Pharmacotherapeutic report, summary

Macitentan (Opsumit®) for the indication pulmonary arterial hypertension WHO class II to III.

Recommendation by Zorginstituut Nederland dated 24-03-2014, based on an evaluation by the WAR (Scientific Advisory Committee),

The WAR has approved a pharmacotherapeutic report for the medicine macitentan (Opsumit®; an endothelin-1-receptor antagonist). In determining its therapeutic value, comparison was made with bosentan (also an endothelin-1-receptor antagonist).
They reached the following conclusion.
- the therapeutic value of macitentan, as monotherapy, or in combination (with other drugs for treating PAH), for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, is comparable to that of bosentan.

Medicine. Macitentan 10 mg tablet

Registered indication. "Macitentan, as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population with idiopathic and heritable PAH, PAH associated with connective tissue disorders and PAH associated with corrected simple congenital heart disease".

Posology. 10 mg; once daily.

Mechanism of action. Macitentan is an endothelin-receptor antagonist, active on both ET_A and ET_B receptors. In vitro macitentan is approximately 100-fold more selective for ET_A as compared to ET_B. Macitentan displays a high affinity and sustained occupancy of the ET-receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cells proliferation.

Specific details. Macitentan is registered as an orphan drug. Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH. The efficacy of macitentan is currently being studied in patients with systemic sclerosis and in patients with recurring glioblastoma.

Summary of the therapeutic value

Intended effects. In a placebo-controlled and randomised clinical trial, macitentan was more effective than placebo on the primary efficacy endpoint ('time to first occurrence of a morbidity or mortality event') and the important secondary efficacy endpoint, the 6-minute walking test (6MWT). Based on an indirect comparison, the effect of macitentan on the 6MWT was comparable to that of bosentan. The placebo-corrected mean increase in 6 minute walking distance of 22 metres is not clinically relevant. In the SmPC, therefore, there is no mention that macitentan has an effect on the exercise capacity. Due to differences in definitions, the results of the endpoint 'time to first occurrence of a morbidity or mortality event' cannot be compared between macitentan and bosentan. After two years about 11% of the patients who were treated with macitentan had died and 8 to 11% of the patients who were treated with bosentan. These drugs have not been shown to have an effect on survival.

Unintended effects. Very common adverse effects of macitentan are nasopharyngitis, bronchitis, anaemia and headache. The adverse event profile of macitentan is comparable to that of bosentan. In general, the adverse effects of both drugs are mild to moderate.

Experience. Experience with macitentan is limited, while ample experience has been gained with bosentan.

Applicability. There are no major differences in applicability between macitentan and bosentan.

Ease of use. There are no major differences between macitentan and (oral) bosentan.

Final conclusion on therapeutic value. The therapeutic value of macitentan, as monotherapy or in combination (with other drugs for the treatment of PAH), for the long-term treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class (FC) II to III, is comparable to that of bosentan.

*The original text of this excerpt from a **WAR-Report** of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's WAR-Report.*
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.