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2024007657

Our reference
2024007657

Date 13 March 2024
RE: Package advice bulevirtide (Hepcludex®) in the treatment of chronic hepatitis D infection

Dear Mrs Dijkstra,

In your letter of 9 January 2024 (reference CIBG-24-06478), you asked the National Health Care Institute to carry out a substantive assessment of whether the medicinal product bulevirtide (Hepcludex®) is interchangeable with a product that is included in the Medicine Reimbursement System (GVS), and if not, to assess its value. The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has completed this assessment. Interested parties were also consulted. The considerations are set out in the attached reports.

Bulevirtide (Hepcludex®) is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

Bulevirtide is administered through a daily subcutaneous injection of 2 mg.

The marketing authorisation holder is asking that the registered indication be included on List 1B of the Health Insurance Regulation.
It is concluded that bulevirtide (Hepcludex®) meets the established medical science and medical practice and can be placed on List 1B. There is added value compared to active monitoring.

In this letter, I explain our findings and final conclusion.

Outcome of the substantive assessment
Assessment of interchangeability
To determine the place of a medicinal product in the GVS, its interchangeability with medicinal products already included in the GVS must first be assessed. Based on the criteria for interchangeability, bulevirtide is not interchangeable with other medicinal products included in the GVS.

Therapeutic value
In the Netherlands, patients with HDV infection and compensated liver disease are generally not treated with medication. If the liver disease worsens and the patient suffers from decompensated liver disease, a liver transplant should be considered. The European guideline recommends treatment with bulevirtide for all patients

with chronic hepatitis D infection and compensated liver disease.

Bulevirtide has been studied in a randomised, open-label study for the above indication compared to active monitoring. The National Health Care Institute considers achieving virological response as a crucial outcome parameter.
The results show that treatment with bulevirtide is likely to result in a significant, clinically relevant increase in the number of patients with virological response compared to active monitoring. Based on liver values (ALAT), which may be considered a surrogate for the crucial outcome parameter 'disease progression', treatment with bulevirtide may result in a clinically relevant reduction of the risk of disease progression. The side effects profile of bulevirtide is acceptable for patients with HDV infection.

Following discontinuation of treatment with bulevirtide, an exacerbation of hepatitis is commonly reported as a serious adverse reaction, possibly related to virological rebound after discontinuation of treatment. This means that adequate patient compliance in the treatment with bulevirtide is very important. However, since bulevirtide must be injected subcutaneously daily and the solution must also be prepared by the patient for administration, the ease of use is low.

Budget impact analysis
It is estimated that the total prevalent HDV population in the Netherlands consists of 176 patients. The incidence of HDV is 5 patients per year. The budget impact calculation assumes a market penetration of 90% in the third year. This results in 170 patients being eligible for bulevirtide treatment in the third year after inclusion in the health insurance package.

Clinical experts indicate that the use of bulevirtide is in practice a treatment of limited duration (i.e. not life-long). However, in the Netherlands, the follow-up described for these patients has not been implemented as such. Therefore, the National Health Care Institute has assumed chronic treatment in the calculation of the budget impact. The physicians' association has indicated that they are already discussing implementation of start and stop criteria. The National Health Care Institute would like these agreements to be formalized.

Due to the low ease of use of bulevirtide, i.e. daily injections that still need to be prepared by the patient, patient compliance is estimated to be between 68% and 85%. The comparative patient treatment according to the registered indication is active monitoring. Therefore, there is no substitution.

The costs per patient per year depend on patient compliance and range between €49,846 and €62,308, at 68% and 85% compliance, respectively.
In the third year after package inclusion, this results in a budget impact between €8,473,822 and €10,592,277 at 68% and 85% compliance, respectively, with uncertainty about market penetration.

Pharmaco-economic analysis
Based on the estimated budget impact, the product is exempt from pharmaco-economic analysis.

Advice
Based on the considerations mentioned above, the National Health Care Institute

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recommends bulevirtide (Hepcludex®) be included on List 1B in the GVS.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Annexes
FT report
BIA
GVS report

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