NEW DRUGS

Selexipag

Approved indication: pulmonary arterial hypertension

Uptravi (Actelion)
200, 400, 600, 800, 1000, 1200, 1400 and 1600 microgram film-coated tablets

An increase in the pulmonary artery blood pressure may be idiopathic or related to conditions such as congenital heart disease, connective tissue disease or chronic obstructive pulmonary disease. Pulmonary arterial hypertension leads to right ventricular dysfunction. Patients with pulmonary arterial hypertension can be classified according to how much it limits their activity. The median survival in the highest class (IV) is only about six months.

Several signalling pathways are involved in the pathophysiology of pulmonary arterial hypertension and are therefore the target of drug therapy. For example, bosentan is an endothelin antagonist, sildenafil acts on the nitric oxide pathway, while epoprostenol is an agonist at the prostacyclin receptor. Stimulating this receptor causes vasodilation.

Epoprostenol requires intravenous infusion while iloprost, another prostacyclin analogue, needs to be nebulised. There was therefore a need for a more convenient way to act on the prostacyclin pathway.

Selexipag is a prostacyclin receptor agonist but has a different structure from the prostacyclins and it can be given by mouth. After it is absorbed selexipag is hydrolysed to an active metabolite. The drug and its metabolite have antiproliferative and antifibrotic effects in addition to vasodilation. As the metabolism of selexipag involves several enzyme systems, including cytochrome P450 and the glucuronosyltransferases, there is a potential for pharmacokinetic interactions, but their clinical relevance is unclear. Concentrations of selexipag and its active metabolite increase with decreasing liver function. The drug should not be used in patients with severe hepatic impairment. Most of the metabolites are excreted in the faeces.

In a phase II trial 43 patients being treated for pulmonary arterial hypertension were randomised to add selexipag or a placebo. The dose was increased over several weeks and the effect was assessed after 17 weeks. In the 33 patients given selexipag, pulmonary vascular resistance declined to 80.7% of its baseline value. As resistance increased in the placebo group, the outcome was effectively a 30.3% reduction in the mean pulmonary vascular resistance.[1]

A phase III placebo-controlled trial studied 1156 patients with pulmonary arterial hypertension that was either idiopathic, heritable, or associated with connective tissue disease, repaired congenital shunts, HIV, drug use or exposure to toxins. The trial enrolled some untreated patients, and excluded patients treated with prostacyclins. The dose was titrated over 12 weeks to an individualised maintenance dose. The 574 patients randomised to receive selexipag continued it for a median of 70.7 weeks, while the other 582 patients took a placebo for a median of 63.7 weeks.[2]

The primary end point of the trial was death or a complication of pulmonary arterial hypertension. These events occurred in 27% of the selexipag group and 41.6% of the placebo group. This reduction was seen in untreated and previously treated patients.[2]

In the phase III trial 14.3% of the patients stopped selexipag, compared with 7.1% of the placebo group, because of adverse effects. They were more likely to experience symptoms such as headache, pain in the jaw, nausea, vomiting and diarrhoea. As selexipag causes vasodilation some patients may develop hypotension, and there can be an increase in heart rate. Selexipag is therefore contraindicated in patients with severe arrhythmia, coronary heart disease, decompensated heart failure or a recent history of myocardial infarction or cerebrovascular events. Although selexipag can inhibit the aggregation of platelets, it did not increase the risk of bleeding. In the phase III trial anaemia and hyperthyroidism were more frequent with selexipag than with placebo. Selexipag may also cause pain in the extremities, myalgia and eye pain.[2]

All patients will experience adverse effects because the recommended regimen is to titrate the dose until the patient cannot tolerate the drug or the dose reaches 1600 micrograms twice daily. In the phase III trial only about 43% of the patients could be maintained on higher doses (1200–1600 micrograms).[2]

Most of the patients in the trial were already being treated and adding selexipag appeared to only have a small effect on disease progression. From a baseline of 353 m, the distance patients could walk in six minutes increased by a median of 4 m following treatment with selexipag. In the placebo group there was a decrease of 9 m. While selexipag had an advantage over placebo in the phase III trial its effect on survival is uncertain. There were fewer hospitalisations for worsening pulmonary arterial hypertension, but more patients died (4.9% vs 3.1%).[2] Despite these limitations, the oral route of administration is likely to see selexipag being used in the management of pulmonary arterial hypertension.

T manufacturer provided relevant information

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Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

REFERENCES

1. Simonneau G, Torbicki A, Hoeper MM, Delcroix M, Karlócai K, Galiè N, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J 2012;40:874-80. https://doi.org/10.1183/09031936.00137511
2. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373:2522-33. https://doi.org/10.1056/nejmoa1503184

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.