

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

09 June 2017

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 full submission assessed under the orphan equivalent process

selexipag (Uptravi®) is not recommended for 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.

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.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

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

**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

Median duration of double-blind treatment was 71 weeks in the selexipag group and 64 weeks in the placebo group. A morbidity or mortality event (composite primary outcome) was reported by 27% (155/574) of the selexipag group and 42% (242/582) of the placebo group, hazard ratio (HR) 0.60 (99% Confidence Interval [CI]: 0.46 to 0.78), $p < 0.001$. Specific event rates for the selexipag and placebo groups respectively, were: hospitalisation for PAH (14% versus 19%), disease progression (6.6% versus 17%), death from any cause (4.9% versus 3.1%), initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH (1.7% versus 2.2%), need for lung transplantation or balloon atrial septostomy for worsening of PAH (0.2% versus 0.3%).⁵ Secondary endpoints, tested in a hierarchical manner, are presented in table 1.

Table 1. Key secondary endpoints in the GRIPHON study.^{5,7}

	Selexipag group	Placebo group	
Median change in 6MWD from baseline to week 26.*	+4m	-9m	treatment effect 12m (99% CI: 1 to 24), p=0.003.
Absence of worsening of WHO FC from baseline to week 26, %	78%	75%	odds ratio 1.16 (99% CI: 0.81 to 1.66), p=0.28**
Death due to PAH or hospitalisation for worsening of PAH by the end of the treatment period, %	18%	24%	hazard ratio 0.70 (95% CI: 0.54 to 0.91), p=0.003.
Death from any cause up to the end of the study, %	17.4%	18.0%	hazard ratio 0.97 (95% CI: 0.74 to 1.28), p=0.42

* Measured at trough level of study drug, missing values were imputed for 22% of patients.

**Due to the hierarchical testing, subsequent results should be interpreted as exploratory.

CI = confidence interval; WHO FC = World Health Organisation functional class; 6MWD = 6-minute walking distance; PAH = pulmonary arterial hypertension

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

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

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

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 endothelin receptor antagonists (macitentan, bosentan [in WHO FC III only] and ambrisentan), the two phosphodiesterase-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.

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

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.*

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with a patient group representative and a clinical specialist 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.
- 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 other 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 less 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 8.5% 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. In the absence of any robust data comparing long term outcomes, inhaled iloprost was assumed to have the same clinical event rate as selexipag.

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. Adverse events were the same for both medicines except that inhaled iloprost was assumed to have additional events due to its administration route. Costs and utility decrements were included for adverse events. Utility values for adverse events and by FC were informed by a literature search. Disutilities were also applied for inhaled and intravenous treatments using values from an unpublished study ie quality of life was assumed to be lower for patients on inhaled or intravenous treatments compared to selexipag.

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.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. The submitting company has also requested that the results without the PAS are also not presented.

Validation of the key parameters (morbidity, mortality and discontinuation rates) in the model to those in the pivotal study indicated good congruence other than the selexipag discontinuation rate modelled was slightly higher than observed in the clinical study.

Sensitivity analysis showed that the findings were stable in the majority of cases. However, the results did show upward sensitivity in a number of scenarios:

- Adopting the lower confidence interval for the disutility adjustment for inhaled iloprost (utility for oral treatment has lower utility than inhaled treatment).
- Reducing the average daily dose of inhaled iloprost from seven to five doses, with no loss in clinical outcomes such that the two medicines remained equivalent.

The main weaknesses are

- Uncertainty on the long-term relative effectiveness of selexipag versus inhaled iloprost in clinical practice was the key weakness.
- The utility benefit from oral selexipag is from an unpublished study which has several weaknesses.

The Committee 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- equivalent medicine, SMC can accept greater uncertainty in the economic case. After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept selexipag for use in NHS Scotland.

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

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 MIMS online on 30 January 2017. 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 would be 76 patients eligible for treatment with selexipag in all years to which confidential estimates of treatment uptake were applied. SMC is unable to present any budget impact estimates due to commercial in confidence issues.

Other data were also assessed but remain commercially confidential.*

References

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2. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: 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): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37(1):67-119.
3. Health and Social Care Information Centre (HSCIC). National Audit of Pulmonary Hypertension 2015. Sixth Annual Report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, Channel Islands, Gibraltar and Isle of Man. Report for the audit period April 2014 to March 2015.
4. European Medical Agency. Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. 2009. Report No.: EMEA/CHMP/EWP/356954/2008.
5. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, *et al.* Selexipag for the Treatment of Pulmonary Arterial Hypertension. *New England Journal of Medicine.* 2015;373(26):2522-33.
6. European Medicines Agency. European Public Assessment Report, selexipag (Uptravi®) 1 April 2016 EMA/CH/C/003774/0000.
7. Commercial In Confidence*
8. Bayer plc. iloprost trometamol (Ventavis®). Summary of product characteristics. Last updated 14 December 2016. www.medicines.org.uk.

This assessment is based on data submitted by the applicant company up to and including 17 March 2017.

**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.