AWMSG Secretariat Assessment Report
Selexipag (Uptravi®▼) 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1,000 microgram, 1,200 microgram, 1,400 microgram, 1,600 microgram film-coated tablets

This assessment report is based on evidence submitted by Actelion Pharmaceuticals UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Selexipag (Uptravi®▼) for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–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. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Dosing	The recommended starting dose is 200 micrograms twice daily. The patient is titrated up to the highest individually tolerated dose, ranging from 200 micrograms twice daily to 1,600 micrograms twice daily. For further information including dose titration refer to the Summary of Product Characteristics[2].
Marketing authorisation date	12 May 2016

2.0 DECISION CONTEXT

2.1 Background

Pulmonary arterial hypertension (PAH) is a rare disease characterised by vascular proliferation and remodelling of the small arteries in the lungs[3]. This results in a progressive increase in pulmonary vascular resistance leading to an increase in blood pressure in the pulmonary arteries, which can cause right heart failure and premature death[3]. Symptoms include shortness of breath, tiredness, feeling dizzy or faint, chest pain, palpitations and swelling of the legs, ankles, feet or abdomen; these often get worse during exercise and can limit a person's physical activities[4].

The World Health Organization (WHO) classifies pulmonary hypertension into four functional classes (FCI–IV) based on the severity of symptoms (see Glossary)[5]. People with pulmonary hypertension in functional class II (FCII) have symptoms that occur with ordinary physical activity; those in FCIII have marked limitation of physical activity: their symptoms occur with less-than-ordinary effort, such as lifting their arms[5]. PAH is also categorised as either low, intermediate or high risk (see Glossary). Intermediate risk is defined as an estimated 1-year mortality of 5–10%; and is associated with a moderately impaired exercise capacity and right ventricular dysfunction. The aim of treatment is to achieve a low-risk status to reduce the risk of disease progression. Low risk is defined as < 5% risk of estimated 1-year mortality and is usually associated with good exercise capacity, good quality of life, good right ventricular function and a low

mortality risk[6]. A person whose PAH is classed as intermediate risk will usually be WHO FCIII and those with low-risk status will usually be WHO FCI or FCII[6].

Treatment is based on three main steps: the first is general measures and supportive therapy; the second involves treatment with high-dose calcium channel blockers in vasoactive patients or other medicines licensed for PAH used alone or in combination; the third step proposes combinations of licensed medicines and lung transplantation if the response to previous treatments has not been adequate[6]. People with PAH FCII and FCIII are mainly treated with endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators and prostacyclin analogues[6].

Selexipag (Uptravi®) is an orally active selective prostacyclin receptor (IP receptor) agonist that has anti-proliferative and anti-fibrotic effects[2]. Based on company-sought clinical expert opinion the company has focused its submission on the use of selexipag as a triple combination therapy for patients with PAH FCIII who are insufficiently controlled on dual therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor[1].

2.2 Comparators

The comparator included in the company's submission is inhaled iloprost (Ventavis®)[1]. Clinical experts in Wales contacted by AWTTC have reported that inhaled iloprost is used in the majority of patients rather than intravenous epoprostenol.

2.3 Guidance and related advice

- NHS England Clinical Commissioning Policy (2016) Selexipag in the treatment of pulmonary arterial hypertension[3]
- European Society of Cardiology & European Respiratory Society (2015) Guidelines for the diagnosis and treatment of pulmonary hypertension[6]

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of macitentan (Opsumit®), riociguat (Adempas®), sildenafil citrate (Revatio®), ambrisentan (Volibris®) and inhaled iloprost (Ventavis®) to treat PAH[7-12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes evidence from a randomised, event-driven phase III study (GRIPHON) comparing the efficacy and safety of selexipag with placebo in the treatment of PAH[1]. The company also provided results from systematic literature reviews conducted in August 2017 for selexipag and inhaled iloprost. No network meta-analysis of the studies identified was conducted because of differences in the study designs and between the characteristics of the patients included.

3.1 GRIPHON study

This study enrolled a total of 1,156 patients (aged 18–75 years; 80% women) with PAH confirmed by right heart catheterisation, who were either not receiving therapy at baseline (n = 236) or who were already receiving therapy with an endothelin receptor antagonist (n = 170) or a phosphodiesterase type 5 inhibitor (n = 374), or both (n = 376)[13]. All patients had a pulmonary vascular resistance of at least 5 Wood units and a 6-minute walk distance of 50–450 m; 98% of them were WHO FCII (n = 529) or FCIII (n = 607). Patients were randomly assigned in a 1:1 ratio to receive either placebo (n = 582) or selexipag (n = 574) at a starting dose of 200 micrograms twice daily. During a 12-week dose-adjustment phase the dose was increased weekly in twice-daily increments of 200 micrograms until unmanageable adverse effects associated with prostaglandin use developed, such as headache or jaw pain. The dose was then decreased by 200 micrograms in both daily doses and this reduced dose was considered to be the

maximum tolerated dose for that patient. The maximum dose allowed was 1,600 micrograms twice daily.

The primary endpoint in a time-to-event analysis was a composite of death or a complication related to PAH (morbidity/mortality event), whichever occurred first, up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo)[13]. Complications related to PAH were: disease progression or worsening of PAH that resulted in hospitalisation; starting parenteral prostanoid therapy or long-term oxygen therapy; or the need for lung transplantation or balloon atrial septostomy as judged by the physician[13]. Disease progression was defined as a decrease of at least 15% from baseline in the 6-minute walk distance and a worsening of WHO FC, or the need for additional treatment of PAH[13]. The study included an open-label extension phase in which patients were eligible to receive selexipag or commercially available medicines; patients entered the extension phase after a primary morbidity or mortality endpoint, or at the end of the double-blind phase[13]. The primary endpoint was analysed in the full analysis set; this included all randomised patients[14].

Clinical assessments, including the 6-minute walk test and determination of WHO FC, were performed at baseline, weeks 8, 16 and 26, and every 6 months afterwards and when worsening of disease was suspected[13]. The median duration of study treatment was 70.7 weeks in the selexipag group and 63.7 weeks in the placebo group[13]. At some study sites (including sites in the UK), changes in quality of life from baseline to week 26 were assessed using the Cambridge pulmonary hypertension outcome review (CAMPHOR) symptoms score and its sub-scale 'Breathlessness' symptoms[14].

The study results are presented in Table 1. Treatment with selexipag twice daily resulted in a significant reduction in the occurrence of morbidity or mortality events up to 7 days after the last dose, compared with placebo (reduction in risk: 40%; hazard ratio [HR] 0.60; 99% confidence interval [CI], 0.46 to 0.78; $p<0.001$)[2].

Data from the health-related quality of life questionnaire were available for 239 patients in the selexipag group and 240 patients in the placebo group[14]. Results for the absolute change from baseline to week 26 showed no difference in treatment effects in terms of symptom score or breathlessness score for selexipag and placebo (Table 1)[14].

The company conducted a post-hoc analysis of the primary endpoint, taking into account all endpoint component events independently of each other; the results supported the main study results[1,14].

Table 1. Results from the GRIPHON study[13,14]

	Selexipag (n = 574)	Placebo (n = 582)	Hazard ratio	P value
	Number of patients (%)			
Primary endpoint: first morbidity or mortality event				
All events	155 (27)	242 (42)	0.60 (99% CI: 0.46 to 0.78)	< 0.001
Hospitalisation for worsening PAH	78 (14)	109 (19)		
Disease progression	38 (7)	100 (17)		
Death from any cause	28 (5)	18 (3)		
Starting prostanoid therapy or long-term oxygen therapy for worsening PAH	10 (2)	13 (2)		
Need for lung transplantation or balloon atrial septostomy for worsening PAH	1 (0.2)	2 (0.3)		
Secondary endpoint: death due to PAH or hospitalisation for worsening PAH up to end of treatment period				
All events	102 (18)	137 (24)	0.70 (95% CI: 0.54 to 0.91)	0.003
Hospitalisation due to worsening of PAH	86 (15)	123 (21.1)		
Death due to PAH	16 (3)	14 (2)		
Secondary endpoint: death up to the end of study				
Death due to PAH	70 (12)	83 (14.3)	0.86 (95% CI: 0.63 to 1.18)	0.18
Death from any cause	100 (17)	105 (18)	0.97 (95% CI: 0.74 to 1.28)	0.42
Secondary endpoint: change in 6-minute walk distance from baseline to week 26				
Median change (metres)	−4.0	−9.0	n/a	n/a
Treatment effect (metres)	12 (99% CI: 1 to 24)			0.003
Health-related quality of life	**(n = 239)**	**(n = 240)**	**Point estimate**	**P value**
CAMPHOR symptoms score - Absolute change from baseline at week 26				
Mean ± SD	0.23 ± 5.69	0.41 ± 6.19	0.0 (99% CL: −1.0 to 1.0)	0.22
CAMPHOR breathlessness score- Absolute change from baseline at week 26				
Mean ± SD	−0.05 ± 1.92	0.05 ± 1.91	0.0 (99% CL: −0.4 to 0.0)	0.17
CAMPHOR: Cambridge pulmonary hypertension outcome review; CI: confidence interval; CL: confidence limit; PAH: pulmonary arterial hypertension; SD: standard deviation				

3.2 Sub-group analysis of patients with WHO FCIII on dual therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor

The company also conducted an exploratory post-hoc analysis on a sub-group of 255 patients in the GRIPHON study who had PAH WHO FCIII (over 50% of all enrolled patients) and who were being treated with an endothelin receptor antagonist plus a phosphodiesterase type 5 inhibitor (32.5% of all patients)[15,16]. This was not a pre-specified sub-group analysis and therefore the study was not powered to show differences within this subgroup.

Results of the analysis showed that selexipag treatment resulted in a 33% risk reduction in the occurrence of morbidity or mortality events up to 7 days after the last dose compared with placebo (HR 0.67; 95% CI: 0.45 to 1.01)[15,16]. The treatment effect with

selexipag was similar to that seen in the overall GRIPHON study population. The distribution of events in the sub-group was similar to that seen in the whole GRIPHON population: the most frequently reported first event was hospitalisation for PAH worsening, followed by disease progression. Selexipag treatment resulted in a 37% reduction in the occurrence of death due to PAH or first hospitalisation due to worsening PAH (HR 0.63; 95% CI: 0.38 to 1.05). The results regarding numbers of deaths in the selexipag and placebo groups were consistent with those of the GRIPHON study (HR 0.95; 95% CI: 0.55 to 1.64)[15,16].

3.3 Comparative safety

Most patients in the GRIPHON study reported at least one adverse event: 98% of the selexipag group and 97% of the placebo group[13]. The most frequently reported adverse events leading to discontinuation in the selexipag group (events for which there was > 1% difference between selexipag and placebo groups) were headache, diarrhoea and nausea. Other adverse events that were more frequent in the selexipag group than in the placebo group were: hypotension, anaemia, hyperthyroidism and acute renal failure[17]. The Summary of Product Characteristics for selexipag reports that hypothyroidism has been observed with selexipag and that thyroid function tests are recommended if there are signs or symptoms of hyperthyroidism[2]. The majority of serious adverse events were related to the underlying PAH condition and there was no difference in serious adverse events reported in the selexipag group compared with the placebo group. In the GRIPHON study there were 46 deaths (8%) in the selexipag group and 37 (6%) in the placebo group reported up to end of treatment plus 7 days; of which 72% and 73%, respectively, were judged to be related to PAH[17].

In the ongoing, open-label, extension study assessing the safety and tolerability of selexipag in 218 patients with PAH, after a median duration of 37.2 weeks, 23.9% of patients had at least one adverse event leading to treatment discontinuation[1]. The most frequent adverse events leading to discontinuation were PAH (8.7%) and right ventricular failure (4.6%)[1].

The company conducted a systematic literature review to identify safety studies in people with PAH treated with selexipag or inhaled iloprost: two relevant primary safety studies were identified, one for selexipag and one for inhaled iloprost. The most frequent adverse events in the selexipag study were headache, diarrhoea, jaw pain and dyspnoea[18]. The most frequent adverse events in the inhaled iloprost study were cough, flushing, peripheral oedema, headache and infection[19].

3.4 AWTTC critique

- The GRIPHON study showed a significant improvement in the primary composite endpoint of first mortality or morbidity event.
- A moderate improvement in the 6-minute walk distance was reported in the GRIPHON study. The Committee for Medicinal Products for Human Use (CHMP) noted that the moderate effect on 6-minute walk distance is likely due to the high number of patients (about 80%) who were on baseline therapy as only smaller effects on 6-minute walk distance can be expected in these patients and this does not indicate an overall lack of efficacy[17].
- Results from the GRIPHON study showed a numerically higher number of deaths in the selexipag group compared to the placebo group for the primary endpoint[13]. No safety issues were identified that could explain an increase in mortality and there was no statistically significant difference between the selexipag and placebo groups for all-cause mortality up to the end of the study. The CHMP concluded that the study's cross-over design may have led to bias in the study's mortality results as all patients randomised to placebo were counted in the placebo arm regardless of whether they remained on placebo or received active treatment in the open-label phase of the study. Two models accounting for

cross-over indicated that treatment with selexipag might in the best case be associated with an improvement in mortality by up to 25%[17].

- The health-related quality-of-life data as measured by the CAMPHOR scale in the GRIPHON study did not show statistically significant improvements with selexipag for breathlessness symptoms and overall quality of life[17]. The CHMP could not determine whether this was due to a low sensitivity of the test or whether the relevant benefits of selexipag on morbidity events do not translate into improvements in the categories investigated by the test[17].
- The company conducted a post-hoc analysis of patients in FCIII in the GRIPHON study who were already taking an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor[15], which is in line with the company's proposed population for the submission. This was not a pre-specified analysis and the results for the occurrence of morbidity/mortality events were similar to those for the whole study population[15].
- There are no studies comparing the clinical effectiveness of selexipag with inhaled iloprost. The company conducted a network meta-analysis feasibility assessment and concluded that constructing a functional network was not feasible due to differences in the study designs and patient populations.
- Selexipag is the only available prostacyclin receptor agonist demonstrating long-term efficacy; there are no long-term efficacy data for the combined morbidity/mortality endpoint available for inhaled iloprost[17].
- Selexipag is the first oral tablet available for treating PAH in people in WHO FCII or III and Welsh clinical experts have noted that oral medication is more convenient for patients than inhaled therapy. Selexipag is taken twice daily which is more convenient than inhaled iloprost which is administered 6 to 9 times daily[2,20].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submitted a cost-utility analysis (CUA) comparing the oral administration of selexipag with inhaled iloprost in adults with PAH in WHO FCIII whose PAH is insufficiently controlled on dual therapy with an endothelin receptor antagonist plus a phosphodiesterase type 5 inhibitor.

The CUA is a patient-level micro-simulation Markov model, which adopts a lifetime horizon (30 years), three-monthly cycles (to coincide with routine clinical appointments), and an NHS Wales perspective, with costs and outcomes accrued beyond one year discounted at a rate of 3.5% per annum. The modelled population demographics are taken from the GRIPHON study[13]. Patients enter the model in FCIII and receive one of the two treatments. Patients can improve or deteriorate and transition between FCII, FCIII and FCIV in the first cycle. In subsequent cycles patients can only deteriorate in FC state. Patients can die in any FC state. Transition probabilities (including risk of a morbidity event and mortality) are informed by parametric survival estimates from patient-level data taken from the GRIPHON study[13]. Given the lack of head-to-head data for inhaled iloprost versus selexipag, equal efficacy is assumed between treatments (which the company claims is a conservative assumption). Due to the small sample of FCIV patients in the GRIPHON study, the increased risk of mortality in this state is informed by PAH registry data[13,21,22]. Non-fatal morbidity events are assumed to lead to deterioration in functional class, and initiation of a new treatment. The probability of mortality increases with worsening functional class state. Background mortality has also been incorporated into the model, informed by Office for National Statistics figures for Wales[23]. Risk of adverse events is also informed by the GRIPHON study for selexipag[13]; inhaled iloprost is assumed to have the same adverse event profile for all events other than pneumonia and sepsis which differ between treatments. FCI is a symptomless state

and is therefore excluded from the model. Heart and lung transplantation has also been excluded; the company justifies this approach on the basis of scarcity of donors in the UK, the lack of data to inform its inclusion, and given that selexipag does not influence the risk of transplant. The probability that a patient will need hospitalisation after a mortality or morbidity event in the model is dependent on their FC state: in FCII and FCIII the probability is 47.4% (informed by the GRIPHON study[13]); in FCIV it is 100% (informed by two clinical expert interviews).

Cost of treatment in the model includes event costs (i.e. resource use associated with mortality/morbidity, morbidity, and/or death), disease management costs stratified by FC state (including GP and outpatient visits, and oxygen therapy), costs associated with severe adverse events, and medicine acquisition and administration costs. The term 'morbidity event' is used to refer to disease progression (a component of the composite endpoint as defined in the GRIPHON study) where the patient does not die (i.e. non-fatal morbidity event), whereas a 'mortality event' includes death occurring with or without a prior morbidity event. Resource use associated with events and disease management, and medicine administration (including hospitalisation and provision of a nebuliser for inhaled iloprost; and hospitalisation, home visits and consumables for intravenous epoprostenol given in the FCIV state) is estimated by three clinical experts based in Scotland and England. Unit costs are taken from NHS Reference Costs 2014/2015 and the Personal Social Services Research Unit's unit costs of health and social care 2016[24,25]. List price has been used in the base case for all medicines other than selexipag which is associated with a Wales Patient Access Scheme (WPAS) discount.

Health state utility values were elicited directly from patients with idiopathic PAH (IPAH) or PAH in FCIII or FCIV using the SF-36 questionnaire. Disutility decrements associated with severe adverse events are taken from the literature. Disutility decrements associated with treatment administration (0.11 decrement for inhaled iloprost) are a key model driver and have been informed by a time-trade off study, which is currently awaiting publication[26].

Sensitivity and scenario analyses test the influence of parameter and structural uncertainty on the robustness of the base case results. These explore the impact of varying: the time horizon, the treatment effects for FCIII, relative risk of FC improvement, the proportion of mortality or morbidity events that need hospitalisation, utility value for FC states, disease management costs, treatment disutility decrements associated with inhaled iloprost and epoprostenol, and introducing discontinuation of selexipag in the model.

4.1.2 Results

The results of the base case analysis are detailed in Table 2. Treatment with selexipag is less costly in the base case as a result of lower drug acquisition, adverse event and prostacyclin initiation costs. Selexipag is also associated with an incremental quality-adjusted life year (QALY) benefit of [commercial in confidence figure removed], which is driven by disutility decrements associated with treatment administration. This results in selexipag being the dominant treatment option. The company sensitivity analyses reveal a high degree of sensitivity around: the disutility adjustments for inhaled iloprost; relative risk functional class improvement for both treatments; mortality/morbidity hazard ratio for both treatments; mortality hazard ratio for both treatments. Much of this sensitivity can be largely attributed to the assumptions of equivalence in efficacy. The scenario analyses also show that selexipag continues to dominate when the time horizon is varied between 5 and 50 years, when the hazard ratio for mortality or morbidity is changed to 0.6 and when 6% of patients receiving selexipag discontinue treatment and progress to inhaled iloprost.

Table 2. Results of the base case analysis

	Selexipag	Iloprost	Difference
Total costs	¶¶	¶¶	¶¶
Total life-years	¶¶	¶¶	-
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	**Selexipag DOMINATES**		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
¶¶ commercial in confidence figure removed

Probabilistic sensitivity analyses (Table 3) show that at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, selexipag has a 95.6% and 98.2% chance of being the most cost-effective treatment option, respectively.

Table 3. Results of sensitivity analyses

Scenarios	ICER	PSA £20,000 WTP	PSA £30,000 WTP	Plausibility
Disutility adjustments for inhaled iloprost a) lower bound b) upper bound	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	This scenario explores the confidence intervals associated with this parameter.
RR FC improvement inhaled iloprost a) lower bound b) upper bound	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	This scenario explores the impact of varying the input by ± one standard deviation.
MM HR selexipag a) lower bound b) upper bound	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	This scenario explores the confidence intervals associated with this parameter.
RR FC improvement selexipag a) lower bound b) upper bound	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	This scenario explores the confidence intervals associated with this parameter.
Mortality HR selexipag a) lower bound b) upper bound	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	This scenario explores alternative assumptions for mortality HR. The confidence intervals for this input are wide, which introduces uncertainty.
Mortality HR inhaled iloprost a) lower bound b) upper bound	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	This scenario explores alternative assumptions for mortality HR. The confidence intervals for this input are wide, which introduces uncertainty.
Cost of inhaled iloprost a) 6 ampoules per day b) 9 ampoules per day	¶¶ ¶¶	¶¶ ¶¶	¶¶ ¶¶	The SPC dosing recommendations range from 6 ampoules per day to 9 ampoules per day. These scenarios may therefore offer plausible alternatives to the base case.

FC: functional class; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; MM: morbidity and mortality; PSA: probabilistic sensitivity analysis; RR: relative risk; SPC: Summary of Product Characteristics; WTP: willingness to pay
Note that the PSA values have not been verified by AWTTC.
¶¶ commercial in confidence information removed

4.1.3 AWTTC critique

The strengths and limitations of the CUAs are listed below.

Strengths

- The submission gives a detailed, transparent account of the methods and data sources used in the base case analysis.
- A variety of scenarios and sensitivity analyses have been considered to test the robustness of the base case results.

Limitations

- The company proposes that it is not feasible to construct a network meta-analysis due to a lack of studies matching the full set of eligibility criteria and across study heterogeneity in potential treatment effect modifiers and primary endpoints. The company further proposes that it was not possible to match-adjust to reduce cross study differences. The model therefore assumes equivalent efficacy, as well as equivalence in risk of severe adverse events, between selexipag and inhaled iloprost based on naive comparisons. This creates uncertainty in terms of both the cost and effects that feed into the base case CUA. However, the company claims that the assumption of equal equivalence is a conservative approach, given the naïve comparisons and the high discontinuation rates associated with inhaled iloprost.
- The key model outcome measure, quality-adjusted life years, is primarily driven by disutility associated with treatment administration route. Treatment administration disutility is informed by an unpublished time-trade-off study. Whilst time trade-off is a long-standing methodology used in health economics to elicit preferences and value health states, this study is subject to a number of limitations. Given that the model is most sensitive to these utilities, this introduces notable uncertainty around the base case findings.
- Four survival distributions were tested, namely: log normal, log logistic, exponential and Weibull. Visual inspection and statistical tests were used to compare the fit of the distributions to the observed trial data. The GRIPHON study data were compared with the data from two registries[21,27] and a clinical expert was also consulted to seek further validation of choice of parametric function. This strengthens the approach taken for extrapolation in the longer term. However, extrapolation over the long term is inherently associated with uncertainty.
- A pragmatic literature review was conducted by the company to inform disutility values associated with severe adverse events. This approach lacks the rigour of a systematic review and, together with the assumption of equivalence in adverse events, introduces uncertainty in the utility function.
- Risk of death is effectively double counted in the model. However, this applies to both treatment arms, and does not therefore introduce bias.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC identified one published ISPOR abstract[28] (co-authored by the submitting company) which focused on the treatment comparisons included in this submission for patients with PAH in Sweden. The incremental QALY gain reported for selexipag is 0.88 QALYs. However, the abstract lacked sufficient detail to determine why this differs from the QALY gain of [commercial in confidence figure removed] reported in this submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

The company estimates that there are 109 people with PAH in Wales. This prevalence estimate is based on the findings from the national audits of pulmonary hypertension in the UK which reports a total of 6,433 patients with pulmonary hypertension in the UK[29]; 3.68% of whom are treated in Wales (n = 237)[30]. Of these 237 patients, it is assumed that 46% have PAH (n = 109)[31]. The proportion of these patients who are reported to be non-vasoreactive is 56% (n = 61)[32] and based on the 6th national audit (2015), it is estimated that 73% of non-vasoreactive patients are classified as FCIII (n = 45)[31]. Expert clinical opinion sought by the company suggests 70% of these patients are prescribed dual endothelin receptor antagonist plus phosphodiesterase type 5 inhibitor combination therapy (n = 31), and that 67% of those patients are likely to have insufficiently controlled PAH (n = 21). Based on the national audit data and clinical expert opinion, it is estimated that there is an annual incidence of 3 patients in Wales whose PAH is insufficiently controlled on dual combination therapy. Combining incidence and prevalence estimates with a mortality rate of 10.9% (which is based on parametric survival estimates informed by the GRIPHON study), results in a total of 22 patients eligible for selexipag in Year 1, increasing to 34 patients in Year 5. These forecasts are a result of all patients who were receiving inhaled iloprost being switched to selexipag, in addition to an assumption that from Year 2 onwards a few more patients, based on market share forecasts, will be treated year on year due to preference for the new mode of delivery (i.e. market expansion due to patients now choosing treatment initiation with the oral formulation as opposed to not initiating treatment when only an inhaled formulation was available). The company forecasts that selexipag will have a market share of 25% in Year 1, rising to 50% in Year 5.

Scenario analyses explore the impact of: selexipag replacing only current inhaled iloprost-treated patients; selexipag treating incident patients only; adjusting the forecast for market share by ±10% [commercial in confidence figures removed]; and exploring the impact of alternative dosing for inhaled iloprost.

5.1.1 Results

The estimated budget impact is presented in Table 4, the cost of selexipag is based on an approved WPAS. The company estimates that the introduction of selexipag would lead to net medicine acquisition cost savings of [commercial in confidence figure removed] in Year 1, after which additional costs would be incurred, ranging from a cost of [commercial in confidence figure removed] in Year 2 to [commercial in confidence figure removed] in Year 5. In the scenario analyses, where selexipag replaces only current inhaled iloprost treatment, this results in cost savings ranging from [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5. In the second scenario, where selexipag is assumed to only be used in treating incident patients, this results in a positive cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. When market share predictions are increased by 10% this results in a positive cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. When the market share forecast is reduced by 10% this results in a cost saving of [commercial in confidence figure removed] in Year 1, increasing to a positive cost of [commercial in confidence figure removed] in Year 5. When a dose of six ampoules is used in the model for iloprost this produces a cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. When nine ampoules of iloprost are modelled, this results in cost savings of [commercial in confidence figure removed] in Year 1, increasing to a positive cost of [commercial in confidence figure removed] in Year 5.

Analysis of the impact on NHS resource use suggests a saving of £1,508 in Year 1; with no further savings to be realised over the following four years.

Table 4. Company-reported costs associated with use of selexipag for the treatment of PAH in adult patients in FCIII whose PAH is insufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (Indication covered in this submission)	22	25	28	31	34
Uptake (%)	25%	25%	35%	35%	50%
Treated patients	5	6	10	11	17
Medicine acquisition costs in a market without selexipag (Treated patient numbers remain static year on year; 5 patients)	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market with selexipag (Market expansion due to incident patients choosing to initiate treatment following introduction of selexipag)	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶

Treated patient numbers may not compute due to rounding.
¶¶ commercial in confidence figure removed.

5.1.2 AWTTC critique

The budget impact analyses are characterised by both strengths and limitations, the most salient of which are detailed below:

- The submission gives a detailed, transparent account of the methods and data sources used in the budget impact analysis.
- Scenario analyses explore the impact of varying structural assumptions.
- Market share has been forecast based on previous product launches and uptake in this disease area, together with anticipated capacity constraints (e.g. limited specialist centres and clinical specialists). As is always the case for market share predictions, it is uncertain whether or not these predictions are likely to be realised.
- The number of patients eligible for selexipag has been estimated based on audit data and clinical opinion sought in England and Scotland. It is uncertain whether the clinical expert opinion in Wales is reflective of that in England and Scotland.
- The mortality rate included in the model is based on parametric survival estimates, and is therefore subject to uncertainty.

5.2 Comparative unit costs
Comparative unit costs based on list price are provided in Table 5.

Table 5. Examples of medicine acquisition costs

Regimens	Example doses	Approximate cost per patient per annum
Selexipag	200 micrograms to 1,600 micrograms orally twice daily	£39,000
Inhaled iloprost	2.5 micrograms to 5 micrograms inhaled via a nebuliser 6 to 9 times daily	£29,614 to £44,020
See relevant Summaries of Product Characteristics for full licensed indications and dosing details. Costs are based on Monthly Index of Medical Specialities list prices as of 4 December 2017. This table does not imply therapeutic equivalence of medicines or the stated doses. Dosing requirements are based on a 365.25 day year. Costs are calculated on a pack basis, rather than individual tablet/ampoule cost.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply
AWTTC is of the opinion that, if recommended, selexipag (Uptravi®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that selexipag (Uptravi®) may be supplied by a home healthcare provider specified by a specialist pulmonary hypertension centre.

6.2 Ongoing studies
The company's submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review
This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search
Date of evidence search: 6–7 November 2017
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases
Selexipag does not have European Medicines Agency (EMA) designated orphan status. The company estimates that the number of patients with FCII–III PAH (full licensed indication) in Wales is 48. This is different to the patient numbers reported in section 5.1 as these are estimates for the subpopulation of PAH FCIII. AWTTC considers selexipag eligible to be appraised as a medicine developed specifically to treat rare diseases as the full population of the licensed indication is equivalent to the population for ultra-orphan status (≤ 1 in 50,000 in the UK [≤ 60 patients in Wales]).

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 6) if they consider selexipag is an ultra-orphan medicine.

Table 6. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers	People with PAH have increasingly debilitating symptoms, increased morbidity, frequent hospitalisations and ultimately develop right heart failure leading to premature death. People in FCIII are at intermediate risk (5–10%) of disease progression and estimated 1-year mortality[6] , and live for an average of 2.5 years if left untreated[33]. PAH places a significant burden on the lives of patients and their carers. Patients have reduced mobility and ability to do everyday tasks and they report a reduced quality of life[34]. Some people may have to stop working, some need help with activities of daily living and some need help administering medicines. A survey of carers of people with PAH reported that 29% of them had to stop working or change their working conditions as a result of caring for someone with PAH; 13% had to stop work completely[34].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	People whose FCIII PAH is not sufficiently controlled with an endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor are currently treated with prostanoid therapies, such as inhaled iloprost. These can often be difficult to administer: inhaled iloprost is administered using a nebuliser up to nine times per day for 5–10 minutes each time. In addition, people need to be trained to make up and administer the treatment, usually during a 3–4 day in-patient stay. Selexipag is an oral tablet, taken twice daily.
Whether the medicine can reverse or cure, rather than stabilise the condition	Selexipag does not reverse or cure PAH. The only cure for PAH is a lung or heart/lung transplant.
Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy), and that this “definitive” therapy is currently in development	Selexipag does not bridge a gap to a definitive therapy.
The innovative nature of the medicine	Selexipag is the first orally available prostacyclin for the treatment of PAH in people with FCII or III. The company suggests that its longer half-life reduces the frequency of administration compared with nebulised prostacyclin analogues: twice daily instead of up to nine times daily. As an oral tablet selexipag also has a more convenient mode of administration than inhaled iloprost, however, specific comparative evidence has not been presented. The company also reports that selexipag does not appear to lead to IP receptor down-regulation over time and is therefore less likely to induce tachyphylaxis[35]
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	The company reports that feedback from clinicians is that the availability of selexipag will provide an oral option for people who have problems administering inhaled iloprost. The company suggests that the convenience of an oral twice-daily tablet would give people more freedom because they would no longer need to plan ahead when going out (as needed with nebulised therapy), and that some people with PAH may be able to return to work or education. The company cited the results of a study performed to elicit utility values associated with different routes of administration, which showed a patient preference for oral treatment[26]. The study, conducted in the UK general public, showed a difference of 0.11 in time trade-off scores between oral and inhaled modes of administration.

NMG/AWMSG considerations	AWTTC comments
Added value to the patient's family (e.g. impact on a carer or family life)	The company suggests that oral selexipag tablets could potentially allow a person to administer their treatment independently, thus reducing the burden on carers and family members. It may also reduce the emotional and physical burden on family and carers by delaying the time to disease progression and reducing the risk of hospitalisation.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics & Toxicology Centre; FCII: WHO functional class II; FCIII WHO functional class III; NMG: New Medicines Group; PAH: pulmonary arterial hypertension; QALY: quality-adjusted life year	

GLOSSARY

World Health Organization classification of functional status of patients with pulmonary hypertension[36]

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.

Risk assessment in pulmonary arterial hypertension[6]

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 VO_2 > 15 ml/min/kg (> 65% predicted) VE/VCO_2 slope < 36	Peak VO_2 11–15 ml/min/kg (35–65% predicted) VE/VCO_2 slope 36–44.9	Peak VO_2 < 11 ml/min/kg (< 35% predicted) VE/VCO_2 ≥ 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 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	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2	RAP > 14 mmHg CI < 2.0 l/min/m^2
BNP: brain natriuretic peptide; CI: cardiac index; CMR cardiac magnetic resonance; NT-proBNP: N-terminal pro-brain natriuretic peptide; 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			

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