BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

NPLATE (romiplostim), REVOLADE (eltrombopag), thrombopoietin receptor agonists

Minor improvement in chronic autoimmune thrombocytopenic purpura when usual treatments have failed, in non-splenectomised adults with no contraindication to surgery

Main points

- Prior to the extension of the Marketing Authorisation of NPLATE and REVOLADE in non-splenectomised adults with no contraindication to surgery, these medicinal products were a treatment for chronic (idiopathic) autoimmune thrombocytopenic purpura (ITP) in adults where the usual treatments have failed in refractory splenectomised patients and in non-splenectomised adults in case of contraindication to surgery.
- Now their use in pre-splenectomy has been validated by Marketing Authorisation. However, they must be used with caution given the uncertainties about long-term safety, as well as in non-splenectomised patients.

Other indications

- NPLATE and REVOLADE already have Marketing Authorisation for splenectomised adults with ITP.
- REVOLADE also has Marketing Authorisation in chronic ITP, refractory to other treatments (such as corticosteroids or immunoglobulins) in patients aged 1 year or older.

Therapeutic use

Patients with ITP are treated if the platelet count is < 30 x 10^9/L. This threshold may be higher depending on predisposition (patient’s age, presence of comorbidities).

- In acute phase, the aim of the treatment is to obtain an increase in the platelet count as quickly as possible to protect the patient from a bleeding complication. Intravenous corticosteroids and/or immunoglobulins are administered. Transfusions of platelets are indicated only in exceptional life-threatening cases.
- In persistent forms (3 to 12 months after diagnosis), there is no consensus about the best treatment option. Options include immunosuppressants, dapsone (DISULONE) or danazol (DANATROL) (without marketing authorisation). Rituximab is a therapeutic option for persistent or chronic ITP in patients refractory to corticosteroids and immunoglobulins.
- In cases of chronic ITP (beyond one year), the aim of treatment is to raise the platelet count and to maintain it above a threshold of 30 to 50 G/L. Curative treatment is based on splenectomy, especially in young adults (about 60% long-term response) despite the surgical risks and infectious and thrombotic complications. Contraindications to splenectomy are rare (about 20% of cases) and may be linked to the existence of severe comorbidities or advanced age.
- In cases of refractory ITP (thrombocytopenia which persists after several lines of treatment including splenectomy have been tried, and an effective treatment is needed to keep platelet levels above 20-30 G/L), treatment options (including rituximab) are limited. In the absence of a consensual therapeutic strategy, the choice of treatment must be personalised, depending on several criteria. In some situations, it may be justified to postpone the splenectomy (history or risk factors for severe infection or venous and/or arterial thrombosis) or to avoid the use of thrombopoietin receptor agonists (history or risk factors for venous and/or arterial thrombosis, hereditary, or acquired; see summaries of product characteristics).

*This summary does not cover these indications.*

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Role of the medicinal product in the therapeutic strategy
In chronic and refractory ITP, after failure of first-line medicinal products (corticosteroids, immunoglobulins) and other treatments, a thrombopoietin agonist, NPLATE or REVOLADE, may be considered in patients who require a therapeutic intervention and for whom there is reason to postpone splenectomy, the curative treatment of choice. However, there are no comparative data available to support this strategy (treatment with NPLATE or REVOLADE, and then, in case of failure, splenectomy). Unlike curative surgery (which allows about two-thirds of patients to remain in clinical remission 5 to 10 years later), these medicinal products increase platelet production with no demonstrated interference on the underlying pathophysiology of this autoimmune disease. Therefore, in most cases, the thrombocytopenia reappears when treatment with NPLATE or REVOLADE is discontinued. The optimal duration of treatment and the methods for discontinuation of treatment in case of lack of response are unknown. There are uncertainties about long-term safety, and specific monitoring is required. When a splenectomy is considered, the benefit of a suspensive treatment with a thrombopoietin agonist may be discussed.

Finally, the ease of prescribing a medicinal product in the French health care system compared to planning a surgical procedure can cause fear of misuse.

Clinical data

This extension of the Marketing Authorisation indication to non-splenectomised adults with no contraindication to surgery is based on the analysis of initial data.

For NPLATE, the main results are from two 6-month, randomised, double-blind, phase III studies that demonstrated its superiority to placebo in terms of sustained platelet response (platelets ≥ 50 G/L at at least 6 weekly controls during the last 8 weeks of the study, in the absence of emergency treatment) in patients refractory to splenectomy [38% (16/42) of responders versus 0% (0/21), p<0.0013]] as well as in non-splenectomised patients [61% (25/41) versus 5% (1/21), p<0.001].

For REVOLADE, in 6-month randomised, double-blind studies that included splenectomised (40%) or non-splenectomised (60%) patients, its short-term efficacy was demonstrated compared to placebo on platelet response (platelets between 50 and 400 G/L): between 37 and 56% with REVOLADE and between 7 and 19% with placebo.

The therapeutic contribution of NPLATE or REVOLADE is difficult to quantify in management that includes splenectomy, especially in young adults, considering:
- their suspensive efficacy, demonstrated on the short-term platelet response versus placebo, the lack of robust data to reach a conclusion on the reduction of major bleeding,
- the lack of comparative data versus splenectomy,
- the lack of demonstration of fewer splenectomies related to their use,
- the uncertainties about long-term safety (in particular the risk of myelofibrosis and malignant blood diseases during long-term treatment),
- the lack of demonstrated impact on quality of life.

Special prescribing conditions

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

Benefit of the medicinal products

The actual benefit* of NPLATE and REVOLADE is substantial.

NPLATE (romiplostim) or REVOLADE (eltrombopag) provides a minor clinical added value (CAV IV) in the treatment of chronic and refractory ITP in non-splenectomised adults with no contraindication to surgery.

Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use in this new indication.
* 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".