HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
30 JUNE 2021

The legally binding text is the original French opinion version

defibrotide
DEFITELIO 80 mg/mL concentrate for solution for infusion
Re-evaluation

Key points

Favourable opinion for maintenance of reimbursement in the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.

What therapeutic improvement?

Therapeutic improvement in the management of the condition.

Role in the care pathway?

The prevention of VOC is primarily related to reducing the intensity of myelosuppressive chemotherapy conditioning before haematopoietic stem-cell transplantation. In recent years, the incidence of the occurrence of hepatic VOD has decreased thanks to changes in its management: patients at high risk are identified, low-intensity conditioning is favoured, cyclophosphamide-free chemotherapy protocols have been introduced, norethisterone-based treatments are no longer used, the concomitant administration of hepatotoxic drugs is avoided, patients are given transplants sooner, the general condition of patients at the time of transplantation is better.

DEFITELIO (defibrotide) is the only curative treatment for hepatic VOD to be approved in the USA and Europe. European Society for Blood and Marrow Transplantation (EBMT) guidelines recommend the use of DEFITELIO (defibrotide) as a treatment for hepatic VOD. In addition, other proprietary medicinal products are used off-label in this indication: recombinant plasminogen activator factor (ACTILYSE), N-acetylcysteine, methylprednisolone. A transjugular intrahepatic shunt may also be created in certain cases. In its opinion of July 2014, the Committee had considered that DEFITELIO (defibrotide) is a first-line treatment for severe hepatic VOD in adults, adolescents, children and infants over one month of age.

To date, DEFITELIO (defibrotide) does not have an MA as prophylactic therapy in adults at risk of developing VOD or in children. It should be noted that a phase 3, randomised, open-label study aimed at comparing DEFITELIO (defibrotide) as prophylaxis for VOD versus the standard of care in adults and children at high or very high risk of developing VOD was stopped for futility after having concluded that it was unlikely that a statistically significant difference would be attained in the final analysis of the primary endpoint (VOD-free survival at D+30 post-HSCT).

Role of the medicinal product in the care pathway:

DEFITELIO (defibrotide) remains a first-line treatment for severe hepatic VOD in adults, adolescents, children and infants over one month of age.

In the French observational study put in place at the request of the Committee following the assessment of 9 July 2014, the off-label use of DEFITELIO (defibrotide) was identified in 70% of cases, particularly in the prophylaxis of VOD. Consequently, the Committee reiterates that, with the aim of ensuring good practice, the use of DEFITELIO (defibrotide) as prophylaxis of VOD is not validated by the MA and DEFITELIO (defibrotide) should be reserved for the treatment of severe hepatic VOD, in accordance with the MA indication.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Severe hepatic veno-occlusive disease is life-threatening in the short term due to resulting multi-organ complications.
◗ The proprietary medicinal product DEFITELIO (defibrotide) is a curative medicinal product.
◗ The efficacy/adverse effects ratio remains moderate, in the absence of precise and reliable quantification of the treatment effect and a bleeding risk.
◗ At this stage of the disease, there are no validated therapeutic alternatives.
◗ It is a first-line treatment.

◗ **Public health impact**
Considering:
- the seriousness of the disease, which can be life-threatening due to its complications,
- its very low prevalence,
- the unmet medical need,
- the lack of additional response to the identified unmet medical need, due to the absence of robust comparative data enabling assessment of the additional impact of defibrotide on morbidity and mortality and quality of life,
- the lack of a demonstrated potential impact on the organisation of care and the patient's care or life pathway,

DEFITELIO (defibrotide) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of DEFITELIO (defibrotide) remains moderate in the MA indication.

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

Clinical Added Value

The new data submitted, based primarily on the final analysis of study 2006-05 previously assessed by the Transparency Committee and on observational data from the DEFIFrance and EBMT-PASS registries do not modify the Committee's previous assessment of DEFITELIO (defibrotide). Consequently, DEFITELIO (defibrotide) provides a minor clinical added value (CAV IV) in the care pathway for the treatment of severe hepatic VOD after HSCT.