SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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Resubmission

selexipag, 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1,000 microgram, 1,200 microgram, 1,400 microgram, 1,600 microgram film-coated tablets (Uptravi®)

SMC No. 1235/17

Actelion Pharmaceuticals Ltd

6 April 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the orphan equivalent process

selexipag (Uptravi®) is accepted for restricted use within NHS Scotland.

Indication under review: For the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II to III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

SMC restriction: combination therapy in a sub-population of patients with PAH specifically those in WHO FC III who are insufficiently controlled with an ERA and a PDE-5 inhibitor and who would be considered for treatment with inhaled iloprost.

In a phase III study of patients with PAH, selexipag was statistically significantly better than placebo as measured by a composite primary outcome of death or a complication related to PAH.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of selexipag. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II to III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.[1]

Dosing Information

Individualised dose titration

Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 micrograms twice daily to 1,600 micrograms twice daily (individualised maintenance dose).

The recommended starting dose is 200 micrograms twice daily, approximately 12 hours apart. The dose is increased in increments of 200 micrograms twice daily, usually at weekly intervals. At the beginning of treatment and at each up-titration step it is recommended to take the first dose in the evening. During dose titration some adverse reactions, reflecting the mode of action of selexipag (such as headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing), may occur. They are usually transient or manageable with symptomatic treatment. However, if a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level.

In patients in whom up-titration was limited by reasons other than adverse reactions reflecting the mode of action of selexipag, a second attempt to continue up-titration to the highest individually tolerated dose up to a maximum dose of 1,600 micrograms twice daily may be considered.

Individualised maintenance dose

The highest tolerated dose reached during dose titration should be maintained. If the therapy over time is less tolerated at a given dose, symptomatic treatment and/or a dose reduction to the next lower dose should be considered.

Selexipag should only be initiated and monitored by a physician experienced in the treatment of PAH.[1]

Product availability date

1 July 2016. Selexipag meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Pulmonary arterial hypertension (PAH) is characterised by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death. There are three signalling pathways known to be involved in PAH that can be targeted by specific medicines: the prostacyclin pathway, the endothelin pathway and the nitric oxide pathway. Selexipag is a selective prostacyclin IP receptor agonist and it is the first oral medicine for the treatment of PAH to target the prostacyclin pathway. Other medicines that target the prostacyclin pathway are inhaled iloprost and intravenous epoprostenol.[1-4]

The submitting company has requested that SMC considers selexipag when positioned for use as combination therapy in a sub-population of patients with PAH specifically those in World Health Organisation Functional Class) (WHO FC) III who are insufficiently controlled with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 (PDE-5) inhibitor and who would be considered for treatment with inhaled iloprost.

The key evidence to support the marketing authorisation was from GRIPHON, a randomised, double-blind, placebo-controlled, event-driven, phase III study of individualised dose titration of oral selexipag in 1,156 patients with symptomatic PAH.[5, 6] Adults (18 to 75 years) with idiopathic or heritable PAH or PAH associated with human immunodeficiency virus infection, drug use or toxin exposure, connective tissue disease or repaired congenital systemic-to-pulmonary shunts were included. Diagnosis was confirmed with right heart catheterisation prior to screening. Patients were required to have a pulmonary vascular resistance of at least 5 Wood units (400 dyn·sec·cm^{-5}) and a six-minute walking distance (6MWD) of 50 to 450m. Patients were included if they were not receiving any PAH-specific treatment or they were receiving an ERA, a PDE-5 inhibitor, or both. For patients on treatment the dose had to be stable for at least three months.[5]

Patients were randomised equally and stratified according to study centre to receive selexipag or placebo. There was a 12-week dose-adjustment phase; selexipag was initiated at 200 micrograms twice daily and the dose was increased weekly in twice-daily increments of 200 micrograms until development of prostacyclin-associated unmanageable adverse events, e.g. headache or jaw pain. The dose was then decreased by 200 micrograms in both daily doses and this was the maximum tolerated dose for that patient. The maximum permitted dose was 1,600 micrograms twice daily. During the maintenance phase, dose reductions were permitted at any time and from week 26, doses could be increased at scheduled visits. The individualised maintenance dose was defined as the dose that the patient received for the longest duration. The end of the treatment period was defined for each patient as seven days after the last intake of selexipag or placebo.[5]

The primary outcome was a composite of death or a complication related to PAH, whichever occurred first, up to the end of the treatment period. Complications related to PAH were disease progression or worsening of PAH that resulted in hospitalisation, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy as judged by the physician. Disease progression was defined as a decrease from baseline of at least 15% in 6MWD accompanied by a worsening in WHO FC (for patients with WHO FC II or III at baseline) or the requirement for additional treatment of PAH (for patients with WHO FC III or IV at baseline). A blinded, independent critical-event committee adjudicated all events, including death, to determine whether the event was caused by PAH.[5]

At study closure (i.e. end of double-blind treatment), median duration of double-blind treatment was 71 weeks in the selexipag group and 64 weeks in the placebo group and for outcomes evaluated at end-of-study, median follow-up was 98.1 weeks. A morbidity or mortality event (composite primary outcome) at the end-of-study-treatment was reported by fewer patients in the selexipag group than in the placebo group which was statistically significant in the overall study population, but not in the post-hoc subgroup (n=255) corresponding to the proposed positioning (patients with WHO FC III receiving dual ERA and PDE-5 inhibitor therapy at baseline), as detailed in table 1. The latter analysis was not powered for a statistically significant difference. The differences between the groups were mainly due to morbidity events (disease progression or hospitalisation for worsening of PAH). Secondary outcomes were tested in a hierarchical order as listed in table 2, with those after the first non-significant result in the overall population considered exploratory. Analyses of all-cause mortality at the end-of-study included data from patients who were in double-blind treatment and from those who had discontinued double-blind treatment and consented to follow-up or entered the extension phase (GRIPHON OL), where they received open-label selexipag. There was no statistically significant difference between the selexipag

and placebo groups for all-cause mortality or for deaths due to PAH at the end-of-study, 12% (70/574) and 14% (83/582) in the respective groups.[1,5-7]

Table 1: Primary endpoint and individual components in total population in GRIPHON study and in post-hoc subgroup with FC III receiving dual ERA and PDE-5 inhibitor therapy.[5-7]

	Total Population		WHO FC III on dual therapy	
	Selexipag (n=574)	**Placebo (N=582)**	**Selexipag (N=122)**	**Placebo (N=133)**
Primary endpoint	155 (27%)	242 (42%)	41 (34%)	59 (44%)
	HR 0.60 (99% CI: 0.46 to 0.78), p<0.001		HR 0.74 (95% CI: 0.50 to 1.10)*	
Hospitalisation for worsening PAH	78 (14%)	109 (19%)	24 (20%)	33 (25%)
Disease progression[a]	38 (6.6%)	100 (17%)	10 (8.2%)	16 (12%)
Death (all cause)	28 (4.9%)	18 (3.1%)	4 (3.3%)	2 (1.5%)
Additional therapy[b]	10 (1.7%)	13 (2.2%)	3 (2.5%)	7 (5.3%)
Need of transplant or septostomy[c]	1 (0.2%)	2 (0.3%)	0	1 (0.75%)

a = a decrease of at least 15% in 6 minute walking distance (6MWD) plus a worsening in functional class (FC) for those with FC II or III or a need for additional treatment for those with FC III or IV.
b = initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH;
c = need for lung transplantation or balloon atrial septostomy for worsening PAH
FC = functional class; ERA = endothelin receptor antagonists; PDE-5 = phosphodiesterase type 5; HR = hazard ratio. * a similar HR of 0.67 (95% CI: 0.45 to 1.01) from an analyses that adjusted for baseline 6MWD was used in economic analysis.

Table 2: Secondary endpoints in hierarchical order in total population of GRIPHON study and post-hoc subgroup with FC III receiving dual ERA and PDE-5 inhibitor therapy.[5-7]

	Total Population		WHO FC III on dual therapy	
	Selexipag (n=574)	**Placebo (N=582)**	**Selexipag (N=122)**	**Placebo (N=133)**
Median change in 6MWD at 26 weeks (metres)	+4.0	-9.0	-	-
	Difference 12.0 (99% CI 1 to 24) p=0.003			
Absence of decline in functional class at 26 weeks	78% (444/471)	75% (430/574)	-	-
	OR 1.16 (99% CI: 0.81 to 1.66) p=0.28			
Death due to PAH or hospitalisation for PAH at end-of-treatment	18% (102/574)	24% (137/582)	21% (26/122)	29% (38/133)
	HR 0.70 (95%: 0.54 to 0.91)		HR 0.71 (95% CI: 0.43 to 1.18)	
Death due to all causes at end-of-study	17% (100/574)	18% (105/582)	20% (25/122)	21% (28/133)
	HR 0.97 (95% CI: 0.74 to 1.28)		HR 1.05 (95% CI: 0.61 to 1.81)	

FC = functional class; ERA = endothelin receptor antagonist; PDE-5 = phosphodiesterase type 5; HR = hazard ratio; OR = odds ratio; 6MWD = 6 minute walking distance; PAH = pulmonary arterial hypertension; CI = confidence interval.

There were no differences in quality of life in the selexipag group and the placebo group measured by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) overall symptom score or the breathlessness subscale.[6]

Summary of evidence on comparative safety

Most patients reported an adverse event; 98% (565/575) of the selexipag group and 97% (559/577) of the placebo group. The proportion of patients with a serious adverse event was 44% and 47% respectively. A significantly higher proportion of patients discontinued selexipag due to adverse events than placebo; 14% and 7.1%, respectively.[5]

The most common adverse events reported in the selexipag and placebo groups respectively were; headache (65% and 33%), diarrhoea (42% and 19%), nausea (34% and 19%), pain in jaw (26% and 6.2%), worsening of PAH (22% and 36%), vomiting (18% and 8.5%), pain in extremity (17% and 8.0%), dyspnoea (16% and 21%), myalgia (16% and 5.9%).[5]

Hyperthyroidism was reported in 1.4% of patients treated with selexipag and no patients receiving placebo.[5] The summary product characteristics (SPC) recommends thyroid function tests as clinically indicated.[1]

Overall, the proportion of patients who were reported to have died up to the end of treatment plus seven days was 8.0% (46/574) of the selexipag group and 6.4% (37/582) of the placebo group. Most of the fatal events were classed as cardiac deaths and the imbalance was restricted to patients with WHO FC I/II.[6]

In the post-hoc subgroup of 255 patients with WHO FC III who were receiving an ERA and PDE-5 inhibitor at baseline within the selexipag and placebo groups 98% (120/122) and 100% (n=133) reported an adverse event; 49% (60/122) and 54% (72/133) reported a serious adverse event; and 20% (24/122) and 7.5% (10/133) discontinued due to adverse events. It has been suggested that the higher rate of discontinuation due to adverse events in this subgroup compared to the whole study population may be due to more intensive treatment in the subgroup. It was also noted that prostacyclin-associated adverse events were more common in the subgroup compared with the overall study population.[7]

Summary of clinical effectiveness issues

In Scotland PAH is managed through a central unit, the Scottish Pulmonary Vascular Unit. SMC has previously accepted the three ERAs (macitentan, bosentan [in WHO FC III only] and ambrisentan), the two PDE-5 inhibitors (sildenafil and tadalafil), riociguat and nebulised iloprost for use, restricted to initiation by specialists in this unit or by similar specialists. The introduction of intravenous epoprostenol for PAH pre-dates SMC. It should be noted that the marketing authorisations for each of these medicines are slightly different. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area as currently available alternatives that target the prostacyclin pathway, nebulised iloprost and intravenous epoprostenol, are cumbersome. Selexipag meets SMC orphan equivalent criteria.

The submitting company has requested that SMC considers selexipag when positioned for use as combination therapy in a sub-population of patients with PAH; those in WHO FC III who are insufficiently controlled with an ERA and a PDE-5 inhibitor and who would be considered for treatment with inhaled iloprost.

In GRIPHON, a statistically significantly lower proportion of patients in the selexipag group experienced a morbidity or mortality event compared with the placebo group (27% versus 42%), which was mainly due to differences in disease progression and hospitalisation for PAH. This is the largest study

conducted in patients with PAH and the median duration of study treatment was over a year.[6] The relevant European Medicines Agency (EMA) guidance encourages the use of the composite endpoint time to clinical worsening as a primary endpoint. The primary outcome used in GRIPHON is broadly similar to the EMA guidance however the guidance suggests including signs or symptoms of right-sided heart failure which was not included in the GRIPHON study.[4] The EMA considered the benefit of selexipag moderate but clinically relevant. Most events (82%, across both study groups) were disease progression or hospitalisation.[6]

The study population is broader than the marketing authorisation granted and the positioning proposed by the company. A post-hoc subgroup analysis in patients with FC III receiving dual ERA and PDE-5 inhibitor therapy at baseline may more closely represent the proposed positioning and indicated a treatment effect. As this was a post-hoc analysis and not sufficiently powered, the results should be interpreted with caution.

The choice of composite endpoint, as well as discontinuing selexipag in patients after the first primary endpoint event and providing the option of switching placebo-treated patients to selexipag after the first event, may have been a relevant weakness of the study design. As most of the primary outcome events were disease progression the study design made it difficult to reliably assess all-cause mortality.[6] The higher mortality rate (as a first primary endpoint event) in the selexipag than placebo group was a cause for concern; the company provided multiple sensitivity analyses to the EMA to address this.[6]

There was no quality of life benefit associated with selexipag as measured by CAMPHOR. The EMA suggested that this tool may not be sensitive enough to changes in quality of life.[6]

An indirect treatment comparison (ITC) was presented, using Bucher methodology, to compare selexipag with inhaled iloprost in patients with PAH. Three studies were used in the base case analyses. The outcomes assessed were short term outcomes of FC improvement, FC worsening and change in 6MWD (mean measurements) as these were where data for inhaled iloprost were available. The limitations of this ITC include inability to compare all clinically relevant outcomes due to lack of data for iloprost and heterogeneity, in particular the differences in baseline FC and background therapy, as well as in study design and imputation rules for missing data.

In the resubmission a naïve ITC of selexipag and inhaled iloprost was performed to provide comparative efficacy for the long-term outcome, overall survival. This included data from GRIPHON study for selexipag and five open-label studies of inhaled iloprost. Two of these studies were of uncontrolled prospective design, one was a registry study, one was a retrospective cohort study and the final study was an open label extension of a three month randomised study. Survival rates were compared at one, two, three and four years. It was suggested that this supported an assumption of equivalence for long-term outcomes. The validity of the naïve ITC is limited by weaknesses, including the naïve design, differences in study design, patient characteristics, sample size, follow-up and statistical methods for analysing overall survival.

In summary, the Bucher and naïve ITCs have limitations, relating to the evidence base for inhaled iloprost, which makes it difficult to draw robust conclusions on comparative efficacy of selexipag versus inhaled iloprost.

Clinical experts consulted by SMC considered selexipag is a therapeutic advancement as it is an oral therapy so may have advantages over iloprost which requires inhalation via a nebuliser six to nine times a day.[8] Selexipag requires individualised dose titration; additional risk minimisation measures have been agreed with EMA to reduce the risk of medication error.[1, 6] There are several cardiac conditions listed as contraindications to the use of selexipag in the SPC, e.g. recent myocardial infarction or cerebrovascular events.[1] Selexipag can cause hypotension and has been associated with

hyperthyroidism and pulmonary veno-occlusive disease. In addition there is limited clinical experience with selexipag in patients >75 years.[1]

*Other data were also assessed but remain commercially confidential.**

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of selexipag, as an orphan-equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- PAH is a devastating, life-threatening and life-limiting condition that dramatically impairs quality of life. Patients can become symptomatic quickly without medication and are typically disabled by breathlessness and fatigue. Patients are often unable to work and need significant care from families.
- There is potential for reduced morbidity/mortality and improvements in quality of life associated with selexipag compared with currently available prostanoids.
- PACE participants considered that current therapies, inhaled iloprost and IV epoprostenol, are highly complex treatment regimens and require good mental function for optimum adherence. They are not suitable for patients with manual dexterity issues or certain co-morbidities.
- The oral selexipag formulation is more convenient for patients and their families/carers compared to the current cumbersome treatments. Patients would no longer need to spend time every two hours of the day, making up the medicine, administering the treatment and cleaning their equipment. Patients always need to plan ahead when going out.
- PACE participants noted that most patients with PAH attending the Scottish Pulmonary Vascular Unit are of working age. Selexipag offers the opportunity for some patients to return to work/education and/or care for family members.
- Clinicians are familiar with managing the adverse events associated with prostanoids and PACE participants highlighted that selexipag may be associated with fewer adverse events than currently available treatments.

Additional Patient and Carer Involvement

We received a patient group submission from the Pulmonary Hypertension Association, UK, which is a registered charity. The Pulmonary Hypertension Association, UK, has received 15% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the Pulmonary Hypertension Association, UK, participated in the PACE meeting. The key points of the submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The submitting company presented a cost utility analysis comparing selexipag to inhaled iloprost for use in patients with pulmonary arterial hypertension, WHO FC III, and insufficiently controlled with combination therapy comprising an ERA and a PDE-5 inhibitor.

A patient-level, micro-simulation Markov model, with half-cycle correction and 3-monthly cycles was used over a 30 year time horizon. All patients entered the model in FC III health state and started selexipag or inhaled iloprost (plus ERA + PDE-5 inhibitor). Patients could deteriorate or improve between FC II, FC III, and FC IV; with improvement only possible during the first cycle that a new

treatment was initiated. Patients experiencing a non-fatal morbidity event were assumed to deteriorate to the next FC and start a new treatment. Discontinuation due to adverse events (AE) and death could occur in all states.

Morbidity and mortality efficacy data came from the selexipag arm of the pivotal study. An exponential function was fitted to extrapolate data from that study. A Bucher ITC was undertaken and inhaled iloprost was assumed to have the same clinical event rate as selexipag. In this resubmission, additional overall survival data (from a naïve indirect comparison) were also provided to support the assumption of comparable efficacy. Furthermore the company submitted post hoc subgroup data for patients receiving dual therapy with an ERA and PDE-5 inhibitor. Based on this analysis selexipag and inhaled iloprost were assumed to reduce morbidity and mortality resulting in a HR of 0.67.

Utility values for FC health states and adverse events were informed by a literature search. Adverse events were largely the same for both medicines, however inhaled iloprost was assumed to have additional events due to its administration route. In this resubmission, the company provided new disutility data from an unpublished UK study. Based on these data, utility decrements were applied to inhaled administration, subcutaneous and intravenous injection respectively, relative to oral administration. These disutilities were the key driver in terms of the incremental quality adjusted life-year (QALY) gain.

Costs associated with drug acquisition, adverse events and treatment initiation were included due to differences between treatments. Use of selexipag was consistent with usage in the pivotal study; use of inhaled iloprost was advised by key opinion leaders who also defined the resources used in each FC health state.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The key results are presented in the table below. Sensitivity analysis, which reduced the number of inhalations of iloprost, was provided and was useful. However, based on SMC expert responses, the mean number of inhalations per day of seven (as per base case) is likely to be reasonable.

Table 3: Base case and subgroup analysis results with PAS

	ICER
Base case	Dominant
Subgroup analysis (patients receiving dual therapy with ERA and PDE-5 inhibitor)	Dominant
Base case sensitivity analysis (reduced mean inhaled iloprost inhalations from 7 to 5 per day)	£46,538

There were a number of weaknesses with the analysis which are as follows;

- There is considerable uncertainty surrounding the long term relative effectiveness of selexipag versus inhaled iloprost (due to the lack of comparative data and the assumed comparable efficacy from the ITCs). In this resubmission, the company has provided additional data supporting similarity in overall survival for both treatments, however these data are from a naïve indirect comparison which had a number of limitations.
- The company was asked to provide the results of a cost minimisation analysis. For both the base case analysis and the subgroup analysis with the PAS, selexipag was estimated to be a cost-effective treatment option versus inhaled iloprost. It should be noted that these results should be interpreted with caution due to the limitations surrounding the assumption of comparable efficacy.
- The extent to which patients prefer oral administration over inhaled, IV and subcutaneous remains uncertain. The company has provided new data (available as a study abstract presented at a conference) outlining disutilities associated with different administration routes.[9] This is the key

driver of the incremental QALY gain within the submission. The study has some strengths (e.g. it was conducted in the UK and participants used the EQ-5D-5L) but is also subject to limitations and results have not been independently verified.

- The company has presented the results of a subgroup analysis which was considered to more closely match the company's positioning i.e. patients receiving dual therapy with an ERA and PDE-5 inhibitor. It is worth noting that these are subject to a number of limitations (similar to the base case analysis) such as a lack of robust comparative data and the results should be treated with caution.

The Committee also considered the benefits of selexipag in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as selexipag is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted selexipag for restricted use in NHS Scotland.

Additional information: guidelines and protocols

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) published the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The available treatments are discussed; ERAs (bosentan, ambrisentan, macitentan), PDE-5 inhibitors (sildenafil, tadalafil), soluble guanylate cyclase stimulator (riociguat), prostacyclin analogues (epoprostenol, iloprost, treprostinil [unlicensed medicine], beraprost [unlicensed medicine]) and the prostacyclin IP receptor agonist selexipag.[2]

Additional information: comparators

Inhaled iloprost. Continuous intravenous infusion of epoprostenol.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Selexipag	**200 micrograms to 1,600 micrograms orally twice daily**	**36,400**
Iloprost	2.5 microgram to 5 microgram inhaled via a nebuliser six to nine times a day	29,134 to 43,701

Doses are for general comparison and do not imply therapeutic equivalence. Costs from Electronic Medicines Compendium Dictionary of Medicines and Devices on 31 January 2018. Costs do not take any patient access schemes into consideration. Epoprostenol, administered by continuous intravenous infusion, has not been included in the cost table as the dose is individualised according to patient tolerability and the mean dose in the only historical study found was higher than the licensed doses.

Additional information: budget impact

The submitting company estimated there to be 71 patients eligible for treatment with selexipag in all years. The uptake rate was estimated to be 15% in year 1 (11 patients) rising to 60% in year 5 (42 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided to NHS health boards to enable them to estimate the predicted budget with the PAS.

References

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8. Bayer plc. iloprost trometamol (Ventavis®). Summary of product characteristics. Last updated 14 December 2016. www.medicines.org.uk.

9. Davies E, Llewellyn S, Beaudet A, et al. Elicitation of disutility values associated with the mode of administration of drugs acting on the prostacyclin pathway in pulmonary arterial hypertension (PAH). Accepted for presentation at British Thoracic Society Winter meeting, December 2017.

This assessment is based on data submitted by the applicant company up to and including 16 March 2018.

*****_Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements_

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.