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Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position PP105

Selexipag for the Treatment of Pulmonary Arterial Hypertension (adults)

May 2019

Version 1.0

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Description	NHS Wales will routinely commission this specialised service in accordance with the criteria described in this policy
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Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) will commission Selexipag for people with Pulmonary Arterial Hypertension in accordance with the criteria outlined in this document.

In creating this policy WHSSC has reviewed the relevant guidance issued by the All Wales Medicine Strategy Group (AWMSG) and has concluded that Selexipag should be made available.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy position statement.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy position statement.

1. Introduction

This policy position has been developed for the planning and delivery of Selexipag for the treatment of pulmonary arterial hypertension for people resident in Wales. This service will only be commissioned by the Welsh Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

1.1 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 (blood vessels 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 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). PAH is a rare subgroup of the more common PH. The World Health Organisation (WHO) has classified PH into 5 groups depending on the underlying cause. **Group 1** is PAH (the population covered by the policy) and includes:

- idiopathic PAH (no known cause)
- heredity PAH (passed from parents to their children through genes)
- drug and toxin-induced PAH (caused by drugs or toxin such as street drugs and certain diet medicine)
- 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 and are not considered in this policy.

PAH can affect people regardless of age, ethnicity or other health risk factors. There is no cure for PAH. It is a disease with poor prognosis with only 48% of people surviving for 4 years after diagnosis. People with PAH experience increasing debilitating symptoms which impact on day to day living and quality of life.

The main treatment for people with PAH is medicines directed at the pulmonary blood vessels connecting to the heart and lungs. As PAH is a condition that worsens over time and eventually causes death the overall goal of treatment is to treat the underlying changes in the blood vessels to

reduce the strain on the heart with the aim of improving its function and improving symptoms. Vasoreactivity testing helps indicate those who may benefit most from these therapies.

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

1.2 Aims and Objectives

This policy position proposal aims to define the commissioning position of WHSSC on the use of Selexipag for people with pulmonary arterial hypertension.

The objectives of this policy are to:

- ensure commissioning for the use of Selexipag is evidence based
- ensure equitable access to Selexipag
- define criteria for people with pulmonary arterial hypertension to access treatment
- improve outcomes for people with pulmonary arterial hypertension

1.3 Epidemiology

Based on the findings from the national audits of pulmonary hypertension in the UK it is estimated that there are 109 people with PAH in Wales. The national audits of pulmonary hypertension in the UK report a total of 6,433 patients with pulmonary hypertension in the UK[1]; 3.68% of whom are treated in Wales (n=237)[2]. Of these 237 patients, it is assumed that 46% have PAH (n=109)[3]. The proportion of these patients who are reported to be non-vasoreactive is 56% (n=61)[4] and based on the 6th national audit (2015), it is estimated that 73% of non-vasoreactive patients are classified as FCIII (n=45)[5]

Based on the national audit data and clinical expert opinion, it is estimated that there is an annual incidence of 3 patients in Wales with PAH that is not sufficiently controlled on dual combination therapy. Combining incidence

[1] Health and Social Care Information Centre. National Audit of Pulmonary Hypertension. 7th Annual Report, April 2015-March 2016. Mar 2017. Available at: https://digital.nhs.uk/catalogue/PUB23648.
[2] Health and Social Care Information Centre. National Audit of Pulmonary Hypertension. 7th Annual Report, April 2015-March 2016. Mar 2017. Available at: https://digital.nhs.uk/catalogue/PUB23648.
[3] Health and Social Care Information Centre. National Audit of Pulmonary Hypertension. 6th Annual Report, April 2014-March 2015. 2015. Available at: https://digital.nhs.uk/catalogue/PUB20043
[4] Health and Social Care Information Centre. National Audit of Pulmonary Hypertension. 5th Annual Report, April 2013-March 2014. 2014. Available at: https://digital.nhs.uk/catalogue/PUB172
[5] Health and Social Care Information Centre. National Audit of Pulmonary Hypertension. 6th Annual Report, April 2014-March 2015. 2015. Available at: https://digital.nhs.uk/catalogue/PUB20043

and prevalence estimated with a mortality rate of 10.9% (which is based on parametric survival estimates informed by the GRIPHON study[6] results in a total of 22 patients eligible for Selexipag in Year 1, increasing to 34 patients in Year 5.

1.4 Current Treatment

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.

[6] Coghlan JG, Channick R, Chin K et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension receiving double combination therapy: insights from the randomized controlled GRIPHON study. *American Journal of Cardiovascular Drugs.* 2018;18(1):37-47

- **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.

1.5 New Treatment

There are three signalling pathways known to be involved in PAH that can be targeted by specific medicines:

- the prostacyclin pathway
- the endothelin pathway
- the nitric oxide pathway.

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.

1.6 What NHS Wales has decided

WHSSC has carefully reviewed the relevant guidance issued by:

- The All Wales Medicine Strategy Group (AWMSG)
- Scottish Medicines Consortium
- NHS England Clinical Commissioning Policy: Selexipag for treating pulmonary arterial hypertension (adults)

We have concluded that there is enough evidence to make Selexipag available for use for Welsh patients included in the criteria described in Section 2.1.

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee approve funding of Selexipag for adult Welsh patients with pulmonary arterial hypertension, in-line with the criteria identified in the policy.

2.1 Inclusion Criteria

Selexipag will be routinely commissioned as an option for people who meet the following criteria:

1. Have a confirmed diagnosis of PAH assessed to be in **WHO functional class III**

   and

2. Belonging to one of the following clinical classifications:
   a) Idiopathic PAH
   b) Hereditary PAH
   c) PAH associated with corrected simple congenital heart disease
   d) PAH associated with connective tissue disease

For these people, Selexipag will be commissioned as a third line therapy for the treatment of PAH in adult patients with **WHO functional class (FC) III** who are insufficiently controlled on dual therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor.

2.2 Exclusion Criteria

Selexipag is not commissioned within NHS Wales for:

- any patients outside of the described clinical classification
- use in any other treatment combinations
- use in patients who display adverse drug reactions to Selexipag
- outside the criteria outlined above in section 2.1.

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

2.3 Stopping Criteria

Treatment with Selexipag should be stopped if the disease does not respond to treatment after 6 months.

The occurrence of any of the following may suggest non-response to Selexipag and clinicians should consider carefully whether discontinuation is appropriate in the event of any of them occurring within 6 months of initiating treatment:

- hospitalisation for worsening PAH

- worsening of PAH resulting in need for lung transplantation or balloon arterial 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.

Patients should be re-evaluated with regards to the effectiveness of Selexipag therapy every 6 months and discontinuation should be considered in the event of any of the non-response criteria above.

Stop treatment with Selexipag if it is no longer the optimal treatment option. If intravenous therapy is initiated then Selexipag should be discontinued and this should also be considered in the event of:

- hospitalisation for PAH where intravenous therapy is an option
- a 15% worsening of 6 minute walk distance if intravenous therapy is an option
- an intravenous prostanoid is indicated based on adverse prognostic indicators according to the ESC/ERS risk assessment tool in Table 1.

Table 1: ESC/ERS risk assessment tool

Determinants of prognosis (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	Repeated syncope
WHO functional class	I, II	III	IV
6-minute walk distance	>440 metres	165–440 metres	<165 metres
Cardiopulmonary exercise testing	Peak VO2 >15 ml/min/kg (>65% predicted) VE/VCO2 slope <36	Peak VO2 11–15 ml/min/kg (35–65% predicted) VE/VCO2 slope 36–44.9	Peak VO2 <11 ml/min/kg (<35% predicted) VE/VCO2 ≥45
NT-proBNP plasma levels	BNP <50 ng/litre NT-proBNP <300 ng/ml	BNP 50-–300 ng/litre NT-proBNP 300–1400 ng/l	BNP >300 ng/litre NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm2 No pericardial effusion	RA area 18–26 cm2 No or minimal pericardial effusion	RA area >26 cm2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m2	RAP 8–14 mmHg CI 2.0–2.4 l/min/m2	RAP >14 mmHg CI <2.0 l/min/m2

BNP: brain natriuretic peptide; CI: cardiac index; CMR cardiac magnetic resonance; NT-proBNP: Nterminal pro-brain natriuretic peptide; RA: right atrium; RAP: right atrial pressure; SvO2 mixed venous oxygen saturation; VE/VCO2: ventilatory equivalents for carbon dioxide; VO2: oxygen consumption; WHO: World Health Organization

2.4 Continuation of Treatment

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating an improvement to their health due to the treatment being given.

If no improvement to a patient's health has been recorded then a clinical judgement on the continuation of treatment must be made by the treating healthcare professional.

2.5 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.6 Patient Pathway (Annex i)

Patients will be referred to one of the following designated PH Centres:

Centre	Hospital
London	Imperial College Healthcare NHS Trust Royal Brompton & Harefield NHS Foundation Trust Royal Free Hampstead NHS Trust
Cambridge	Papworth Hospital NHS Foundation Trust
Sheffield	Sheffield Teaching Hospitals NHS Trust (Royal Hallamshire Hospital)
Newcastle	The Newcastle upon Tyne Hospitals Foundation Trust (Freeman Hospital)

***NB**: Great Ormond Street Hospital is designated to provide pulmonary hypertension services for children.*

2.7 Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.8 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner. (These standards can include clinical outcomes, PROMS, Quality of Life etc.).

The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

2.9 Responsibilities

Referrers should:

- Inform the patient that this treatment is not routinely funded outside the criteria in this policy.
- Refer via the agreed pathway.

Clinician considering treatment should:

- Discuss all the alternative treatment with the patient.
- Advise the patient of any side effects and risks of the potential treatment.
- Inform the patient that treatment is not routinely funded outside of the criteria in the policy.
- Confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Documents which have informed this policy

The following documents have been used to inform this policy:

- **All Wales Medicine Strategy Group (AWMSG) guidance**
  - Selexipag (Uptravi®).Final Appraisal recommendation. Advice no: 0918 – May 2018.

- **NHS England policies**
  - Clinical Commissioning Policy: Selexipag for treating pulmonary arterial hypertension (all ages). NHS England Reference: 170104P. 21st December 2018.

- **Other published documents**
  - 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal 2015.
  - Selexipag (Uptravi®). Scottish Medicines Consortium. SMC 1235/17. 6th April 2018.

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

4. Date of Review

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

5. Putting Things Right: Raising a Concern

5.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

6. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex i Codes

Code Category	Code	Description
ICD-10	I272	Other secondary Pulmonary Hypertension

Annex iv Abbreviations and Glossary

Abbreviations

AWMSG All Wales Medicines Strategy Group

IPFR Individual Patient Funding Request

PAH Pulmonary Arterial Hypertension

PH Pulmonary Hypertension

WHO World Health Organisation

WHSSC Welsh Health Specialised Services Committee

Glossary

Individual Patient Funding Request (IPFR)

An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

Welsh Health Specialised Services Committee (WHSSC)

WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.

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.

Annex v World Health Organisation classification of functional status of patients with pulmonary hypertension

Class	Description
I.	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or presyncope.
II.	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or presyncope.
III.	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain and presyncope.
IV.	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.