GRANUPAS (para-aminosalicylic acid), antituberculosis agent

Minor clinical added value in combination with other antituberculosis agents in multidrug resistant tuberculosis when compared with the usual treatment

Main points

- GRANUPAS has Marketing Authorisation for multidrug resistant tuberculosis in combination with other antituberculosis agents. This is the first medicinal product with this indication.
- The WHO has included it in the treatment strategy for multidrug resistant tuberculosis in combination with several second-line antituberculosis agents.
- The evidence for its efficacy is based on a long experience in tuberculosis treatment and on the follow-up of a non-comparative cohort. The adverse effects, for the most part gastrointestinal or cutaneous, are not of a serious nature.

Therapeutic use

- Multidrug resistant tuberculosis is a mycobacterial infection resistant to isoniazide and rifampicin, the two first-line drugs used in the treatment of tuberculosis. It is said to be ultraresistant when the mycobacteria are also resistant to both a fluoroquinolone and a second-line injectable antituberculosis drug. Resistance – whether secondary or acquired – is caused by poor use of the medicinal products. The two main risk factors of resistance to antituberculosis agents are treatment history and country of origin. Multidrug resistant tuberculosis is especially common in Africa, eastern Europe, Russia, China, and India.
- Resistance to antituberculosis agents worsens the prognosis of the disease. The patients concerned need to be specifically managed by specialist teams so they can adapt to the bacteriological data and to the patient’s clinical characteristics.
- The treatment of multidrug resistant tuberculosis combines at least four medicinal products, active or presumed to be active against the resistant strain, for an extended period of over 18 months, and in general 2 years. The choice of combinations of antituberculosis agents will depend on the resistances. For the treatment of multidrug resistant tuberculosis, the recommended combination is pyrazinamide, a preferred latest-generation fluoroquinolone, an injectable antituberculosis agent – ethionamide or prothionamide – and either cycloserine or para-aminosalicylic acid (PAS) in cases where cycloserine cannot be used.
- To avoid a therapeutic dead end in certain cases of multidrug resistant tuberculosis, it is good to have a sufficient quantity of second-line antituberculosis agent to use in combination in order to be able to adjust the treatment in the event of any contraindication or intolerance.

Role of the proprietary medicinal product in the therapeutic strategy

- In Europe, PAS is indicated in combination with other medicinal products in the treatment of multidrug resistant tuberculosis in adults and children aged 28 days and over, when the use of any other effective treatment regimen is impossible for reasons of resistance or intolerance.
- Para-aminosalicylic acid is a bacteriostatic antituberculosis agent; it has the advantage of limiting the appearance of resistance to the antituberculosis agents with which it is combined.
Clinical data

- The efficacy of GRANUPAS is based essentially on many years of experience:
  - Regular use of para-aminosalicylic acid between 1946 and the 1960s, when the medicinal product gradually fell into disuse with the appearance of more effective treatments.
  - Primarily two clinical studies, published in 1950 and 1960, which made it possible, given the methodological requirements of the time, to show the efficacy of PAS compared with not having any treatment at all, and the benefit of combining PAS with another antituberculosis agent as a means of keeping resistance at bay. These two studies were conducted on pulmonary tuberculosis in patients without resistance to antituberculosis agents, with treatment durations of 3 and 6 months. These studies do not comply with current methodological requirements.

- There are no clinical studies or observational data on the efficacy of GRANUPAS in its current indication (multidrug resistant tuberculosis) in combination with at least four antituberculosis agents over a treatment period of at least 18 months.

- In a non-comparative French cohort consisting of 231 patients followed up for multidrug resistant tuberculosis in the context of a temporary authorisation for use by a cohort, GRANUPAS was used in combination with at least two other antituberculosis agents. In 63% of cases, the strains were resistant to at least one antituberculosis agent other than rifampicin and isoniazide, 55 of the 231 patients stopped the treatment, but the reasons for stopping cannot be interpreted in terms of efficacy or safety. There were no reports of serious adverse effects. The Committee regrets that the temporary usage authorisation cohort data were not put to better use.

The most common adverse effects are nausea, vomiting, diarrhoea, abdominal pain, and bloating, which can be significant at times. The current gastro-resistant formulation is designed to be better tolerated, but these effects persist, without it being known if their intensity has diminished. Cytolysis and anomalous laboratory findings were observed. No serious adverse effects were observed either in the past or in current more limited use.

- Clinical experience in children is limited to a few cases in the old studies and to 11 cases involving a temporary authorisation for use by a named patient, in none of which were there any adverse effects attributable to GRANUPAS.
  [ATU nominative in French]

Benefit of the medicinal product

- The actual benefit* of GRANUPAS is substantial.

- In view of the substantial but poorly demonstrated need for efficacy in the treatment of multidrug resistant tuberculosis, GRANUPAS (para-aminosalicylic acid) in combination with other antituberculosis agents provides a clinical added value** (CAV IV) in the treatment strategy of these patients.

- Recommends inclusion on the list of reimbursable products for hospital use.

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* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.

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