Cost-effectiveness of 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.

The NCPE assessment of selexipag has not demonstrated any additional clinical benefit in PAH compared with the comparator, inhaled iloprost. As an oral therapy, selexipag may be more convenient than inhaled therapies which can be quite time-consuming as a result of the frequency and length of the inhalations, as well as the time required for drug preparation and device maintenance. There is no evidence to demonstrate improved persistence and adherence with selexipag compared with inhaled iloprost. The incremental cost-effectiveness ratio far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that selexipag not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Actelion Pharmaceuticals UK Ltd) economic dossier on the cost effectiveness of selexipag (Uptravi®). The NCPE uses a decision framework to systematically assess whether a technology is clinically effective and cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **May 2018**

In October 2017, Actelion Pharmaceuticals UK Ltd submitted a dossier of clinical, safety and economic evidence in support of selexipag, 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. Selexipag is a selective prostacyclin receptor agonist distinct from prostacyclin and its analogues. Stimulation of the prostacyclin receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. The recommended starting dose is 200 mcg given twice daily, approximately 12 hours apart. Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 mcg given twice daily to 1,600 mcg given twice daily. It is anticipated that selexipag will primarily be used in triple combination therapy with an ERA and a PDE5i for the treatment of PAH in adult patients in WHO functional class (FC) II–III (low or intermediate risk), who are insufficiently controlled on dual therapy with an ERA plus a PDE5i. Selexipag is the first oral medicine for the treatment of PAH to target the prostacyclin pathway to be licensed in Ireland. Selexipag it is not a substitute for injectable therapies as it has not been studied in high-risk patients in WHO FC IV.

1. Comparative effectiveness of selexipag

- The effect of selexipag on progression of PAH was demonstrated in a multi-centre, long-term (maximum duration of exposure approximately 4.2 years), double-blind, placebo-controlled, parallel-group, event-driven Phase 3 study (the GRIPHON study) in 1,156 patients with symptomatic (WHO FC I–IV) PAH. Patients were randomised to either placebo (N = 582) or selexipag (N = 574) twice daily. The primary study endpoint was the time to first occurrence of a morbidity or mortality (M/M) event up to end of treatment, defined as a composite of death (all causes); or hospitalisation for PAH; or progression of PAH resulting in need for lung transplantation or balloon atrial septostomy; or initiation of parenteral prostanoid therapy or chronic oxygen therapy; or other disease-progression events (patients in WHO FC II or III at baseline) confirmed by a decrease in 6-minute walk distance (6MWD) from baseline (≥ 15%) and worsening of WHO FC or (patients in WHO FC III or IV at baseline) confirmed by a decrease in 6MWD from baseline (≥ 15%) and need for additional PAH-specific therapy. Treatment with selexipag resulted in a 40% reduction (24.4% vs 36.4%;

hazard ratio (HR) 0.60, 99% CI: 0.46, 0.78; p < 0.0001) in the occurrence of M/M events up to 7 days after last dose compared to placebo. Despite a statistically significant and clinically relevant benefit as measured by the primary endpoint, the interpretation of results of composite endpoint is challenging when individual components are not associated with equal importance. Despite a primary outcome of "morbidity or mortality events", the beneficial effect of selexipag was primarily attributable to a reduction in hospitalisation for PAH and a reduction in other disease-progression events. No significant difference was observed between selexipag and placebo for the risk of PAH worsening (p = 0.5342). There was no beneficial effect on all-cause mortality or quality of life. Mortality was numerically higher in the selexipag group compared to the placebo group (46 vs. 37 cases, HR 1.17). The observed increased mortality in the primary M/M endpoint analysis is most likely due to informative censoring and/or a chance finding and was considered by the CHMP of the EMA to lack biological or clinical plausibility.

- Post-hoc subgroup analysis of the GRIPHON study was required in order to demonstrate clinical efficacy in the population in which selexipag is expected to be used, as while the vast majority of patients were in FC II-III, just 33% of patients were on dual therapy with an ERA and PDE5i. This analysis demonstrated consistency in the efficacy of selexipag in this subgroup, though analyses should be interpreted with caution as patients were not stratified according to subgroups at baseline and GRIPHON was not powered to show differences within subgroups.
- The most relevant comparator for selexipag is the inhaled prostacyclin therapy, iloprost. There is no evidence to demonstrate comparative effectiveness with iloprost. In the economic evaluation, the applicant assumed the treatment effect for inhaled iloprost to be equal to selexipag. Differences between the patient populations and outcomes studied in the selexipag and iloprost studies make a robust comparison very difficult.

2. Safety of selexipag

- A challenge with prostacyclin therapy is the requirement for up-titration of initial doses to achieve the clinically appropriate dose for each individual patient, whilst managing potential side-effects associated with activation of the prostacyclin pathway. Selexipag was generally well tolerated and exhibited the typical AE profile

known for the class of prostacyclin (analogues). The most commonly reported adverse reactions are headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing. These reactions are more frequent during the up-titration phase. The majority of these reactions are of mild to moderate intensity, and transient or manageable with symptomatic treatment.

3. Cost effectiveness of selexipag

Methods

- A cost-utility analysis, comparing selexipag with inhaled iloprost in adult patients with PAH in FCIII who are insufficiently controlled with an ERA plus a PDE5i, from the perspective of the Irish Health Services Executive, was submitted by the applicant. On request from the NCPE, the applicant updated the submission to include the cohort of patients in both FC II and III.
- The cost effectiveness model was a patient-level, micro-simulation following a Markov approach. The NCPE review group was critical of the applicant's choice of model, being unnecessarily complex at the expense of limiting the range of feasible analyses, particularly probabilistic analyses. The model comprised of health states based on FC I-IV and an absorbing dead state. Patients enter the model and initiate selexipag or comparator therapy in FCII or III, and may experience FC improvement or deterioration (based on the observed treatment effect for selexipag on the M/M outcome from the GRIPHON trial subgroup of interest) or die (based on the GRIPHON trial) during the first cycle after treatment initiation. In subsequent cycles, patients can only deteriorate. Depending on patients' FC at the time of deterioration, treatment switches to best supportive care, inhaled iloprost or IV epoprostenol are assumed.Patients are at risk of death during each cycle, based on data from the GRIPHON trial. Heart and lung transplant was not included. Parametric models were used to estimate the per-cycle transition probabilities for M/M and for mortality events. Discontinuation due to adverse events was not included in the model due to lack of data. This was considered by the NCPE review team to be a major limitation of the model, given the high rates of discontinuation reported in the GRIPHON trial, and in observational studies of inhaled iloprost. The applicant was requested to include discontinuations due to AEs in the model, in line with the available data.
- The primary health outcome of the model was the quality adjusted life year (QALY)

as per national guidelines. A study sponsored by the applicant was used to inform the quality of life decrements (disutilities) associated with method of treatment administration. Utility differences compared to the oral therapy showed that there are disutilities associated with the inhaled, subcutaneous, and intravenous continuous modes of treatment administration. Disutilities were −0.11 for inhaled, −0.26 for subcutaneous, and −0.30 for intravenous administration. The disutility values have a critical impact on the cost effectiveness of selexipag, given that the efficacy of selexipag and iloprost is assumed to be equivalent. Resources and costs were estimated by a UK Key Opinion Leader interview conducted by the applicant, and included health state costs associated with FC, M/M event costs with and without hospitalisation, severe AE costs, and non-hospital death costs.

Results

- A number of adjustments were made to the applicant's based case to account for errors in the calculation of drug acquisition costs. The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's adjusted base case was €170,899/QALY (incremental cost €50,113; incremental QALY 0.29). The inputs into the applicant's probabilistic analysis reflected deviation from the assumption of equivalent efficacy. The probabilistic analysis was therefore difficult to interpret in the context of the base-case model. The NCPE review group did not consider that the applicant's submitted model and resulting ICER to be a complete reflection of the cost effectiveness of selexipag, and implemented a number of changes to the model based on plausible alternative assumptions and explored the impact of the relevant population and iloprost dose, alternative utility values and treatment discontinuation rates on cost effectiveness results. In the population most relevant to the decision problem i.e. eligible patients in both FCII and FCIII insufficiently controlled with an ERA plus a PDE5i, the ICER is €344,043/QALY. Further changes based on more realistic dosing of inhaled iloprost increased the ICER to €402,530/QALY.

4. Budget impact of selexipag

- Selexipag is submitted for reimbursement under the High-tech drug scheme. The proposed ex-manufacturer price of selexipag is €9333.33 for the titration pack (140

tablet pack of 200mcg tablets) and €4000 for the maintenance pack (60 tablet pack available in a range of doses from 200mcg to 1600mcg tablets, flat-priced). The cost of the initial 3-month titration phase is assumed to be €24,256, assuming no wastage. The annual reimbursement cost for maintenance treatment is €49,918 per person.

- Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €21.2 million. Correction of inappropriate assumptions regarding the timing of mortality increases this figure to €23.7 million. The uptake of selexipag is assumed to displace the use of inhaled iloprost, resulting in net savings leading to a net budget impact in the order of €14-15 million over five years.

5. Conclusion

- The NCPE assessment of selexipag has not demonstrated any additional clinical benefit in PAH compared with inhaled iloprost. As an oral therapy, selexipag may be more convenient than inhaled therapies which can be quite time-consuming as a result of the frequency and length of the inhalations, as well as the time required for drug preparation and device maintenance. There is no evidence to demonstrate improved persistence and adherence with selexipag compared with inhaled iloprost. The incremental cost-effectiveness ratio far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that selexipag not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.