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EPAR summary for the public

Granupas[1]

para-aminosalicylic acid

This is a summary of the European public assessment report (EPAR) for Granupas. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Granupas.

For practical information about using Granupas, patients should read the package leaflet or contact their doctor or pharmacist.

What is Granupas and what is it used for?

Granupas is a tuberculosis medicine that contains the active substance para-aminosalicylic acid (PAS). It is used in combination with other medicines to treat adults and children from 28 days of age who have multi-drug resistant tuberculosis when combinations without this medicine cannot be used, either because the disease is resistant to them or because of their side effects.

Multi-drug resistance is when the bacteria causing tuberculosis (*Mycobacterium tuberculosis)* are resistant to treatment with at least isoniazid and rifampicin, two standard tuberculosis medicines.

Because the number of patients with tuberculosis is low in the EU, the disease is considered 'rare', and Granupas was designated an 'orphan medicine' (a medicine used in rare diseases) on 17 December 2010.

How is Granupas used?

Granupas can only be obtained with a prescription. It is available as 4 g sachets containing 'gastro-resistant' granules that allow the active substance to reach the intestine without being released in the stomach, thus reducing side effects in the stomach.

[1] Previously known as Para-aminosalicylic acid Lucane

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The recommended dose for adults is one sachet three times a day. Treatment is usually continued for 2 years.

In children and adolescents, the daily dose depends on their weight. They should be given a total of 150 mg per kilogram body weight every day, split into two doses. A dosing spoon is used to measure small doses for young children.

How does Granupas work?

The active substance, PAS, is a 'bacteriostatic agent', which means that it works by stopping the growth of *M. tuberculosis* bacteria. PAS is similar to a chemical (para-aminobenzoic acid) that is used by the bacteria to make folic acid needed for new bacteria to grow. By interfering and taking the place of this chemical in the processes that make folic acid, para-aminosalicylic acid reduces the amount of folic acid produced and thereby stops or slows the growth of *M. tuberculosis*.

What benefits of Granupas have been shown in studies?

PAS has been used for many years in the EU for the combination treatment of tuberculosis. The benefits in combination with other tuberculosis treatments were shown in published studies presented by the company, two of which were considered to be the main studies for the application.

The first of these involved 166 patients with tuberculosis aged between 15 to 30 years. The patients were treated for 3 months with either PAS or another medicine called streptomycin, or with a combination of PAS and streptomycin, and then followed up for 3 extra months. At the end of the 6 months, 87% of patients on the combination had improvements in their chest x-rays compared with 56% of patients in the group taking PAS alone. In addition,33% of patients in the combination group had no bacteria detected in their phlegm (sputum) compared with 8% in the PAS group. PAS in combination with streptomycin also helped reduce the emergence of resistance to streptomycin: in 89% of patients receiving the combination the bacteria remained responsive to streptomycin, compared with 21% of patients who were given only streptomycin.

In the second main study involving 341 patients aged over 12 years, PAS in combination with isoniazid was compared with isoniazid alone. After 12 months, 90% of patients in the combination group did not have the bacteria in their phlegm compared with 51% of patients given a comparable dose of isoniazid alone. In addition, the PAS-isoniazid combination helped reduce the emergence of resistance to isoniazid: after 1 year, while 47% of patients in the isoniazid-only group had resistant bacteria the figure was only 8% in the combination group.

The applicant also provided published data on the doses of PAS to be used in children.

What are the risks associated with Granupas?

The most common side effects with Granupas (which may affect up to 1 in 10 people) are abdominal pain (stomach ache), vomiting, nausea, bloating, diarrhoea and soft stools, giddiness, disturbance in gait and balance, and allergic skin reactions and rash. For the full list of all side effects reported with Granupas, see the package leaflet.

Granupas must not be taken by patients with severely reduced kidney function. For the full list of restrictions, see the package leaflet.

Why is Granupas approved?

The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Granupas's benefits are greater than its risks and recommended that it be approved for use in the EU.

The Committee noted that the active substance, PAS, has been shown to be beneficial when used in combination with other medicines to treat tuberculosis and that it helps reduce the emergence of resistance to other medicines.

PAS had been widely used in the past for combination treatment but was largely discontinued due to adverse effects on the stomach. The CHMP noted that Granupas contains gastro-resistant granules, designed to allow PAS to reach the intestine without being released in the stomach, and thus reduce the potential for side effects.

The Committee also noted that the World Health Organization continues to recommend PAS as an option to be used in combination with other medicines for treating multi-drug resistant tuberculosis.

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

A risk management plan has been developed to ensure that Granupas 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 Granupas, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Granupas

The European Commission granted a marketing authorisation valid throughout the European Union for Para-aminosalicylic acid Lucane on 7 April 2014. The name of the medicine was changed to Granupas on 15 May 2014.

The full EPAR and risk management plan summary for Granupas 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 Granupas, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

The summary of the opinion of the Committee for Orphan Medicinal Products for Granupas can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

This summary was last updated in 07-2014.