HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 DECEMBER 2020

The legally binding text is the original French opinion version

bulevirtide

HEPCLUDEX 2 mg powder for solution for injection

First assessment

Key points

Favourable opinion for reimbursement only in the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease, in combination with a maintenance therapy against HBV and in the event of failure, intolerance or contraindication to PEGylated interferon alpha.

Unfavourable opinion for reimbursement in other situations, including bulevirtide monotherapy, in particular.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

PEGylated interferon alpha (PEG-IFNα-2a) is currently the only medicinal product to have demonstrated its antiviral efficacy against HDV and to be recommended for the treatment of this infection. It reduces the viral load of HDV and can be used in combination or otherwise with another anti-HBV treatment with nucleoside/nucleotide inhibitors (intrinsically ineffective against HDV). The minimum treatment duration is one year, irrespective of the evolution of the response during treatment. It should be noted that interferon is poorly tolerated (influenza-like illness, depression, etc.) and that the tolerance reduces with age and in the event of advanced fibrosis. Intolerance leads to treatment discontinuation in 10 to 30% of cases within the first 6 months. In addition, many patients are not eligible for treatment with interferon alpha due to a contraindication or advanced disease, in particular: auto-immune hepatitis, treatment with immunosuppressive therapy, psychiatric or decompensated thyroid disorders, severe renal impairment and decompensated cirrhosis.

Liver transplantation may be considered in the event of fulminant hepatitis or end-stage liver disease.

The prevention of hepatitis D involves vaccination against hepatitis B.

Role of the medicinal product in the care pathway

HEPCLUDEX (bulevirtide) is a first or second-line option, in combination with maintenance therapy for hepatitis B virus (HBV) (nucleoside or nucleotide analogue), in the management of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease, in combination with a maintenance therapy against HBV and in the event of failure, intolerance or contraindication to PEGylated interferon alpha.

The Committee highlights the fact that exacerbations of hepatitis occurring after treatment discontinuation possibly related to a virologic rebound, as identified in the risk management plan (RMP), require the long-term maintenance of treatment, for which the optimal duration is not known. In addition, given that HDV inhibits the replication of HBV, the risk of reactivation of HBV in the event of control of HDV replication by bulevirtide requires maintenance of optimal concomitant HBV treatment.

Special recommendations

In view of the current uncertainties concerning the efficacy, safety and conditions of use of HEPCLUDEX (bulevirtide) and the complexity of management (clinical stage, optimal treatment duration an patient follow-up), the Committee recommends restricting the prescription of HEPCLUDEX (bulevirtide) to physicians experienced in the management of patients with chronic HDV infection and following discussion at a multidisciplinary team meeting.

01 COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Chronic hepatitis D is a chronic liver disease that can be life-threatening. HDV infection is considered to be the most serious form of chronic viral hepatitis due to its rapid progression to cirrhosis (annual rate of 4%) and hepatocellular carcinoma (annual progression rate of 2.7%). Consequently, the mortality associated with chronic hepatitis D is higher than that for chronic hepatitis B.

◗ This is a curative treatment.

◗ The efficacy/adverse effects ratio of HEPCLUDEX (bulevirtide) has not currently been adequately established. However, preliminary data (MYR 202 and 203 studies) are reassuring and suggest a clinical benefit that is:

- substantial in combination with maintenance therapy for HBV, in patients in whom PEGylated interferon alpha has failed, or is poorly tolerated or contraindicated,
- uncertain in the other situations covered by the MA, including in bulevirtide monotherapy, in particular.

Additional data are required and expected, particularly concerning virologic control and the impact on morbidity and mortality, as well as the long-term safety, in order to be able to determine, with a better level of evidence, the efficacy, adverse effects and risks of HEPCLUDEX (bulevirtide) in the MA indication.

◗ There is a therapeutic alternative: the use of PEGylated alpha interferon.

◗ This is a first or second-line treatment.

Public health impact

Considering:

- the seriousness of the disease,
- its low prevalence (estimated prevalence < 4/10,000 in Europe[Erreur ! Signet non défini.]),
- the major medical need to have access to medicinal products that are at least as effective to those used in current strategies (based on the use of interferon), with a better efficacy and safety profile, making it possible to expand the cover to include patients who are currently ineligible to interferon treatment and are therefore in a situation where all the treatment options have been exhausted,
- the fact that HEPCLUDEX (bulevirtide) provides a response to the identified medical need, due to its virologic activity (reduction of viral load) and its biochemical activity (normalisation of ALT), but for which the impact on morbidity and mortality and/or quality of life, as well as on the care and life pathway is difficult to assess based on the limited data available.

HEPCLUDEX (bulevirtide) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of HEPCLUDEX (bulevirtide) is:

- **substantial only in the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease, in combination with a maintenance therapy against HBV and in the event of failure, intolerance or contraindication to PEGylated interferon alpha;**
- **insufficient to justify public funding cover in the other situations, including bulevirtide monotherapy, in particular.**

The Committee issues a favourable opinion for inclusion of HEPCLUDEX (bulevirtide) in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only in the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease, in combination with a maintenance therapy against HBV and in the event of failure, intolerance or contraindication to PEGylated interferon alpha.

- **Recommended reimbursement rate: 65%**

The Committee issues an unfavourable opinion for inclusion of HEPCLUDEX (bulevirtide) in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other situations, including bulevirtide monotherapy, in particular.

Clinical Added Value

Considering:

- **the demonstration of its virologic efficacy against HDV, in combination with a nucleoside/nucleotide analogue active against HBV, in patients in whom PEGylated interferon alpha has failed or is poorly tolerated (reduction by at least 2 log or conversion to negative viral load in approximately 50% of patients after 24 weeks, but with an undetectable viral load in only 4%),**
- **the combined response (virologic response and normalisation of ALT) in only 20% of patients after 24 weeks,**
- **the expected impact of virologic control on the clinical progression of the disease,**
- **the acceptable short-term safety profile,**
- **the substantial medical need in patients in whom PEGylated interferon alpha has failed or is poorly tolerated and in the absence of an alternative in this situation,**

and despite:

- **preliminary clinical data (2 phase 2 studies), and**
- **the limited experience in terms of maintenance of efficacy, impact on the reduction of morbidity and mortality and long-term safety,**

the Committee considers that HEPCLUDEX (bulevirtide), in combination with maintenance therapy for HBV, provides a minor clinical added value (CAV IV) in the care pathway for the treatment of patients infected with HDV for whom it is impossible to establish a suppressive antiviral treatment regimen with PEGylated alpha interferon, particularly in the event of failure, intolerance or contraindication.