New drugs

Riociguat

Approved indication: pulmonary hypertension

Adempas (Bayer)

0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg film-coated tablets

Australian Medicines Handbook section 6.6

There are several causes of hypertension in the pulmonary circulation. They include pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In pulmonary hypertension there is an imbalance between vasodilators, such as nitric oxide and vasoconstrictors such as endothelin-1. Nitric oxide activates guanylate cyclase which leads to relaxation of smooth muscle. Riociguat is a drug which acts synergistically with nitric oxide and also independently stimulates guanylate cyclase.

Riociguat is taken three times a day. It is converted by the cytochrome P450 system to an active metabolite. There are many potential interactions and co-administration with drugs such as ketoconazole and ritonavir is not recommended. The use of nitrates and phosphodiesterase inhibitors, such as sildenafil, is contraindicated. Riociguat and its metabolites are eliminated in bile and urine. It is not recommended for patients with severe hepatic or renal impairment. As smoking reduces plasma concentrations of riociguat, the doses may need to be adjusted in patients who stop or start smoking during treatment.

The effect of riociguat on exercise tolerance was studied in a phase III placebo-controlled trial of 443 patients. These patients had pulmonary arterial hypertension that was mainly idiopathic or associated with connective tissue disease or congenital heart disease. In one group of patients the dose of riociguat was adjusted up to a maximum of 2.5 mg three times daily while another group was limited to a maximum of 1.5 mg three times daily. After 12 weeks the patients in the 2.5 mg group could walk an extra 30 metres and those in the 1.5 mg group could walk an extra 31 metres. In the placebo group the patients walked on average six metres less than they did at the start of the study. Riociguat also improved cardiac output and mean pulmonary artery pressure. The benefits of treatment were seen irrespective of whether the patients were already taking prostanoids or endothelin-receptor antagonists.[1]

Riociguat has also been studied in 261 patients with chronic thromboembolic pulmonary hypertension. The 173 patients who took riociguat started at a dose of 1 mg three times a day which was adjusted up to a maximum of 2.5 mg three times a day. After 16 weeks their mean six-minute walking distance had increased from 342 metres to 381 metres. This increase of 39 metres was significantly better than the six metre decrease in the placebo group. Cardiac output and pulmonary artery pressure also improved.[2]

Systemic hypotension is a predictable adverse effect of riociguat. Relaxation of smooth muscle could also contribute to complaints of headache, dizziness and dyspepsia. Nausea, vomiting and diarrhoea are also more frequent with riociguat than with placebo.[1,2] Approximately 3% of the patients taking riociguat withdrew from the trials because of adverse events.[1,2]

Riociguat increases the risk of bleeding and anaemia. In the clinical trials serious bleeding affected 2.4% of patients, but none of the placebo group. There was serious haemoptysis in 1% of the patients taking riociguat and one case was fatal.[2]

In animal studies, riociguat was teratogenic so it is contraindicated in pregnancy. It is also contraindicated in lactation.

Extensions of the main clinical trials showed that the increase in walking distance was at least maintained, but the long-term clinical efficacy and safety of riociguat is unknown. Thromboembolic pulmonary hypertension can be treated by pulmonary endarterectomy. Riociguat may be an option for patients who cannot have surgery or who do not improve after surgery. In pulmonary arterial hypertension only 21% of patients have an improvement in their functional class.[2] Although riociguat has a dual mechanism of action it is unclear if this gives it any clinical advantage over the phosphodiesterase inhibitors.

A phase II trial involving 201 patients with pulmonary hypertension due to left ventricular dysfunction found that after 16 weeks the effect of riociguat on mean pulmonary artery pressure was not statistically different from placebo.[3]

T manufacturer provided the product information

REFERENCES *†

1. Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369:330-40.
2. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369:319-29.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary. At the time of publication, there may be limited published data and little experience in Australia of 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.

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3. Bonderman D, Ghio S, Felix SB, Ghofrani HA, Michelakis E, Mitrovic V, et al. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. Circulation 2013;128:502-11.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).