HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New medicinal product
April 2019

**TRANSPARENCY COMMITTEE OPINION SUMMARY**

# **ADYNOVI** (rurioctocog alfa pegol), antihaemophilic factor (factor VIII)

**Insufficient clinical benefit to justify its reimbursement in haemophilia B due to uncertainties as to the long-term consequences of the accumulation of PEG in tissue and failing any data demonstrating that ADYNOVI provides a benefit over available alternatives**

## Main points

- ADYNOVI has been granted a marketing authorisation for the treatment and prevention of bleeding episodes in patients over 12 years with haemophilia A**.**
- It is a factor VIII (FVIII) with half-life extended by conjugation with a polyethylene-glycol (PEG) molecule. The FVIII with half-life extension already on the market does not contain PEG.
- We cannot rule out the potential long-term risks related to the accumulation of PEG molecules in tissue, especially in the plexus choroideus.

## Therapeutic strategy

- The first-line treatment for haemophilia A is replacement treatment and is based on administration of clotting factor VIII (FVIII) concentrates. They can be administered:
  - curatively ("on demand" treatment) on occurrence of a bleeding event that cannot be controlled by local haemostatic methods or cannot be treated with tranexamic acid,
  - to prevent bleeding: in primary prophylaxis in children with severe haemophilia before the age of two years, and before onset of the second haemarthrosis, in secondary prophylaxis (long-term or periodic) after onset of the second haemarthrosis or in the event of surgery or invasive procedures (according to severity and the expected risk of bleeding).
- Long-term prophylaxis is the conventional treatment in children with severe haemophilia. There is no consensus as to the role of prophylaxis in adults.

### Role of the medicinal product in the therapeutic strategy

In view of:
- the demonstration of its efficacy in the treatment and prevention of bleeding in cases of severe haemophilia A, in non-comparative studies,
- the lack of data demonstrating that ADYNOVI provides a benefit, particularly in terms of efficacy or quality of life, over available alternatives,
- the fact that, to date, no elements can exclude the onset of deleterious clinical effects associated with potential PEG accumulation, particularly in the plexus choroideus, after numerous years of treatment, in a context in which available alternatives do not present this risk,
- the large number of therapeutic alternatives,

ADYNOVI does not have a role in the treatment and prevention of bleeding episodes in patients over the age of 12 years with haemophilia A.

## Clinical data

- Two non-randomised open studies assessed ADYNOVI in adults and adolescents over the age of 12 years suffering from severe haemophilia A, all of whom had previously been treated with another factor VIII and with no history of inhibitor antibodies.
- One study assessed ADYNOVI as long-term prophylaxis or on-demand treatment in 137 adolescents and adults aged 12 to 58 years. Patients were distributed to two groups according to the details of their prior treatment. One

group (n=17) was treated on demand, while the other received long-term prophylaxis, with exposure for at least 50 days, or 6 months. The mean annualised rate of bleeding (ARB) in patients receiving prophylactic treatment was of 4.3 (3.4; 5.5). Over the duration of the study, 37.5% (n=45/120) of patients receiving prophylactic treatment did not present with any bleeding events requiring treatment with ADYNOVI.
In total, 591 bleeding episodes were treated with this FVIII, with an overall success rate of 96%, similar in both treatment groups and in both adolescents and adults. A single injection was sufficient to resolve most bleeding episodes (85%).

- In the study conducted specifically in surgery, haemostatic efficacy was assessed during 24 surgical procedures (21 major and 3 minor). Efficacy was deemed “excellent” for all procedures.
- The safety profile derived from the studies appeared comparable to that of the other FVIIIs available. No allergic reactions were reported during these studies. No patient developed FVIII inhibitor antibodies, though cases were reported in the context of pharmacovigilance. The most frequent adverse reactions with ADYNOVI are nausea, rash, diarrhoea and headache.
- The lack of marketing authorisation for children under the age of 12 years is associated with the risk of PEG accumulation in tissues, particularly in the plexus choroideus, after numerous years of treatment. Although this risk is particularly preoccupying for the youngest children, at an early stage in their development, we cannot fully rule out a risk for children over the age of 12 (ongoing neurogenesis), or for adults. The laboratory has been asked to implement a post-authorisation safety study aimed at documenting this potential long-term risk. This study should also assess possible off-label use in patients under the age of 12 years.
- None of these studies compared ADYNOVI with another factor VIII, particularly the already available extended half-life FVIII ELOCTA. In light of the available data, there is thus no evidence that ADYNOVI can offer a benefit in terms of reduced bleeding, prophylactic injection frequency or quality of life relative to the other FVIIIs.

## Special prescription requirements

- Medicinal product subject to initial six-month hospital prescription.

## Benefit of the medicinal product

- The actual clinical benefit* of ADYNOVI is insufficient.
- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 10 April 2019 (CT-16988) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".