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EPAR summary for the public

Tracleer

bosentan

This is a summary of the European public assessment report (EPAR) for Tracleer. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Tracleer.

What is Tracleer?

Tracleer is a medicine that contains the active substance bosentan. It is available as 'film-coated' tablets (62.5 mg; 125 mg) and as dispersible tablets (32 mg).

What is Tracleer used for?

Tracleer is used to treat patients with class III pulmonary arterial hypertension (PAH) to improve exercise capacity (the ability to carry out physical activity) and symptoms. PAH is abnormally high blood pressure in the arteries of the lungs. The 'class' reflects the seriousness of the disease: 'class III' involves marked limitation of physical activity. The PAH can be:

- primary (with no identified cause or inherited);
- caused by scleroderma (also called systemic sclerosis, a disease where there is abnormal growth of the connective tissue that supports the skin and other organs);
- caused by congenital (inborn) heart defects with shunts (abnormal passageways) causing abnormal flow of blood through the heart and lungs.

Some improvements have also been shown in patients with class II PAH. 'Class II' involves slight limitation of physical activity.

Tracleer can also be used in adults with systemic sclerosis in whom poor blood circulation caused by the disease has led to the development of 'digital ulcers' (sores on the fingers and toes). Tracleer is intended to reduce the number of new digital ulcers that are formed.

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The medicine can only be obtained with a prescription.

How is Tracleer used?

Treatment with Tracleer should only be started and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis.

Tracleer is taken morning and evening. In adults, it should be started at a dose of 62.5 mg twice a day for four weeks and then increased to the usual dose of 125 mg twice a day. In children with PAH aged 1 year and older, the recommended starting and maintenance dose is 2 mg per kilogram body weight twice a day.

Patients should swallow the film-coated tablets with water. The dispersible tablets are only for use in patients who cannot take the film-coated tablets. They should be dissolved in a little water on a spoon before being taken. The dispersible tablets have score lines so that they can be broken into quarters, each containing 8 mg bosentan. See the package leaflet for full details.

The doctor should assess the patient's response to Tracleer and review the need for further treatment after eight weeks in patients with PAH who have not improved, and on a regular basis in patients with systemic sclerosis and ongoing digital ulcer disease. If the doctor decides to stop Tracleer, the dose should be gradually reduced.

Patients who take Tracleer must be given the special reminder card that summarises the safety information about the medicine.

How does Tracleer work?

The active substance in Tracleer, bosentan, blocks a naturally occurring hormone called endothelin-1 (ET-1), which causes blood vessels to narrow. Tracleer therefore causes blood vessels to expand.

PAH is a debilitating disease where there is severe narrowing of the blood vessels of the lungs. It causes high blood pressure in the vessels taking blood from the right side of the heart to the lungs. This pressure reduces the amount of oxygen that can get into the blood in the lungs, making physical activity more difficult. By expanding these blood vessels, the blood pressure is reduced and symptoms are improved.

In patients with systemic sclerosis and ongoing digital ulcer disease, bosentan improves blood circulation in the fingers and toes, preventing the development of new digital ulcers.

How has Tracleer been studied?

In PAH, Tracleer film-coated tablets have been studied in four main studies: two in a total of 245 adults with class III or IV disease that was either primary or caused by scleroderma, one in 54 adults with class III PAH that was associated with congenital heart defects, and one in 185 patients with class II disease. The studies compared Tracleer with placebo (a dummy treatment), when they were added to standard treatment. The main measure of effectiveness was how far the patients could walk in six minutes (a way of measuring exercise capacity), but the study in class II disease also looked at the change in the resistance to blood flow in the lungs' blood vessels (a marker of how narrow the blood vessels are). A study was also carried out with the film-coated tablets in 19 children aged between three and 15 years. Two additional studies looked at the effects of Tracleer dispersible tablets in children: the first study included 36 children with PAH who were aged between two and 11 years, while the second study included 64 children with PAH from three months up to 11 years of age.

In systemic sclerosis with digital ulcers, two studies have compared Tracleer film-coated tablets with placebo in a total of 312 adults. The main measure of effectiveness was based on the number of new digital ulcers developing during the studies. One of the studies also looked at the effect of Tracleer on healing in 190 patients, by measuring the time taken for one selected digital ulcer in each patient to heal completely.

What benefit has Tracleer shown during the studies?

In class III or IV PAH that was either primary or caused by scleroderma, the two studies showed that patients treated with Tracleer were able to walk further than patients treated with placebo after 16 weeks (44 metres further in the larger study), but there were too few patients with class IV disease to support the use of the medicine in this group. Similar results were seen in the patients with congenital heart defects.

In patients with class II disease, Tracleer caused the resistance of the blood vessels to decrease by 23% compared with placebo after six months of treatment, but the distance the patients could walk over six minutes was similar in the two groups.

Improvements were also seen in the study of children taking the film-coated tablets. In the studies looking at the dispersible tablets, the levels of bosentan were lower than expected from the results of other studies, and could not be increased by using a higher dosing of Tracleer. However, PAH seemed to remain stable in almost all of the children during the 12 or 24 weeks of treatment periods.

In systemic sclerosis with digital ulcers, Tracleer was more effective at reducing the development of new digital ulcers than placebo. In the first study, patients taking Tracleer had an average of 1.4 new digital ulcers after 16 weeks, compared with 2.7 in the patients taking placebo. Similar results were seen in the second study after 24 weeks, but Tracleer did not have any effect on digital ulcer healing.

What is the risk associated with Tracleer?

The most common side effects with Tracleer (seen in 1 or more patients in 10) are headache, oedema (swelling) or fluid retention, anaemia (low levels of haemoglobin, the protein found in red blood cells that carries oxygen around the body) and abnormal results of tests carried out to check the liver. Because of the risk of liver problems, the doctor will measure the levels of liver enzymes before treatment, and every month during treatment with Tracleer. For the full list of all side effects reported with Tracleer, see the package leaflet.

The effectiveness of some medicines (such as the contraceptive pill) can be affected by taking Tracleer at the same time. See the package leaflet for full details.

Tracleer must not be used in patients who have certain liver problems, who are pregnant or could become pregnant because they are not using reliable contraceptive methods or who are taking ciclosporin A (a medicine that acts on the immune system). For the full list of all restrictions, see the package leaflet.

Why has Tracleer been approved?

The CHMP decided that Tracleer's benefits are greater than its risks and recommended that it be given marketing authorisation.

What measures are being taken to ensure the safe and effective use of Tracleer?

A risk management plan has been developed to ensure that Tracleer is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Tracleer, including the appropriate precautions to be followed by healthcare professionals and patients.

In addition, the company that makes Tracleer will provide an educational kit for prescribers and an information booklet for patients in each Member State, explaining the safety of Tracleer (especially its effects on the liver and in pregnancy) and its interactions. The company will also carefully control the distribution of the medicine in each Member State, and collect information on its use in patients with systemic sclerosis and ongoing digital ulcers. A study in children with PAH will also be carried out to collect further long-term safety data in this population.

Other information about Tracleer

The European Commission granted a marketing authorisation valid throughout the European Union on 15 May 2002.

The full EPAR for Tracleer can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports. For more information about treatment with Tracleer, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

The summaries of opinion of the Committee for Orphan Medicinal Products for Tracleer can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation (PAH), and ema.europa.eu/Find medicine/Human medicines/Rare disease designation (systemic sclerosis).

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