HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
20 JANUARY 2021
The legally binding text is the original French opinion version

avatrombopag
DOPTELET 20 mg film-coated tablets

First assessment

Key points

Unfavourable opinion for reimbursement in the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

Role in the care pathway?

Thrombocytopenia is the most common haematological complication associated with chronic liver disease. While the mechanisms of thrombocytopenia are multifactorial, the reduction in the hepatic synthesis of thrombopoietin (TPO) related to changes in the liver architecture and sequestration of platelets in the spleen are primarily involved in patients with chronic liver disease.

The prevalence of severe thrombocytopenia (< 50 x10^9/L) is estimated to be 1% in cirrhosis patients and to be similar in chronic hepatitis C, but it may be lower in other chronic liver diseases.

Few studies are available enabling the surgical risk to be assessed on the basis of platelet counts. There is currently little consensus with respect to the benefit of correcting thrombocytopenia and the threshold to be used, particularly in the context of an invasive procedure and chronic liver disease. **Nevertheless, it is generally accepted that the need for prophylactic platelet transfusion should be based on an individual assessment of the bleeding risk, which is not only based on the platelet count but should also take into account the type of invasive procedure and patient**

characteristics (age, co-morbidities, treatments, etc.). Irrespective of the risk assessment, correction of bleeding risk factors should be undertaken in all cases and the use of non-specific bleeding reduction measures is recommended.

Where it appears to be warranted, the treatment of severe thrombocytopenia is currently based on prophylactic platelet transfusion, the aim being to prevent bleeding.

According to French HAS/ANSM guidelines, platelet transfusion can only be used curatively in the event of bleeding when the underlying disease suggests an associated thrombotic risk; this is the case of cirrhosis patients, in whom parallels can be drawn with situations of DIC not complicated by haemorrhage.

The recent guidelines issued by the French Society of Anaesthesia and Intensive Care (SFAR) also suggest that plasma, platelets or fibrinogen should not be systematically administered as a preventive measure to limit bleeding before an invasive procedure in cirrhosis patients. In particular, it mentions that cirrhosis patients present disorders of pro- and anticoagulant factors leading to a new haemostatic equilibrium, that the usual laboratory tests are unable to predict bleeding related to an invasive procedure, that bleeding complications in cirrhosis patients in the event of an invasive procedure are usually the consequence of portal hypertension (rupture of oesophageal varices) or infections of the ascites fluid, and that the platelet transfusion yield is very poor in these patients.

According to the recommendations of the French Radiology Society issued in 2013 in its "Practical Interventional Radiology Guide", which are not specific to patients with chronic liver disease, a platelet count < 50 $x10^9$/L represents a relative or absolute contraindication to certain invasive procedures. The 2019 international interventional radiology guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided Interventions, supported by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), suggest a platelet count of > 20 or 30 $x10^9$/L, depending on the risk level of the procedure to be performed, in patients with chronic liver disease.

Hence the need to correct haemostasis, as well at the methods of doing so, prior to an invasive procedure in cirrhosis patients still need to be better defined.

Role of the medicinal product in the care pathway

As the data currently stands and considering, in particular:

- the absence of data demonstrating that DOPTELET (avatrombopag) reduces the risk of peri- or postprocedural bleeding, despite its demonstrated efficacy to increase platelet counts in comparison with placebo,
- uncertainties with respect to the risk of thromboembolic events associated with its use, particularly the risk of portal vein thrombosis, due to the small sample sizes assessed and the non-inclusion in the studies of certain at-risk populations, such as patients with a history of thrombosis or those with a portal flow velocity < 10 cm/s,
- the invasive procedures during which DOPTELET (avatrombopag) was evaluated, which were very heterogeneous and mostly presented a low bleeding risk, which does not correspond to the guidelines and raises questions about the proper use of the drug in routine practice,
- the lack of consensus, due to insufficient evidence, with respect to the situations in which severe thrombocytopenia needs to be corrected in order to limit the risk of bleeding before an invasive procedure in patients with chronic liver disease, and in particular the recommendations against routine prophylactic platelet transfusion in cirrhosis patients, who accounted for around 75% of the patients evaluated in the studies and,
- despite a potential organisational benefit of oral administration compared to platelet transfusion, in a population that is difficult to determine as knowledge currently stands and in a context where this medicinal product cannot be used in an emergency given the time to onset of its efficacy, which takes several days,

the Transparency Committee considers that DOPTELET (avatrombopag) has no role in the care pathway for severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Severe thrombocytopenia is one of the factors that can contribute to an increase in the bleeding risk in a surgical context. It is rare in patients with chronic liver disease, with a presence of around 1% in cirrhosis patients.

◗ DOPTELET (avatrombopag) increases the platelet count and is therefore a treatment that aims to prevent bleeding.

◗ Its efficacy/adverse effects ratio has not been adequately established given:
- the absence of data demonstrating that DOPTELET (avatrombopag) reduces the risk of peri- or postprocedural bleeding, despite its demonstrated efficacy to increase platelet counts in comparison with placebo,
- uncertainties with respect to the risk of thromboembolic events associated with its use, particularly the risk of portal vein thrombosis.

◗ There is an alternative: intravenous platelet transfusion.
◗ DOPTELET (avatrombopag) has no role in the care pathway for severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure (see section 08).

Public health impact
Considering:
- the fact that severe thrombocytopenia is one of the factors that can contribute to an increase in the bleeding risk in a surgical context, and its low prevalence in patients with chronic liver disease,
- the partially met medical need,
- the lack of response to the identified partially met need, given the absence of any demonstrated additional impact to date on morbidity and mortality or on quality of life,
- the potential additional impact on the organisation of care given the oral administration at home, but in a context in which the population in whom this treatment may be justified cannot be specified,

DOPTELET (avatrombopag) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of DOPTELET (avatrombopag) is insufficient to justify public funding cover in the MA indication.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.