New drugs

Macitentan

Approved indication: pulmonary arterial hypertension

Opsumit (Actelion)

10 mg film-coated tablets

Australian Medicines Handbook section 6.6.2

Pulmonary arterial hypertension can cause dyspnoea on exertion and leads to right heart failure. It can be idiopathic and familial or can be associated with connective tissue diseases and congenital heart disease with repaired shunts.

The available treatments for pulmonary arterial hypertension include calcium channel blockers, endothelin antagonists, phosphodiesterase 5 inhibitors and prostacyclins. Some patients require combinations of these drugs and some will not respond and will need a lung transplant.

Macitentan was developed by modifying the structure of the endothelin receptor antagonist bosentan. It stops endothelin from binding to the endothelin A and B receptors. These receptors are associated with vasoconstriction. Although the maximum plasma concentration is reached eight hours after an oral dose, macitentan has a rapid onset of effect. The drug is metabolised, mainly by cytochrome P450 3A4, to form an active metabolite. Macitentan has a half-life of 16 hours and its active metabolite has a half-life of 48 hours. Most of the metabolites are excreted in the urine.

The main trial of macitentan involved 742 patients with an average age of 45.6 years. Most of the patients had idiopathic or heritable pulmonary arterial hypertension or an associated connective tissue disease. They were randomised to start macitentan 3 mg or 10 mg, or a placebo, once daily. Other treatments for pulmonary arterial hypertension could be continued. The primary end point of the study was a composite of clinically worsening pulmonary arterial hypertension, the need for prostanoids, lung transplant or death.[1]

After a median treatment duration of 115 weeks, one of these events had occurred in 38% of the macitentan 3 mg group, 31.4% of the 10 mg group and 46.4% of the placebo group. Another composite end point of death or hospitalisation for pulmonary arterial hypertension was reached by 26% of the 3 mg group, 20.7% of the 10 mg group and 33.6% of the placebo group. The advantages of macitentan over placebo in these composite end points were statistically significant. There were also improvements in exercise capacity.[1]

Adverse events led to treatment discontinuation in 13.6% of the 3 mg group, 10.7% of the 10 mg group and 12.4% of the placebo group. Compared with placebo, patients taking macitentan 10 mg (the dose recommended in Australia) more frequently developed respiratory infections, headache and anaemia.[1] The blood count should be measured before and during treatment. As liver function can be affected, macitentan is contraindicated in patients with aminotransferase concentrations greater than three times the upper limit of normal. Monthly monitoring of liver function is recommended. Patients with renal impairment may have an increased risk of hypotension or anaemia. Macitentan is teratogenic.

Although exercise tolerance improved with macitentan, the increase was relatively small. At the start of the study the patients could walk an average of 360 metres in six minutes. After six months the patients taking macitentan 10 mg could walk 12.5 metres further.[1] As this change may not be a good surrogate for clinical outcomes, it is important that mortality was studied. However, the drug did not have a significant effect on all components of the primary composite outcome. Most of the benefit was due to macitentan 10 mg reducing the proportion of patients with worsening pulmonary arterial hypertension. Deaths from any cause and from pulmonary arterial hypertension were not significantly different from placebo.[1]

T manufacturer provided the product information

REFERENCE *†

1. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.

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Correction August 2014

The 3 mg dose has been deleted as only the 10 mg dose is available

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.

NEW DRUGS

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).