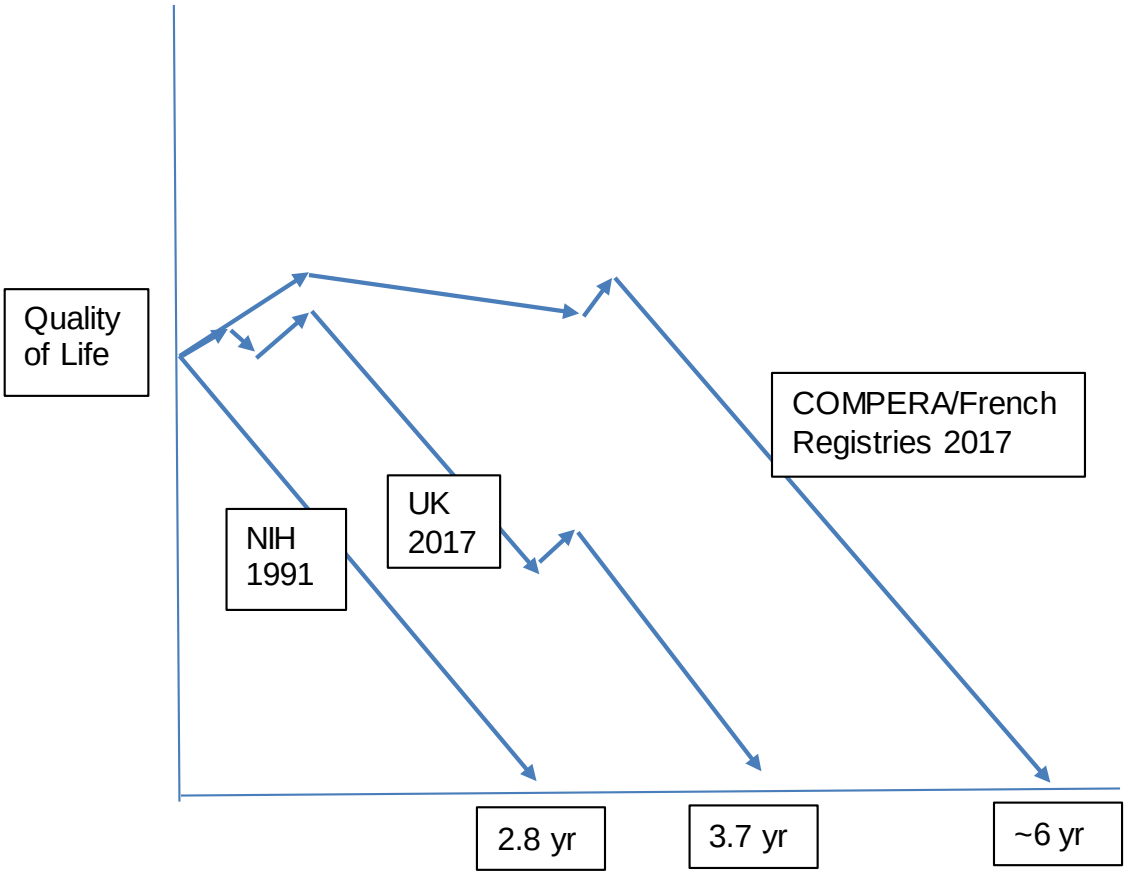
To highlight the magnitude of the un-met need the following schematic representation of the trajectory of PAH under various conditions is presented:

The NIH registry (D'Alonzo et al 1991) provides the baseline information on the natural history before specific treatment was available, average survival was 2.8 years.

In the UK patients are started on a single agent; usually a PDE5 inhibitor and a second therapy only commissioned after subsequent deterioration. IV therapy is added later in the pathway as this is usually commissioned only as a replacement for endothelin receptor antagonist (ERA) therapy. Outcome is much poorer than in other European centres (based on the 8th Annual National Audit of Pulmonary Hypertension 2017).

In the COMPERA (Hoeper et al 2017) and French registries (Boucly et al) 5-year survival has been reported (see Table 1) (54% COMPERA, 59% in the French Registry). As there are fewer restrictions on access to advanced therapies in Germany and France, the possible explanation for this is that combination therapy is started early and IV is added to background combination therapy when deterioration occurs.

Table 1: Survival rates by patient registries



This policy is for patients to receive selexipag for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO FC 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 require high levels of patient training and support, and is intrusive on patients' lives, whereas selexipag is administered orally (twice daily). In contrast Iloprost is usually inhaled into the lungs using a nebuliser and this must be taken 6 – 9 times daily, and nebuliser maintenance takes around 15 minutes per session. The alternative, commissioned in England, is intravenous prostanoid therapy.

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.

COMPERA: a structured, observational registry for patients of all age groups, with any form of pulmonary hypertension (PH) or pulmonary arterial hypertension (PAH).

Dyspnoea: Sudden shortness of breath or breathing difficulty.

Endothelin receptor antagonists (ERAs): a type of targeted therapy used to treat people with pulmonary hypertension (PH). Targeted therapies slow the progression of PH and may even reverse some of the damage to the heart and lungs.

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.

Pulmonary vascular resistance (PVR): A measure of the resistance in the pulmonary circulation to the lungs.

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 considered the evidence in line with the license 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.

The objectives were to:

- Define the eligibility criteria for selexipag.
- Define the commissioning arrangements required for selexipag.

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 would be considered for treatment with selexipag if using the criteria for commissioning outlined in section 8 (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). These are the groups most likely to receive treatment with selexipag in clinical practice and the criteria for commissioning reflects this (see section 8).

- 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 commissions a prostanoid for these patients (Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015), although the uptake 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). The low uptake of the prostanoid therapy in the UK reflects the commissioning policy, will generally only allow two therapies to be combined. Convincing patients to move to IV therapy in such circumstance is difficult, and inhaled therapy lacks evidence of long-term efficacy. Patients currently on prostanoids have not been taken into account in eligibility calculations for selexipag, as IV therapy when indicated, is regarded as superior to selexipag.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication.

Summary of evidence

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), 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 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.

Twenty percent of 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 both 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 head-to-head comparison with 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 FC III to IV (HR 0.60, 99% CI: 0.43 to 0.83, reported in the EPAR), and for people on background combination therapy (an ERA and a PDE-5 inhibitor) and the following disease classes:

- FC I to II (HR 0.63, 99% CI: 0.39 to 1.01, reported in the European public assessment report [EPAR]),
- FC II (HR 0.36, 95% CI: 0.14 – 0.91 Coghlan et al. 2018)
- FC III (HR 0.74, 95% CI: 0.45 to 1.10, 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). Of note the Simonneau study was designed to determine whether a 300dyne.s.cm-5 reduction in PVR relative to placebo could be achieved on per-protocol and was powered for this endpoint, a sensitivity analysis demonstrated that a significant reduction was also achieved on intention to treat analysis.

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).

Progression free survival

In the main study by Sitbon et al (2015), 93% of the events contributing to the primary end point were recognised clinical deterioration events (Death, PAH hospitalisations and $\geq$ 15% reduction in 6MWD – supported in this study by a deterioration of FC or if FC III or IV the need for additional PAH medicines). Death, PAH hospitalisation or a > 15% fall in 6MWD with worsening FC or need for

additional therapy occurred in 39% (227/582) of the placebo patients and 25% (144/574) among those randomised to selexipag.

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 Criteria for Commissioning

In addition to the patient population and disease-targeted treatments commissioned in the published NHS England commissioning policies, selexipag will be routinely commissioned as an option for adults who meet the following criteria:

1. Confirmed diagnosis of pulmonary arterial hypertension assessed to be in WHO functional class III

AND

2. Belonging to one of the following clinical classifications:
    a. Pulmonary arterial hypertension
    b. Idiopathic PAH
    c. Heritable PAH
    d. PAH associated with corrected simple congenital heart disease
    e. PAH associated with connective tissue diseases

For these patients, selexipag will be commissioned as a third line therapy for functional class III patients in combination with a PDE5 inhibitor plus an ERA, after failure to respond, or a sub-optimal response, to PDE5 inhibitor plus an ERA.

(Note: an optimal response is a low risk of progressive right heart failure [hospitalisation for PAH or need for intravenous therapy] with improved quality of life however measured).

Selexipag will not be commissioned:

1. For any patients outside of the described clinical classification.
2. For use in any other treatment combinations.
3. For use in patients who display adverse drug reactions to selexipag.

Stopping criteria

Stop treatment with selexipag if the disease does not respond to treatment after 6 months.

- Non-response to treatment measured as the occurrence of any one of the following morbidity outcomes within 6 months of initiating selexipag:
    - 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
- disease progression (defined by a decrease in 6-minute walk distance from baseline combined with worsening of WHO FC, or combined with the need for additional PAH-specific treatment).

Stop treatment with selexipag if it is no longer the optimal treatment option.

- Effectiveness monitored every 6 months
- Effectiveness measured as the occurrence of any one of the following morbidity outcomes; stop treatment if:
  - Hospitalisation for PAH if intravenous therapy is an option
  - 15% worsening of 6-minute walk distance if intravenous therapy is an option
  - Need for an intravenous prostanoid based on adverse prognostic indicators according to the ESC / ERS risk assessment tool below.

The policy does not support use in children less than 18 years old as this is outside the license and is not recommended as there is a lack of data on safety and efficacy in this age group.

Table 2: Risk Assessment in PAH, taken from 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Table 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

[c]Repeated episodes of syncope, even with little or regular physical activity.

7 Patient Pathway

The following describes the treatment pathway for PAH FC III only (the population covered by this policy).

All people with PAH will receive structured care and follow up as recommended by the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Patients are referred to a pulmonary hypertension service by a consultant physician (typically cardiology or respiratory but also from other services including haematology, rheumatology, infectious disease) where PAH is suspected as a cause of symptoms. A multi-disciplinary team (MDT) discuss and develop an individualised management plan, and a member of the MDT will be present with the patient when the final diagnosis is discussed.

Treatment:

If appropriate, disease-targeted therapy will only be initiated by the pulmonary hypertension centre, which is responsible for monitoring and ensuring the safe, long-term prescribing of continuing treatments, where required.

NHS England's Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015 and Riociguat for Pulmonary Arterial Hypertension outlines current eligibility for treatment for:

- PDE-5 inhibitors
- ERAs
- Soluble Guanylate Cyclase Stimulators (SCGS)
- Prostanoids

The routine commissioning of selexipag as described in section 8 does not affect the commissioning positions of the disease-targeted therapies or combinations in NHS England's Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015 and Riociguat for Pulmonary Arterial Hypertension.

Typically, any new therapy or change in regimen is reviewed at three months and then every three to six months as an outpatient. Patients treated with disease targeted therapy will have lifelong follow up within the pulmonary hypertension service. The pulmonary hypertension centre will identify those patients suitable for shared care and ensure effective communication with shared care centres to plan patient reviews. Patients will be reviewed at least once each year by the visiting pulmonary hypertension specialist or at the pulmonary hypertension centre.

First line treatment

For first line treatment, NHS England's Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015 states that PDE-5 inhibitors are routinely commissioned, or an ERA may be used if a PDE-5 inhibitor is not clinically appropriate.

Second line treatment

For second line treatment, NHS England's Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015 states that if a person has not responded to a trial of therapy of adequate dose or duration (typically eight to twelve weeks) or people cannot tolerate one of the oral treatments (PDE-5 inhibitor or an ERA), they should try the alternative oral monotherapy. If people have disease that initially responded but then either deteriorated or did not respond adequately, they may be considered for dual therapy.

NHS England's clinical commissioning policy Riociguat for Pulmonary Arterial Hypertension states that riociguat can also be considered for people with FC III PAH who are contraindicated to a PDE-5 inhibitor, or as an alternative to ERA.

Third line treatment

For people with FC III PAH that has not responded to dual therapy with an ERA and a PDE-5 inhibitor, NHS England's Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015 states that a prostanoid is routinely commissioned (in exceptional circumstances a prostanoid may be given as monotherapy instead of dual therapy if the person is acutely unwell and requires hospital treatment). NHS England's clinical commissioning policy Riociguat for Pulmonary Arterial Hypertension states that people with FC III PAH who have failed to respond to a PDE-5 inhibitor and an ERA can also be prescribed riociguat and an ERA.

Selexipag will provide an oral prostanoid treatment for people with FC III PAH at high risk of deterioration despite maximally tolerated PDE5i and ERA treatment. In addition, selexipag will provide a new option for a small proportion for who a non-oral treatment is not appropriate, for example people with disabilities or issues with manual dexterity which mean they are unable to administer injectable treatments. It will be commissioned in combination with a PDE-5 inhibitor and an ERA.

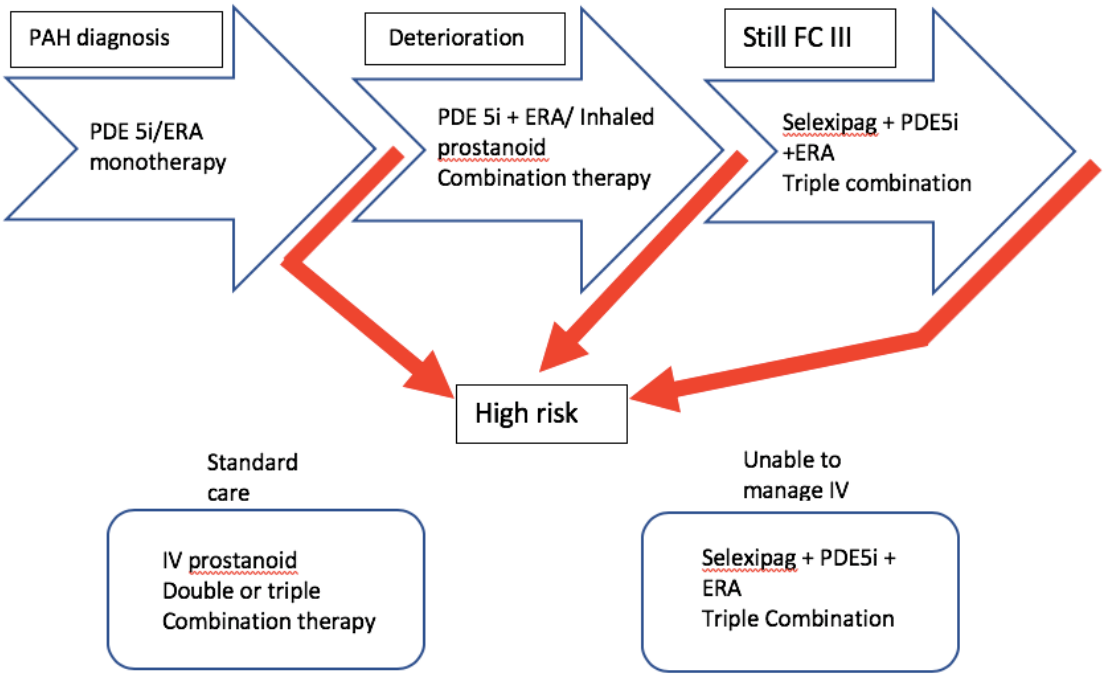
Fourth line treatment:

NHS England's clinical commissioning policy Riociguat for Pulmonary Arterial Hypertension states that riociguat is considered as a fourth line therapy for people with FC III PAH in combination with prostaglandin after failure of the disease to respond to, or, a sub-optimal response to a PDE-5 inhibitor plus an ERA plus a prostaglandin.

Surgery

For those patients who are eligible for lung transplantation, referral will be sent, using the nationally agreed proforma, to the lung transplant centre within five working days of the clinician's decision.

Table 3: Schematic of proposed new treatment pathway for patients remaining FC III or progressing to 'high risk' despite therapy



8 Governance Arrangements

Six centres in England are designated to provide pulmonary hypertension services for adults. These centres should be responsible for prescribing selexipag, monitoring and follow up of patients. There is one national centre for children which can consider appropriate use in this age group.

The centres offer investigation and treatment of patients with idiopathic pulmonary hypertension, pulmonary hypertension complicating other diseases and assessment of response to treatment. The centres and staff also provide support for patients and their families.

Any provider organisation treating patients with this intervention is required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval system software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

9 Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

10 Audit Requirements

Each centre will need to provide commissioners with a monthly monitoring statement covering the following fields:

- ID number
- Patient Initials
- NHS number
- CCG codes

- Drug and dose
- Notification of changes to drugs and dosage
- Date of stopping therapy
- Reason for stopping therapy
- Monthly cost
- Annual cost
- Survival
- Quality of Life estimate (emphasis 10)
- Exercise capacity assessment

This will be recorded in the National Audit of Pulmonary Hypertension.

11 Documents which have informed this Policy

This document updates and replaces 170065/P NHS England Clinical Commissioning Policy: Selexipag for treating pulmonary arterial hypertension (June 2018).

12 Date of Review

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

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