NCPE Assessment

Technical Summary

Bulevirtide (Hepcludex®)

22067

February 2024

Applicant: Gilead

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

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of bulevirtide (Hepcludex®).

Following assessment of the Applicant's submission, the NCPE recommends that bulevirtide (Hepcludex®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Merck Serono Ltd) Health Technology Assessment of bulevirtide (Hepcludex®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In September 2023, Gilead submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of bulevirtide (Hepcludex®) for the treatment of chronic hepatitis delta virus (HDV) infection in adult patients with compensated liver disease. Best supportive care treatment option for patients with CHD is generally defined as symptomatic treatment in addition to treatment for the underlying CHB with nucleos(t)ide analogues. The Applicant anticipates that bulevirtide will be used as treatment for adults with chronic hepatitis D (CHD) who have compensated liver disease, and evidence of significant fibrosis (METAVIR Stage ≥F2), whose disease has responded inadequately to PegIFNα treatment, or who are ineligible to receive PegIFNα treatment due to intolerance or contraindication. This is more restrictive than the licensed indication which is for the treatment of chronic HDV in adults with compensated liver disease. Gilead is seeking reimbursement of bulevirtide (Hepcludex®) on the High-Tech Drug Arrangement (HTDA).

1. Comparative effectiveness of **bulevirtide (Hepcludex®)**

The clinical trial programme examining the efficacy and safety of bulevirtide, in this submission, consists of one trial (MYR 301) with results available for two time-point analyses at weeks 48 and 96. MYR 301 is an ongoing multi-centre, open-label, randomised phase 3 study assessing the efficacy and safety of bulevirtide treatment in patients with CHD at two treatment doses of 2mg and 10mg subcutaneously once daily for 144 weeks compared with the control arm of delayed treatment (BSC for 48 weeks followed by 10mg once daily bulevirtide for 96 weeks). An off-treatment follow-up period of 96 weeks is also planned for all arms. The primary endpoint, at week 48, is combined treatment response defined as (i) a virologic response defined as undetectable HDV-RNA or a decrease in HDV-RNA by ≥2 $\log_{10}$ IU/mL, and (ii) biochemical normalisation defined as normalisation of alanine aminotransferase (ALT) levels.

For the primary outcome, at week 48 for the full analysis set (FAS), a statistically significant treatment effect was obtained for the bulevirtide 2mg group compared to the delayed treatment group, 45% (22/49) vs 2% (1/51), $p<0.001$. At week 96, the proportion of patients treated with bulevirtide 2mg who achieved the combined treatment response was 56% (27/49), with 20% (10/49) achieving undetectable HDV RNA at this timepoint. No statistical

significance was reported for these week-96 analyses.

2. Safety of **bulevirtide (Hepcludex®)**

Clinical safety in the submission was based on MYR 301 48-week data. Of the 150 patients enrolled in MYR 301, 82% reported any treatment-emergent adverse event (TEAE) which was fairly consistent across the three arms. Overall, the majority were classified as mild in nature (76%), no patient withdrew from the study secondary to TEAEs and there were no deaths reported. Serious TEAEs were reported in four patients (3%) overall. Grade 3 TEAEs were reported in 8% of the total study population (n=12). The most common Grade 3 TEAEs, experienced in more than one patient were thrombocytopenia (n=5) and neutropenia (n=4). Headache, eosinophilia and injection site reactions were also commonly reported.

3. Cost effectiveness of **bulevirtide (Hepcludex®)**

Methods

The analysis was conducted from the perspective of the Health Service Executive (HSE). Treatment effects for responders, captured in the Markov model, were based on combined treatment response data from MYR 301. Treatment effects for non-responders were predominantly derived from studies on patients with HBV, with multipliers applied to increase risks for HDV. Partial responders follow the same model pathways as non-responders, but with different transition probabilities from the fibrosis stage health states; with lower risk of worsening fibrosis, decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). For responders, no worsening of fibrosis or hepatitis disease progression was modelled, with improvements in fibrosis allowed (unlike non and partial responders). The model assumes that 'response' would prevent any disease progression.

The efficacy input parameter in the model was informed by a *post hoc* subgroup analysis of MYR 301 for patients with FibroScan scores ≥8 at baseline. Treatment stopping rules for bulevirtide were applied at 48 weeks for non-responders, and at 96 weeks for partial responders who were subsequently assumed to become non-responders.

The Review Group identified a number of limitations in the model, which were addressed in

the NCPE-adjusted base case including:

- The Applicant assumption that complete responders will not experience disease progression is not supported by evidence. The NCPE adjusted base case includes a continued risk of fibrosis progression and HCC for complete responders.
- The Review Group had concerns regarding the subjectivity of the FibroScan score cut-point selection and *post hoc* analyses. Therefore, the Review Group used data from the FAS to inform response.
- The Review Group removed an unvalidated additional utility gain applied for response and applied age-related utility decrements

Results

Incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE adjusted base case model assumptions are presented in Tables 1 and 2 respectively.

Table 1: Applicant base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	€37,966	6.08	-	-	-
Bulevirtide	€594,997	9.84	€557,031	3.75	€148,342

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year.
Corresponding probabilistic ICER using 1,500 iterations =€151,353/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

Table 2: NCPE adjusted base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	€46,541	5.96	-	-	-
Bulevirtide	€570,372	8.67	€523,831	2.71	€193,273

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year.
Corresponding probabilistic ICER using 1,500 iterations =€193,184/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analyses

The probability of bulevirtide being cost-effective at both willingness-to-pay thresholds of €20,000/QALY and €45,000/QALY in both the Applicant and NCPE base cases was 0%. Sensitivity analyses indicate that the ICER is sensitive to assumptions about treatment effects in relation to response, utility values, baseline heath state distribution (fibrosis stage)

and disease progression for non-responders. A price-ICER analysis indicates that a price reduction of 85.4%(inclusive of the Framework Agreement rebate) on the price to wholesaler, is required in order to reduce the ICER to below €45,000/QALY.

4. Budget impact of **bulevirtide (Hepcludex®)**

The price-to-wholesaler of bulevirtide is €8,547.92 per pack (pack size: 30 single doses). The expected per-patient annual cost is about €129,402 including VAT (€103,551 excluding VAT). The Applicant estimates 74 patients would be eligible for treatment with bulevirtide under its full marketing authorisation in Year 1. However, the Applicant has focused on a subpopulation of the licence for which they estimate 33 patients would be eligible for treatment in Year 1. Of this subpopulation the Applicant predicted 5 patients would receive treatment with bulevirtide in Year 1, increasing to 26 patients by Year 5. Under the Applicant's base case assumptions, the five-year cumulative gross drug budget impact was estimated at €12.03 million including VAT (€9.63 million excluding VAT).

The Review Group note the following issues with the Applicant's budget impact estimates:

- The number of individuals with chronic HBV, who test HDV-RNA positive in Ireland could be substantially higher than that estimated by the Applicant as testing for HDV has not been routine in the absence of available treatments.
- The Applicant assumes only a restricted subpopulation of the product licence will be eligible for treatment with bulevirtide.
- The Applicant assumes a gradual uptake; however, it is likely that when cohorts suitable for treatment are identified via testing that treatment numbers may be more immediate rather than a gradual uptake.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that bulevirtide not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.