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Clinician and Patient Involvement Group (CAPIG)
Summary of meeting held on 26 April 2018
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

Marketing authorisation holder

Actelion Pharmaceuticals UK Ltd.

Licensed indication

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.

Company's proposed positioning (if any)

For use 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. Severity of the condition

Pulmonary arterial hypertension (PAH) is a serious, progressive condition in which there is raised blood pressure in the blood vessels supplying the lungs, resulting in damage to the heart and lungs. All people with PAH will experience increased morbidity, frequent hospitalisations and ultimately develop right heart failure leading to early death. Despite advances in treatment, PAH is a life-shortening condition, with 48% of people surviving for only four years after diagnosis.

PAH affects people of all ages and some may have a number of co-morbidities. People with PAH develop shortness of breath, extreme tiredness, weakness and chest pain; these symptoms worsen as their disease progresses and severely affect their day-to-day life. People living with PAH can experience continual breathlessness: this has a constant physical and emotional impact on their quality of life. The symptoms of PAH can vary widely from one day to the next; it is a disease of great uncertainty for patients and their families and carers. As their disease progresses and symptoms become worse some people may have to stop working, some may need help with activities of daily living, some may need help administering medicines and many will need frequent hospitalisations.

In the 2016 Pulmonary Hypertension Association UK survey, 60% of respondents said that pulmonary hypertension had a major impact on their quality of life.

The prognosis is poor. Because PAH is progressive and ultimately terminal, treatment aims to improve symptoms and quality of life, and to achieve a low-risk status to reduce the risk of disease progression. People with PAH FCIII have symptoms that occur with less than ordinary effort, such as washing, dressing or preparing a meal. They are at intermediate risk (5–10%) of disease progression and estimated 1-year mortality, and may live for an average of 2.5 years if their disease doesn't respond to treatment or if they have no access to treatment.

People with PAH FCII and FCIII are mainly treated with oral medicines targeting the endothelin and nitric oxide pathways: endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. These are used first-line either alone or in combination. For people whose PAH is not sufficiently controlled by a combination of an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor, medicines that target the prostacyclin pathway are added to other treatments. These include inhaled or intravenous prostanoids, such as iloprost. These treatments can be effective but are often difficult to administer (see Section 3b).

PAH has a high burden of symptoms and places a significant burden on the lives of patients' families and carers. People with PAH may need help with activities of daily living, healthcare visits and some need help with 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. If the person they care for feels socially isolated, partners and carers often find it difficult to go out or to leave them alone for prolonged periods.

2. Unmet need

People whose PAH doesn't respond to dual therapy have the option to begin triple therapy by adding in a medicine targeting the prostacyclin pathway. Currently these are intravenous prostacyclins or inhaled iloprost; both are difficult to administer.

The lack of an oral medicine targeting the prostacyclin pathway to treat PAH is a significant unmet need. Because of the administration challenges of current prostanoid treatments, these are often delayed or sometimes never started. Some people with PAH who are currently eligible to have triple therapy choose not to have it because of the time and inconvenience of inhaled iloprost or the difficulties and high level of risk associated with intravenous prostanoid treatment and the long-term management of these regimens. Some older patients are put off starting treatment because they feel it is too complicated for them and the inhaled and intravenous treatments are not suitable for some patients due to co-morbidities. These patients are currently offered best supportive care. The 7th annual report of the National Audit of Pulmonary Hypertension showed that only 2% of patients with FCIII PAH received a prostanoid within one month of death, and only 10% ever received a prostanoid.

Selexipag is the first orally available prostacyclin for treating PAH in people with FCII or FCIII. As an oral tablet it has a more convenient mode of administration than inhaled iloprost. Taking selexipag tablets twice-daily is more convenient than administering inhaled iloprost 6–9 times a day, or an intravenous prostacyclin treatment using a Hickman line. Selexipag would provide a potential option for people with PAH for whom current third-line options are unsuitable and for whom there are currently no other treatment options. The patient organisation reported that in some countries where selexipag is available it has met a significant unmet need for those patients with co-morbidities for whom the currently available treatments are not suitable.

3. Added value of the medicine for the patient:
3a. How would this medicine be expected to add value to the patient's wellbeing and experience of care?

Selexipag is an easy-to-use oral alternative for people with PAH FCIII who need treatment with a prostacyclin as well as an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor. Selexipag would enable patients to take an all-oral combination treatment.

Oral selexipag has a less complex administration regimen than inhaled iloprost. Selexipag may therefore provide people with more freedom and flexibility as they

would not need to plan ahead to schedule-in treatment administration. Some people may be able to return to work or education, thereby reducing the burden on family members and carers. This may have societal benefits and significantly improves a patient's quality of life and self-esteem.

People who can't use inhaled iloprost because of physical or mental dysfunction, or problems with manual dexterity, may be able to take oral selexipag. This would provide these patients with a third-line treatment option. There is widespread support amongst the PAH specialist community for selexipag as a treatment option when patients are unable to have inhaled iloprost.

3b. How is this medicine better than current treatments?

Selexipag is the first oral tablet available for treating PAH in people with FCII and FCIII PAH. It is taken orally, twice daily which may reduce administration burden to patients and carers. Oral selexipag is stable in the bloodstream over 24 hours compared with inhaled and intravenous iloprost which have a much shorter half-life. This may reduce the variability of PAH symptoms and reduce the fluctuation in the adverse event profile. These factors, as well as the less frequent administration, may improve compliance and result in the better management of PAH in these patients. Welsh clinical experts highlighted that selexipag may provide a more convenient treatment option for people with PAH FCIII who opt out of triple therapy because they can't use the current treatments, or can't travel to specialist centres to receive them.

Inhaled iloprost is given using a nebuliser 6–9 times a 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. It was recognised that inhaled iloprost is an effective treatment for some FCIII PAH patients but that the administration of inhaled iloprost is often difficult for people with manual dexterity problems or certain co-morbidities. Other patients may need considerable support from carers and for some people, the complex administration regimen of inhaled iloprost may lead to poor compliance.

Intravenous prostacyclins have a half-life of 5–6 minutes in the bloodstream; therefore continuous administration is needed. Treatment is given using a Hickman line (a central venous catheter) and patients need to spend several days in hospital learning how to self-administer the treatment. This line into the chest remains in place for extended periods and patients must take constant care to keep it clean and to avoid dislodging it. There is a high risk of infection, which would result in urgent hospitalisation, sometimes for several weeks. Patients often worry about intravenous treatments failing and commonly feel immense anxiety about having a Hickman line. Its presence hampers physical activity and makes personal intimacy difficult. Patients, particularly younger people, feel self-conscious of the line and pump attached to their body, and it can trigger withdrawal and social isolation.

Administering prostaglandin treatment subcutaneously also presents major challenges, including high levels of pain at the site of the injection. It can also affect the patient's psycho-social wellbeing.

Selexipag could provide a third-line treatment option for people with PAH for whom currently available prostaglandins are not suitable.

3c. Does this medicine have the potential to make a significant and substantial impact on health related benefits?

A new oral prostaglandin treatment has the potential to be 'revolutionary' for patients. It could remove all the healthcare risks and psycho-social problems associated with injected and inhaled prostaglandins. It could also open up the possibility of treatment with this class of medicines to people who have been excluded from them because of the complexity of administering the current treatments. Clinicians have also said that the availability of selexipag will provide an oral option for people who have problems administering inhaled iloprost.

Selexipag is the first oral medicine to target the prostacyclin pathway. Its longer half-life reduces the frequency of administration compared with nebulised prostacyclin analogues: twice daily instead of up to nine times daily. This may improve compliance with treatment which may result in the better management of PAH. Taking an oral treatment could give patients the confidence to go out more, or help their partners or carers to leave them alone for longer periods. It is also likely to reduce anxiety about the risks of having intravenous and inhaled prostaglandins, and the pain associated with those treatments; for example, being in hospital for weeks because of an infection when using a Hickman line. Selexipag may enable a patient to feel more in control of their PAH and therefore improve a patient's quality of life.

The convenience of an oral twice-daily tablet could give people more freedom and flexibility because they would no longer need to plan ahead when going out (as needed with nebulised therapy). Patients might be able to travel more easily and some people with PAH may be able to return to work or education.

Actelion Pharmaceuticals UK Ltd provided a patient's story that described how a PAH patient in Europe who was afraid of missing their son grow up was now taking selexipag. The patient reported that the medicine has given them hope, and enabled them to travel by aeroplane, something that was previously not an option. The patient is now able to travel the world with their young son and go back to work. The patient described the medicine as feeling like "a life saver".

4. Added value of the medicine for the patient's family or carers

Patients should be able to administer their selexipag treatment independently, and won't need help to prepare and administer it. This will reduce the burden of medicine administration on patients and carers. Patients won't be limited to having to administer treatment at home, so may have more flexibility for their work and social lives.

Selexipag may reduce the emotional and physical burden on family and carers by delaying the time to disease progression and reducing the risk of hospitalisation. If their disease is more stable, patients will need fewer hospitalisations; therefore selexipag may result in "hidden cost savings".

5. What is the most appropriate position for the medicine in the pathway of care for the condition? Does this differ from the company's proposed positioning?

The use of selexipag to treat PAH in people in Wales would be directed by national UK centres, for example, the Hammersmith Hospital and Royal Free Hospital in London. Clinicians in Wales agreed that the most likely use of selexipag would be as add-on therapy in people whose PAH is not sufficiently controlled on dual therapy (endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor) and who are unable to travel to specialist centres for treatment or for whom inhaled iloprost or subcutaneous or intravenous prostanoid treatments are unsuitable. In Wales, inhaled iloprost is offered to most people rather than intravenous epoprostenol.

In line with clinician feedback the company has restricted its submission for use as a triple combination therapy for people whose PAH FCIII is insufficiently controlled on dual therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor.

6. Are there specific patient groups for whom the medicine is particularly beneficial? If so, please specify

The company proposes that people with PAH FCIII that is insufficiently controlled on dual therapy are the most likely group to benefit from this medicine.

Older patients and patients who can't use inhaled iloprost because of physical or mental dysfunction, or problems with manual dexterity, may be able to take oral selexipag. Selexipag could also benefit patients who currently opt-out of triple therapy because of the difficulties involved with administering the current treatment options, or due to the problems associated with travelling to the specialist centres. This may overcome some issues with inequity.

7. Are there any important considerations in relation to treatment delivery (e.g. how treatment should be monitored, how long it should be continued etc.)?

Selexipag is an oral tablet, given twice daily. There is no complex delivery system needed, and no burdensome monitoring requirements.

8. Other considerations

Selexipag treatment should be initiated by specialist centres but patients would not be required to stay in hospital. This should benefit the healthcare service compared with iloprost, for which patients tend to stay in hospital for 3–4 days to start treatment and learn how to self-administer it.

9. Is there a key factor, or combination of factors, that would justify this medicine being available in NHS Wales?

- Results from the GRIPHON study show that selexipag has long-term, meaningful clinical benefits and is well tolerated in people with PAH FCII–FCIII. Selexipag treatment reduced the number of hospitalisations for PAH. This could result in savings in healthcare costs.
- Selexipag is the first and only oral prostanoid therapy licensed for PAH. The longer half-life of selexipag may reduce the variability of PAH symptoms, and thereby reduce the uncertainty associated with the disease. This may improve treatment compliance.
- Currently available treatments have more complex routes of administration which can cause a significant physical and emotional burden to the patient and their families and carers.
- Selexipag may be more convenient to take than inhaled iloprost. It may reduce the restrictions on a patient's family, social and working lives caused by the current treatment regimens. It could give patients more freedom and flexibility, and may enable patients, and their carers, to return to work or education.
- There is an unmet need for an oral prostanoid treatment. Some people with reduced mental function or dexterity problems are unable to administer current prostanoid treatments and therefore have no other third-line treatment option. Some people in Wales choose not to have third-line treatment because of the difficulties associated with the current treatments.
- Selexipag treatment could reduce morbidity or mortality and improve quality of life for patients and reduce the burden and stress for carers compared with

current prostanoid therapies. These improvements in quality of life were not captured in the quality of life data presented from the pivotal (GRIPHON) study.

One patient organisation involved in compiling this response had received funding from pharmaceutical companies in the past two years, including funding from Actelion Pharmaceuticals UK Ltd.