BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**REVOLADE** (eltrombopag), thrombopoietin receptor agonist

Moderate improvement in chronic autoimmune thrombocytopenic purpura where usual treatments have failed in children ≥ 1 year

Main points

- ▶ REVOLADE now has Marketing Authorisation in the treatment of chronic (idiopathic) autoimmune thrombocytopenic purpura (ITP) that is refractory to other treatments in children ≥ 1 year.
- ▶ A galenic presentation in the form of a powder for oral suspension allows adapted administration, especially in children < 6 years.
- ▶ In children > 1 year, the efficacy data are very short-term, but in this population the medical need is substantial.

Pre-existing indications^{*}

REVOLADE already has Marketing Authorisation in adults with chronic ITP refractory to other treatments (such as corticosteroids or immunoglobulins).

Therapeutic use

The usual management of ITP in paediatrics mainly involves the following treatments:

- in acute ITP: depending on the bleeding risk, infusions of immunoglobulins or corticosteroids or abstinence;
- in persistent ITP: depending on the bleeding risk of each episode: infusions of immunoglobulins or corticosteroids or therapeutic abstinence. Other second-line treatments may be considered: rituximab in the case of a temporary recommendation for use (RTU) under validation, immunosuppressants;
- in chronic ITP: same strategy as the persistent stage and in case of refractory ITP, splenectomy may be considered.
- in an absolute haemorrhagic emergency (very rare): polyvalent immunoglobulins, and/or corticosteroids and/or platelet transfusions;

■ Role of the medicinal product in the therapeutic strategy

In the management of chronic and refractory ITP, after failure of first-line medicinal products (corticosteroids, immunoglobulins) and of a second-line treatment (immunosuppressant, rituximab in RTU), REVOLADE has a restricted place given the rarity of chronic ITP in children aged 1 year and older in whom spontaneous remissions are possible even after several years of the disease. In view of the limited efficacy and safety data and the lack of long-term data, the duration of treatment with REVOLADE should not exceed 6 or even 12 months in paediatric patients. As in adults, specific monitoring is required.

Due to the suspensive activity on thrombocytopenia, occasional use of REVOLADE in temporary situations could be considered (on expert opinion):

- in case of ITP with severe bleeding: in combination with therapies with documented efficacy in this context (corticosteroids, infusions of immunoglobulins or even platelet transfusions)
- in case of chronic ITP with marked thrombocytopenia, at the time of a bleeding challenge (scheduled surgical procedure)
- when the following 3 criteria are met: pronounced thrombocytopenia (10 G/L) refractory to first-line treatments (corticosteroids and immunoglobulins) and with severe impact (Buchanan bleeding score ≥ 3) and refractory/contraindicated/pending efficacy of a second-line or higher treatment.

^{*} This summary does not cover these indications.

Clinical data

- Paediatric data are primarily from a 13-week randomised, double-blind phase III study versus placebo followed by a 24-week open-label treatment period with eltrombopag. This study evaluated the efficacy of eltrombopag, possibly in combination with concomitant ITP treatments at a stable dose (corticosteroids or azathioprine), in 92 children with a median age of 9 years, with a chronic ITP of variable severity: refractory, in relapse after prior treatment or more, or having stopped their other ITP treatments due to a medical reason. Of the 63 children randomised into the eltrombopag group and the 29 in the placebo group, more than 60% (57/92) had a baseline platelet count ≤ 15 G/L. The children were mostly (96%) non-splenectomised (4 splenectomised children). The children randomised into the eltrombopag group received concomitant ITP treatments in 21% (13/63) of cases and in 3% (1/29) of cases in the placebo group. Most patients had received at least 2 prior treatments for ITP: 73% (46/63) in the eltrombopag group and 90% (26/29) in the placebo group.
- At 3 months, the percentage of children who had achieved a platelet count ≥ 50 G/L during at least 6 of the 8 weeks between weeks 5 and 12 of the randomised phase, in the absence of rescue treatment (primary endpoint), was 40% (25/63) in the eltrombopag group versus 3% (1/29) in the placebo group, OR=18 95% CI [2.3 - 141.9], $p < 0.001$.
- The difference in percentage of use of a rescue treatment was modest: 19% (12/63) in the eltrombopag group and 24% (7/29) in the placebo group ($p = 0.032$). There was no difference in the proportion of clinically significant bleeding: 33% (21/63) in the eltrombopag group and 41% (12/29) in the placebo group, NS. Data evaluating the long-term maintenance of the response are not available. Safety data are limited and the risk of myelofibrosis was not evaluated.
- The impact beyond 6 to 12 months of treatment was not evaluated. No improvement in quality of life was demonstrated.

Special prescribing conditions

- Medicine for hospital prescription.
- Prescription restricted to specialists in departments of haematology, hepatology/gastroenterology, infectious diseases, internal medicine or paediatrics.
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual benefit* of REVOLADE is substantial.
- REVOLADE (eltrombopag) provides moderate clinical added value (CAV III) in the treatment of chronic and refractory ITP in children aged 1 year and older.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use in these new indication.

HAUTE AUTORITÉ DE SANTÉ

This document was created on the basis of the Transparency Committee Opinion of 22 February 2017 (CT-15376) and is available at www.has-sante.fr

* The actual benefit (AB) of a 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".