

Addenda to this Public Summary Document been included at the end of the document.

7.01 BULEVIRTIDE

Powder for injection 2 mg,

Hepcludex®

Gilead Sciences Pty Ltd

1 Purpose of resubmission

- 1.1 The integrated codependent resubmission requested MBS listing of ribonucleic acid (RNA) polymerase chain reaction (PCR) testing and PBS listing of bulevirtide for the treatment of chronic hepatitis D (CHD) in patients positive for hepatitis D virus (HDV) RNA as detected by PCR. In the resubmission, the proposed treatment was not restricted to patients ≥ 18 years old compared to the previous submission.
- 1.2 Listing was requested based on a cost-utility analysis versus symptom management of CHD (also referred to as best supportive care (BSC)), including routine management of chronic hepatitis B (CHB) infection. Key components of the clinical issues addressed by the resubmission have not changed from the previous submission.

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Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: People diagnosed with chronic hepatitis B who have tested positive for serum anti-hepatitis D virus (anti-HDV) antibodies and are suspected of having chronic hepatitis D (CHD) Medicine: Patients with positive CHD with detectable polymerase chain reaction (PCR) results for serum/plasma HDV ribonucleic acid (RNA)
Prior tests	Diagnosis of HBV by hepatitis B surface antigen (HBsAg), Anti-HDV antibody testing
Intervention	Test: HDV RNA PCR on serum or blood Medicine: HEPCLUDEX (bulevirtide)
Comparator	Test: No HDV RNA testing Medicine: Symptomatic chronic HDV management
Clinical utility standard	Robogene® HDV RNA Quantification Kit 2.0 with a lower limit of detection (LLoD) of 6 IU/mL Test used in key clinical trial MYR301
Outcomes	Test: Concordance of the test with the clinical utility standard Predictive validity of the test (distinguished from HDV as a prognostic marker) Suitability of the test for monitoring (ability to distinguish response to treatment from background random variation, i.e. signal to noise ratio). Change in clinical management from initial and ongoing testing Medicine: Primary endpoint, composite endpoint at Week 48 of: Undetectable HDV RNA (HDV RNA < LLoD) or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline, and ALT normalisation (i.e. below the central laboratory defined ULN). Secondary endpoints at Week 48 of: Undetectable HDV RNA at Week 48 ALT normalisation at Week 48 Proportions of patients achieving HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL, Quality of life using EQ-5D, FSS and HQLQ Safety (adverse events, physical examinations, laboratory findings)
Clinical claims	In adults with chronic HDV infection, HEPCLUDEX (bulevirtide) is superior to current chronic HDV symptom management and is associated with a favourable safety profile. The MBS listing HDV RNA PCR testing and the PBS listing of HEPCLUDEX (bulevirtide) for the diagnosis and the treatment of chronic HDV will result in superior health outcomes compared to no testing and no access to HEPCLUDEX.

Source: Table 1.1-1, p3 of the resubmission

ALT = Alanine Aminotransferase; EQ-5D = EuroQol 5-Dimensions; FSS = Fatigue Severity Scale; HBV = Hepatitis B Virus; HQLQ = Hepatitis Quality of Life Questionnaire; MBS = Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; ULN = Upper Level of Normal.

Note: Blue shading indicates components and descriptions unchanged from the previous submission.

2 Background

Registration status

- 2.1 Bulevirtide was granted Priority Review Determination and Orphan Drug Designation on 15 March 2023 by TGA. Bulevirtide has been registered on the ARTG since 30 July 2024, with the TGA approving it for the treatment of chronic HDV infection in adults with compensated liver disease.

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Previous PBAC consideration

2.2 Table 2 summarises the key matters from the previous PBAC consideration of bulevirtide and how the resubmission addressed these concerns.

Table 2: Summary of key matters of concern in the March 2024 submission

Component	Matter of concern (bulevirtide PSD, March 2024 PBAC meeting)	How the resubmission addresses it
Restriction	Restriction should be revised to ensure patients are not inappropriately excluded from being able to continue bulevirtide if they achieve an undetectable viral load and/or ALT normalisation whilst on treatment (paragraph 7.17)	Issue not addressed in the resubmission and restriction not revised.
Relationship between virological response and liver complication outcomes	Uncertainties concerning the correlation between virological response (i.e., the $\geq 2\log_{10}$ reduction in HDV RNA load) and long-term clinical benefits from bulevirtide treatment (paragraph 7.9-7.10)	The resubmission attempted to address this issue by providing additional evidence from the published literature to establish the association between virological response and long-term liver-related outcomes in CHD.
Measure of treatment response used in the economic model	The PBAC agreed with the MSAC and PBAC ESCs that there are likely to be differences in outcomes between patients who are able to clear HDV infection (undetectable HDV RNA) and those who are achieving and/or sustaining virologic suppression with ongoing treatment. Whilst there may be improvements in tests over time, the use of undetectable viral load as the response measure would be more consistent with studies used to quantify the effect of virological response on outcomes (paragraph 12). The PBAC considered that, given this issue, the inputs to the economic model for long-term outcomes were highly uncertain and likely to overestimate the effectiveness of bulevirtide (paragraph 7.12)	The resubmission maintained the use of $\geq 2\log_{10}$ IU/mL reduction in HDV RNA levels as the measure of response to be applied in the economic model. The evidence presented in the resubmission was not adequate to show that a $\geq 2\log_{10}$ IU/mL reduction in viral load, by itself, is a reliable prognostic indicator of liver-related mortality and morbidity.
Other economic parameters	The PBAC noted that there were a number of other areas of uncertainty in the model including the assumption of a utility gain in the target population, the time horizon (58 years), and the source used to model the natural history of chronic HDV. Further, the role of testing to monitor HDV RNA levels and duration of therapy is highly uncertain and compliance to treatment applied in the model was not consistent with the trial data, though no adjustment was made to the efficacy outcomes. As such, the PBAC considered that the model likely did not reflect how bulevirtide would be used in Australian clinical practice (paragraph 7.12).	Most of these economic inputs/assumptions remained the same as in the previous submission, including time horizon, modelling of disease progression of HDV in non-responders, application of a utility gain in responders, treatment compliance, and the role of HDV RNA testing for monitoring.

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Component	Matter of concern (bulevirtide PSD, March 2024 PBAC meeting)	How the resubmission addresses it
Cost-effectiveness of bulevirtide	The PBAC noted that the modelled duration of treatment was 8.8 years, and ongoing treatment is required to maintain viral suppression. In this context, the PBAC considered the undiscounted life year gain estimated in the model (~6.3 years) appears highly implausible. Therefore, the PBAC considered the economic model likely substantially underestimated the ICER. The PBAC considered the listing of bulevirtide was not cost effective at the requested price (paragraph 7.13).	The modelled life years gained from the current economic model was 8.3 years (undiscounted), compared with a modelled treatment duration of 12.3 years. The survival benefit associated with bulevirtide is likely to have been overestimated.
Approach to manage economic uncertainties	The PBAC agreed with the ESC that it would likely be a long time before the patient-relevant impacts of bulevirtide treatment are well-characterised, and considered there remains uncertainty regarding how bulevirtide is likely to be used in clinical practice. As such, the PBAC considered the most appropriate way to manage the substantial uncertainties would be to adopt a conservative approach to the model inputs and advised that a revised economic model would be required (paragraph 7.14).	The resubmission did not take a conservative approach in the economic evaluation. The ICER increased by 400% when several model inputs were revised for consistency with previous PBAC advice.
Previous consideration of ICER for other antivirals for chronic viral hepatitis	The PBAC recalled that other antivirals for chronic viral hepatitis have previously been considered cost-effective with ICERs less than \$45,000/QALY, although the PBAC noted that the frequency of CHD infection in Australia is much lower than for hepatitis B or hepatitis C, treatment options for CHD are limited, and the TGA granted orphan drug designation to bulevirtide (paragraph 7.14).	The ICER estimated in the current resubmission was \$ ¹ /QALY but increases to > \$ ² /QALY in some of the multivariate analyses.
Prevalence and incidence data	The PBAC considered a resubmission for bulevirtide should address: Revised utilisation and financial estimates to ensure the most recent prevalence/incidence data are used, and addressing the issues raised by DUSC and the PBAC (paragraph 7.17)	The resubmission presented updated prevalence and incidence data where available. The resubmission addressed the issues raised by DUSC and PBAC where alternative data sources were suggested or available.

Source: Modified from Table 1.2-1, p9 of the resubmission

ALT = alanine aminotransferase; CHD = chronic hepatitis D; HDV = hepatitis D virus; ICER = incremental cost-effectiveness ratio; PSD = Public Summary Document; QALY = quality-adjusted life year; RNA = ribonucleic acid

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$355,000 to < \$455,000

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The requested restriction is shown below, with Secretariat additions in *italics* and deletions in ~~strikethrough~~.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Dispensed Price for Max. Qty	Available brands
BULEVIRTIDE						
Bulevirtide acetate 2 mg injection, 30 vials	NEW	2	60	5	Public Hospital Published: \$ [REDACTED] Effective: \$ [REDACTED] Private Hospital/Community Access Published: \$ [REDACTED] Effective: \$ [REDACTED]	HEPCLUDEX®
Restriction Summary / Treatment of Concept:						
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)						
Prescriber type: ☒ Medical Practitioners						
Restriction type: ☒ Authority Required (Streamlined) [new]						
Authority type: ☒ Non-complex Authority Required (non-CAR)						
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.						
Administrative Advice: No increase in the maximum number of repeats may be authorised.						
Administrative Advice: Special Pricing Arrangements apply.						
Episodicity: Chronic						
Condition: Hepatitis D infection						
Indication: Chronic Hepatitis D infection						
Clinical criteria: Patient must have detectable hepatitis delta virus (HDV) RNA levels <i>prior to commencing treatment with bulevirtide</i>						
AND						
Clinical criteria: Patient must have elevated serum alanine transaminase (ALT) <i>level prior to commencing treatment with bulevirtide</i>						
AND						
Clinical criteria: Patient must not have current or previous (within last 2 years) decompensated liver disease						
AND						
Treatment criteria: The treatment must be initiated in consultation with a physician experienced in the management of patients with viral hepatitis						
AND						

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Administrative Advice: Treatment can be as monotherapy for chronic hepatitis D virus or in co-administration with another therapy for Hepatitis B virus infection.

Note: Blue shading denotes components unchanged from the previous submission.

- 3.2 The resubmission proposed a Special Pricing Arrangement (SPA). The effective dispensed prices for maximum quantity (DPMQ) (60 x 2 mg vials) proposed in the resubmission are \$| for public hospital (vs. the previously requested \$|) and \$| for private hospital and community access (vs. the previously requested \$|), representing a |% price reduction compared with the effective prices proposed in the previous submission. The pre-PBAC Response proposed an additional |% price reduction to the effective AEMP (from \$| to \$|) resulting in a DPMQ of \$| (public hospital) and \$| (private hospital/community access).
- 3.3 The resubmission requested PBS Section 100 Highly Specialised Drugs Program listing of bulevirtide in public and private hospitals, as well as community access.
- 3.4 The PBAC previously advised that given the rarity of CHD in Australia, and the potential access issues for patients in rural and remote communities it was appropriate for prescribing to be in consultation with physicians with experience in the management of viral hepatitis (paragraph 7.5, bulevirtide Public Summary Document (PSD), March 2024 PBAC Meeting). For initiation of bulevirtide treatment the resubmission proposed restricting to prescribing by medical practitioners only, while in the previous submission, medical practitioners, as well as nurse practitioners, were allowed to prescribe bulevirtide. The ESCs noted that restricting prescribing of bulevirtide (initial and ongoing) to medical practitioners was consistent with its suggestion that the MBS item for monitoring HDV viral load during bulevirtide treatment should be limited to specialists.
- 3.5 Age criteria were removed from the proposed PBS restriction in the resubmission consistent with the PBAC's previous advice (paragraph 7.5, bulevirtide PSD, March 2024 PBAC Meeting).
- 3.6 The proposed restriction in the resubmission still inappropriately excluded patients who are responders to the treatment and do not have detectable HDV RNA, from being eligible for continuous treatment. This issue was raised at the March 2024 PBAC meeting i.e. "A revised restriction that ensures patients are not inappropriately excluded from being able to continue bulevirtide if they achieve an undetectable viral load and/or ALT normalisation whilst on treatment" (paragraph 7.17, bulevirtide PSD, March 2024 PBAC meeting). The pre-PBAC Response agreed with the PBAC ESC's advice to include "prior to commencing treatment with bulevirtide" in the clinical criteria of detectable viral load and elevated serum alanine transaminase (ALT) to allow continuation of bulevirtide.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 The population and disease described in the resubmission were unchanged from the previous submission. HDV infection is caused by the hepatitis D virion, which is a defective virus and relies on an established HBV infection and the presence of hepatitis B surface antigen (HBsAg) to complete its life cycle in the infected host's hepatocyte¹. Coinfection of HDV and HBV (i.e., the infection of HDV and HBV occurs at the same time) usually has a transient and self-limiting disease course and most patients are able to spontaneously clear both viruses with their own immune system and recover from the liver injury. However, superinfection of HDV in patients who are chronic HBV carriers usually becomes long-term and results in persistent viraemia, elevated alanine aminotransferase (ALT) levels, and a more rapid disease progression to cirrhosis and liver decompensation, as well as an increased risk of hepatocellular carcinoma (HCC)^{2,3}.
- 4.2 CHD occurs predominantly in high risk groups in Australia. Risk factors include intravenous drug use, men who have sex with men and persons migrating from countries such as Sudan, Vietnam and Pakistan.
- 4.3 CHD is currently diagnosed by a positive serum anti-HDV antibody test. The standard treatment for CHD includes BSC or symptom management and long-term follow up by a liver specialist. For patients whose liver disease has progressed to an advanced stage, or those who have developed HCC, liver transplantation is the only treatment option.
- 4.4 Bulevirtide is a TGA approved treatment (registered with ARTG since 30 July 2024) specifically for CHD in adult patients with compensated liver disease. Bulevirtide is a lipopeptide with a structure mimicking the pre-S1 domain of the surface protein of HBV. The mechanism of action of bulevirtide involves inhibition of HBV and HDV virion entry into the hepatocytes through blocking the sodium taurocholate cotransporting polypeptide (NTCP) binding site on hepatocytes. Bulevirtide was proposed to be used for treatment of patients diagnosed with CHD who have tested positive for HDV RNA detected by PCR, with compensated liver disease, as well as an elevated ALT level. Patients receiving bulevirtide treatment will simultaneously receive management for the underlying HBV infection as clinically appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

¹ Bichko V et al. Pathogenesis associated with replication of hepatitis delta virus. *Infectious Agents and Diseases*. 1994; 3: 94-97.

² Miao Z et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis Delta virus infection. *Journal of Infectious Diseases*. 2020; 221:1677-1687.

³ Fattovich G et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *The European Concerted Action on Viral Hepatitis (Eurohep)*. *Gut*. 2000; 46: 420-426.

5 Comparator

- 5.1 The resubmission nominated no HDV RNA PCR testing as the comparator for HDV RNA PCR testing, and symptomatic CHD management or BSC as the comparator for bulevirtide. These were unchanged from the previous submission. The PBAC considered the nominated comparators for HDV RNA testing and bulevirtide as reasonable (paragraph 7.8, bulevirtide PSD, March 2024 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from consumer group/organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted the comments from Hepatitis Australia and Liver Foundation supporting the listing of bulevirtide noting there is a high unmet demand for effective hepatitis D treatment. The PBAC noted Hepatitis Australia reiterated its support as provided in its March 2024 submission (paragraphs 6.2-6.3, bulevirtide PSD, March 2024 PBAC meeting).

Overview of the evidence base

- 6.3 The approach taken in the submission was to present evidence that has been linked to support the contention that targeting HDV RNA with bulevirtide will result in improved clinical outcomes compared with no HDV RNA testing and BSC (Table 3).

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Table 3: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias
Accuracy and performance of the test (cross-sectional accuracy)	Concordance of quantitative HDV RNA levels between different tests and RNA extraction methods.	☒ k=3 n=335	High
Prognostic evidence (longitudinal accuracy)	Comparison of outcomes in patients receiving usual care, conditioned on the presence, absence or reduction of HDV RNA at baseline	☒ k=14 retrospective cohorts n=2,749 ☒ k=2 prospective studies n=154 ☒ k=1 systematic review n=4,853	High
Predictive effect	Comparison of outcomes in patients receiving usual care, conditioned on the reduction of HDV RNA	☒ k=5 retrospective cohorts n=244	High
Change in patient management	Evidence to show that HDV RNA test results guide decisions about stopping treatment (due to response or lack of response) or intensifying treatment (due to limited response)	☒ k=2 uncontrolled before/after studies n=129	High
Health outcomes (clinical utility)	No evidence presented.	☐ k=0 n=0	
Predictive effect (treatment effect variation)	Comparison of outcomes in patients receiving usual care, conditioned on the reduction of HDV RNA	☐ k=0 n=0	
Treatment effect (enriched)	Single randomised controlled trial of bulevirtide vs symptom management of CHD in patients that are tested for HDV RNA by PCR in both arms and found to be positive.	☒ k=1 n=150	Low

Source: Table compiled during the evaluation.

CHD = Chronic Hepatitis D; HDV = Hepatitis D Virus, k=number of studies, n=number of patients, NA=not applicable; RNA = Ribonucleic Acid.

Note: Blue shading denotes clinical evidence unchanged from the previous submission.

Note: Data of treatment effect provided in the resubmission was from the same key trial (MYR301) used in the previous submission, but the data provided in the resubmission covered a longer treatment duration (up to 144 weeks) compared to 96 weeks in the previous submission.

6.4 The resubmission was based on the same clinical trial of bulevirtide versus symptom management (MYR301) as presented in the previous submission. In the MYR301 trial, enrolled patients with positive HDV RNA detected by PCR, elevated serum ALT level, and compensated liver disease received bulevirtide or symptom management as a first line treatment for CHD.

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Table 4: Data availability to inform comparisons

Proposed test vs no test	No evidence presented	
Proposed test vs alternative test	3 additional small studies reporting concordance of quantified HDV RNA results	
	Proposed drug	Comparator drug
Biomarker test positive	Updated data from MYR301	Updated data from MYR301
Biomarker test negative	No evidence presented	No evidence presented

Source: Table compiled during the evaluation.

- 6.5 The populations and tests were largely transferable across the linked evidence, but the treatment regimens identified in the literature searches largely used treatment with interferon (IFN), which is not routinely used in Australia for CHD.
- 6.6 The risk of bias was considered high for the studies which informed assessments of the accuracy and performance of the test, prognostic value of HDV RNA and change in patient management. The overall risk of bias in the trial (MYR301) was considered low. The limitation of the MYR301 trial design was the open-label design of the study, in which patients and investigators were not blinded to the treatment group assignment. The risk of bias was considered low for the efficacy endpoints (i.e., serum HDV RNA level and ALT level), as they were objective outcomes and as those who assessed these endpoints were blinded to treatment allocation. However, there is potential for bias in assessment of patient reported outcomes such as adverse events (AEs) and quality of life.

Clinical trials on the effectiveness and safety of bulevirtide

- 6.7 MYR301 was a head-to-head, Phase 3, multicentre, open-label trial that assessed the effectiveness and safety of bulevirtide in adult patients diagnosed with CHD who had serum HDV RNA detected by PCR, elevated serum ALT level, as well as compensated liver disease (n=150). In the trial, patients were randomly assigned to three treatment arms: 1) bulevirtide 2 mg arm (bulevirtide 2 mg once daily for 144 weeks) (N=49); 2) bulevirtide 10 mg arm (bulevirtide 5 mg twice daily for 144 weeks) (N = 50); and 3) delayed treatment arm (symptom management of CHD or BSC for the first 48 weeks, followed by bulevirtide 10 mg daily for 96 weeks) (N=51). In the resubmission, effectiveness and safety data covering Week 96 to Week 144 of the treatment period of the trial were presented, in addition to the data that had been presented in the previous submission which included the first 96 weeks of the study. As bulevirtide 5 mg twice daily is not the recommended dose regimen, the results of this treatment arm of the MYR301 trial are not presented.
- 6.8 In the MYR301 trial, patients randomised to the two bulevirtide treatment arms received bulevirtide for 144 weeks, regardless of their response status. The bulevirtide product information (PI) states that the optimal treatment duration is unknown, and that treatment should be continued as long as it is associated with clinical benefit. In

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the March 2024 PBAC meeting, it was concluded that “the decision to continue or cease treatment, based on response, was a matter of clinical judgement” (paragraph 7.6, bulevirtide PSD, March 2024 PBAC meeting). See also ESCs discussion of HDV testing to monitor treatment response and inform management decisions (paragraphs 6.38-6.41).

- 6.9 In the MYR301 trial, 60.7% of the patients received anti-HBV treatment during the course of the study, of these, 54.7% had started anti-HBV treatment prior to baseline and 6.0% had started anti-HBV treatment at baseline (by Day 2). Patients who had used interferon (IFN) within 6 months of screening were not included in the study and no patients received pegylated (PEG) IFN concomitantly with bulevirtide during the study.
- 6.10 The primary efficacy endpoint of the MYR301 trial was a combined response at Week 48. A combined response was defined as simultaneous achievement of 1) undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline, and 2) ALT normalisation. Undetectable HDV RNA, ALT normalisation, and virological response (defined as HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL or undetectable HDV RNA) were also reported as secondary and exploratory outcomes in the trial.
- 6.11 There is a body of evidence supporting the association between undetectable HDV RNA (either at baseline or achieved through treatment) and improved liver-related health outcomes. The ESCs noted the additional evidence presented in the resubmission addressing the correlation between viremia and clinical outcomes. The ESCs accepted that the evidence presented in the resubmission, including evidence based on detectable versus undetectable RNA levels, was indicative of the biologically plausible claim that a drop in HDV viral load levels relative to baseline was indicative of clinical response to treatment insofar as patients with lower viral loads may have a reduced risk of developing liver-related clinical events compared to patients with higher viral loads. However, the ESCs agreed with the evaluation that no studies provided conclusive evidence to support that the $\geq 2 \log_{10}$ IU/mL decline in HDV RNA level, as a surrogate marker by itself, is correlated with improved long-term liver-related health outcomes. The evaluation considered virological response to treatment on its own may not be a clear predictor for the prognosis of chronic viral hepatitis because liver injury in viral hepatitis is the consequence of not only the viral infection but also the infected individual's immunological response to the virus. This response can vary between patients. ALT is a liver enzyme produced in hepatocytes and is released when there is hepatocellular injury. ALT, in combination with viral load, is usually used as an indicator to measure the severity of liver disease in CHD patients.
- 6.12 The Pre-Sub-Committee Response (PSCR) argued that achieving undetectable viral load is the ideal goal of treatment for any viral hepatitis patient. However, the assays used to quantify HDV RNA in older CHD studies that reported improved clinical outcomes due to the viral load declining to a level reported as “undetectable” had

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LLoD levels that are substantially higher (less sensitive) than the assay used in the pivotal MYR301 trial for bulevirtide in this resubmission. As such, the PSCR argued that use of the term “undetectable” based on older assays is conflating and is not the appropriate outcome for assessing response or to determine surrogacy of viral load to clinical outcomes. The PSCR also presented additional analyses of HDV RNA response rates using different viral load cutoff levels using the pivotal MYR301 trial data at Week 144 (Table 8). The PSCR argued $\geq 2 \log_{10}$ responders it is a good proxy for responses that were previously quantified as undetectable using less sensitivity assays, and that HEPCLUDEX ‘undetectable’ responders using the 930 IU/mL LLoD are similar to $\geq 2 \log_{10}$ responders.

6.13 While noting the limitations of the concept of “detectable” vs “undetectable”, the ESCs considered the evidence provided did not adequately support the surrogacy of a $\geq 2 \log_{10}$ IU/mL decline in HDV RNA level, for improved long-term liver-related health outcomes. The ESCs noted that one publication provided evidence for this relationship (Farci et al 2004), however this analysis was based on data from a 1994 study of treatment with interferon, and two more recent studies (Palom 2021 and Wranke 2020) failed to show a statistically significant difference in clinical outcomes based on $\geq 2 \log_{10}$ IU/ml reduction.

6.14 Details of the MYR301 trial presented in the resubmission are provided in the table below.

Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MYR 301 (NCT03852719)	A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta. MYR301- Interim Week 144 Clinical Study Report	Report date: 17 April 2024
	Wedemeyer H, Aleman S, et al. Bulevirtide monotherapy in patients with chronic HDV: efficacy and safety results through week 96 from a phase III randomized trial.	Journal of Hepatology 2024; 1-9
	Wedemeyer H, Aleman S, et al. Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis delta: results from an interim analysis of a phase 3 randomized study.	Gastroenterology 2024; 166(5) S-1600
	Lampertico P, Wedemeyer H, et al. Continued treatment of early nonresponder or partial virological responders with bulevirtide monotherapy in patients with chronic hepatitis delta (CHD) through week 96 leads to improvement in virological and biochemical responses.	Gut 2023; 82: A101-A102
	Aleman S, Wedemeyer H, et al. High rates of adherence to bulevirtide monotherapy for chronic hepatitis delta through 96 weeks: results from an interim analysis of the phase 3 study MYR301.	Gastroenterology 2024;166(5): S-1603-S-1604
	Wedemeyer H, Aleman S, et al. Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis delta: results from an interim analysis of a phase 3 randomized study	Gut 2023;72:A103-A104
	Aleman S, Liu Y, et al. No detectable resistance to bulevirtide monotherapy through 96 weeks treatment in patients with chronic hepatitis D.	Hepatology 2023; 78: S398-S399

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Trial ID	Protocol title/ Publication title	Publication citation
	Wedemeyer H, Aleman S, et al. Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis D: results from an interim analysis of a phase 3 randomized study.	Journal of Hepatology 2023; 78: S57-S58
	Lampertico P, Wedemeyer H, et al. Continued treatment of early nonresponder or partial virological responders with bulevirtide monotherapy in patients with chronic hepatitis delta (CHD) through week 96 leads to improvement in virological and biochemical responses.	Journal of Hepatology 2023; 78: S111-S114
	Wedemeyer H, Aleman S, et al. Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis D: results from an interim analysis of a phase 3 randomized study.	Gut Liver 2023; 17:165
	Wedemeyer H, Aleman S, et al. A phase 3, randomized trial of bulevirtide in chronic hepatitis D.	New England Journal of Medicine 2023; 389(1): 22-32.
	Buti M, Wedemeyer H, et al. Bulevirtide improves health-related quality of life measured by EQ-5D VAS in patients with chronic hepatitis delta: An exploratory analysis of a Phase 3 trial at 48 weeks.	Digestive and Liver Disease 2023; 55: S72-3.
	Wedemeyer H, Aleman S, et al. Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study.	Digestive and Liver Disease 2022; 54: S24-5.
	Wedemeyer H, Aleman S, et al. Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study.	Hepatology International 2022; 16: S234.
	Wedemeyer H, Aleman S, et al. Efficacy and safety of bulevirtide monotherapy given at 2 mg or 10 mg dose level once daily for treatment of chronic hepatitis delta: week 48 primary end point results from a phase 3 randomized, multicenter, parallel design study.	Journal of Hepatology 2022; 77 (suppl1): 4-5.
	Buti M, Wedemeyer H, et al. Treatment with bulevirtide improves patient-reported outcomes in patients with chronic hepatitis delta: An exploratory analysis of a Phase 3 trial at 48 weeks.	Journal of Hepatology 2022; 77 (suppl1): S103
	Freismuth A, Wedemeyer H, et al. Bulevirtide monotherapy at low and high doses in patients with chronic hepatitis delta: 24-week interim data of the Phase 3 MYR301 study.	Journal of Gastroenterology and Hepatology 2022; 37(suppl1): 52-53.
	Buti M, Wedemeyer H, et al. Bulevirtide improves health related quality life measured by EQ-5D VAS in patients with chronic hepatitis delta: an exploratory analysis of a phase 3 trial at 48 weeks.	Hepatology 2022; 76: S224-5.
	Allweiss L, Dettmer C, et al. Strong intrahepatic decline of hepatitis D virus RNA and antigen after 24 weeks of treatment with Myrcludex B in combination with tenofovir in chronic HBV/HDV infected patients: Interim results from a multicenter, open-label phase 2b clinical trial.	Hepatology 2021; 74(suppl1): 148A.
	Wedemeyer H, Aleman S, et al. Treatment with bulevirtide improves patient reported outcomes in patients with chronic hepatitis delta (CHD): An Interim exploratory analysis at week 24.	Hepatology 2021; 74: 413A-414A
	Wedemeyer H, Aleman S, et al. Efficacy and safety of bulevirtide monotherapy given at 2 mg or 10 mg dose Level once daily for treatment of chronic hepatitis delta: Week 48 primary endpoint results from a Phase 3 randomized, multicenter, parallel design study.	Zeitschrift für Gastroenterologie 2023; 61(01): e45-6

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Trial ID	Protocol title/ Publication title	Publication citation
	Lee S, Wedemeyer H, et al. S1179 bulevirtide monotherapy at low and high dose in patients with chronic hepatitis Delta: 24-week interim data of the Phase 3 MYR301 study.	Official Journal of the American College of Gastroenterology 2022; 117(10S): e858-9.
	Buti M, Wedemeyer H, et al. Treatment with bulevirtide improves patient-reported outcomes in patients with chronic hepatitis delta: An exploratory analysis of a Phase 3 trial at 48 weeks.	Zeitschrift für Gastroenterologie 2023; 61(01): e47-.

Source: Table 2.6-1, pp57-59 of the resubmission

EQ-5D VAS = EuroQoL-5 Dimension Visual Analogue Scale

Note: Blue shading denotes reports used in the previous submission

6.15 The key features of the direct randomised trial are summarised in the table below.

Table 6: Key features of the included evidence

Trial	N	Design/ duration	Patient population	Outcome(s)	Use in modelled evaluation
Bulevirtide versus symptom management of CHD					
MYR301	150 ^a	R, MC, OL Trial duration: 144 weeks	Patient with CHD, compensated liver disease, positive HDV RNA detected PCR and elevated serum ALT level	Primary efficacy endpoint: combined response defined as virological response ^b and ALT normalisation Key secondary and exploratory efficacy endpoints: - Undetectable HDV RNA - Virological response^b - ALT normalisation - Change from baseline in liver stiffness as measured by elastography Quality of life outcomes: EQ-5D, FSS and HQLQ Key safety outcomes: TEAEs	Virological response ^b , EQ-5D, and ≥ Grade 3 TEAEs, up to week 144

Source: developed during the evaluation

ALT = alanine aminotransferase; CHD = chronic hepatitis D; FSS = Fatigue Severity Scale; HDV = hepatitis D virus; HQLQ = Hepatitis Quality of Life Questionnaire; LLoD = lower limit of detection; MC = multi-centre; OL= open label; PCR = polymerase chain reaction; R = randomised; RNA = ribonucleic acid; TEAEs = treatment emergent adverse events

^a Of the 150 patients randomised, 50 patients were randomised into bulevirtide 10 mg treatment group. As a daily dose of bulevirtide 10 mg is not the recommended dosing regimen, the results from this treatment arm were not presented in the Commentary.

^b Virological response was defined as undetectable HDV RNA (HDV RNA < lower limit of detection - LLoD) or decrease in HDV RNA by ≥ 2 log₁₀ IU/ml from baseline

Note: Blue shading denotes features unchanged from the previous submission.

Comparative effectiveness

6.16 A summary of the MYR301 trial results in patients in the bulevirtide 2 mg treatment arm and in the delayed treatment arm is provided in the table below. As patients in the delayed treatment arm were switched to bulevirtide 10 mg at Week 48, data at Week 96 and Week 144 for this treatment arm, and the differences between the bulevirtide 2 mg arm and the delayed treatment arm at these two data cut-off timepoints, are not presented.

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Table 7: Key efficacy results reported in the MYR301 trial

Endpoint	Bulevirtide 2 mg (N=49)	Delayed treatment (N=51)
Combined response ^a	Week 48 (primary endpoint)	
	Number of responders	22
	Proportion responders, % (95% CI)	44.9 (30.7, 59.8)
	Difference in proportions (96% CI) (bulevirtide 2 mg vs delayed treatment)	42.9 (27.0, 58.5)
	p-value ^e	<0.0001
	Week 96 (exploratory endpoint) ^d	
	Number of responders	27
	Proportion responders, % (95% CI)	55.1 (40.2, 69.3)
	Week 144 (exploratory endpoint) ^d	
	Number of responders	28
	Proportion responders, % (95% CI)	57.1 (42.2, 71.2)
Virological response ^b	Week 48 (additional endpoint)	
	Number of responders	36
	Proportion responders, % (95% CI)	73.5 (58.9, 85.1)
	Difference in proportions (95% CI) (bulevirtide 2 mg vs delayed treatment)	69.5 (54.1, 81.9)
	p-value	< 0.0001
	Week 96 (exploratory endpoint) ^d	
	Number of responders	37
	Proportion responders, % (95% CI)	75.5 (61.1, 86.7)
	Week 144 (exploratory endpoint) ^d	
	Number of responders	36
	Proportion responders, % (95% CI)	73.5 (58.9, 85.1)
Undetectable HDV RNA	Week 48 (key secondary endpoint)	
	Number of responders	6
	Proportion responders, % (95% CI)	12.2 (4.6, 24.8)
	Difference in proportions (96% CI) (bulevirtide 2 mg vs delayed treatment)	12.2 (3.7, 24.8)
	p-value ^e	0.0117
	Week 96 (exploratory endpoint) ^d	
	Number of responders	10
	Proportion responders, % (95% CI) (bulevirtide 2 mg vs delayed treatment)	20.4 (10.2, 34.3)
	Week 144 (exploratory endpoint) ^d	
	Number of responders	14
	Proportion responders, % (95% CI)	28.6 (16.6, 43.3)
ALT normalisation ^c	Week 48 (secondary endpoint)	
	Number of responders	25
	Proportion responders, % (95% CI)	51.0 (36.3, 65.6)
	Difference in proportions (95% CI) (bulevirtide 2 mg vs delayed treatment)	39.3 (19.9, 55.8)
	p-value	< 0.0001
	Week 96 (exploratory endpoint) ^d	
	Number of responders	31
	Proportion responders, % (95% CI)	63.3 (48.3, 76.6)
	Week 144 (exploratory endpoint) ^d	
	Number of responders	29
	Proportion responders, % (95% CI)	59.2 (42.2, 73.0)

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Change in liver stiffness from baseline	Week 48 (secondary endpoint)		
	Baseline means (SD), kPa	14.0 (8.2)	15.3 (9.0)
	Number of participants in analysis	48	45
	Least square means (95%CI)	-3.1 (-4.7, -1.5)	0.9 (-0.8, 2.6)
	Difference in least square means (95% CI) (bulevirtide 2 mg vs delayed treatment)	-4.0 (-6.3, -1.6)	
	p-value	0.0010	
	Week 96 (secondary endpoint) ^d		
	Number of participants in analysis	48	n/a
	Least square means (95% CI)	-4.3 (-5.5, -3.1)	n/a
	Week 144 (secondary endpoint) ^d		
	Number of participants in analysis	45	n/a
	LS mean (95% CI)	-5.22 (-6.8, -3.6)	n/a

Source: developed during the evaluation based on pp88-108 of the Interim Week 144 Clinical Study Report of the MYR301 trial

ALT = alanine aminotransferase; BSC = best supportive care; CI = confidence interval; N = total participants in group; n/a = not applicable

^a Defined as undetectable HDV RNA (HDV RNA < lower limit of detection (LLOD)) or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/ml from baseline and ALT normalisation (i.e., below the central laboratory defined upper limit of normal (ULN))

^b Defined as undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/ml from baseline

^c ALT normalisation: ≤ 31 U/L for females and ≤ 41 U/L for males (Russian sites); ≤ 34 U/L for females and ≤ 49 U/L for males (all other sites)

^d Patients in the delayed treatment arm were switched to bulevirtide 10 mg at Week 48. Data for this arm is not included in the Week 96 and Week 144 presentation nor are the differences between the delayed treatment arm and the 2 mg arm at these timepoints.

^e There was a statistically significant difference at Week 48 if $P < 0.04$.

Note: for the result of least square means of the change in liver stiffness from baseline in the bulevirtide 2 mg arm at Week 96, the figures presented in the previous submission were different (in the previous submission, LS means was presented as -4.0, and the 95% CI was presented as -5.6, -2.5)

Note: Blue shading denotes endpoints and results presented in the previous submission

- 6.17 The primary combined response (achieving both virological response and ALT normalisation) at Week 48 occurred in 22 of the 49 patients (44.9%; 95% confidence interval (CI): 30.7%, 59.8%) who received bulevirtide 2 mg once daily treatment, and in one of the 51 patients (2.0%; 95% CI: 0.0%, 10.4%) who were in the delayed treatment arm and received BSC/no active treatment for the first 48 weeks in the trial. The difference between the two arms was statistically significant (difference: 42.9%; 96% CI: 27.0%, 58.5%; $p < 0.0001$). The number of responders in the bulevirtide 2 mg treatment arm increased from 22 (44.9%) at Week 48 to 27 (55.1%; 95% CI: 40.2%, 69.3%) at Week 96. At Week 144, one additional patient (57.1%; 95% CI: 42.2%, 71.2%) achieved a combined response. After Week 48, patients in the delayed treatment arm started to receive bulevirtide 10 mg once daily. Therefore, there was no comparative data on bulevirtide 2 mg once daily versus BSC after Week 48.
- 6.18 At Week 48, virological response (defined as HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL from baseline or undetectable HDV RNA) was achieved by 36 patients in the bulevirtide 2 mg treatment arm (73.5%; 95% CI: 58.9%, 85.1%), compared with two patients in the delayed treatment arm (3.9%; 95% CI: 0.5%, 13.5%). The difference in virological response rate between the two arms was 69.5% (95% CI: 54.1%, 81.9%; $p < 0.0001$). From 48 weeks to 96 weeks, the proportion of responders in the bulevirtide 2 mg treatment arm increased by 2.0% to 75.5% (95% CI: 61.1%, 96.7%). However, at Week 144, the proportion decreased to 73.5% (95% CI: 58.9%, 85.1%).

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- 6.19 Six of the 49 patients (12.2%; 95% CI: 4.6%, 24.8%) in the bulevirtide 2 mg treatment arm had undetectable HDV RNA at Week 48, compared with no patient in the delayed treatment arm with undetectable HDV RNA at Week 48. Between Week 48 and Week 96, the proportion of patients with undetectable HDV RNA increased from 12.2% to 20.4% (95% CI: 10.2%, 34.3%) in the bulevirtide 2 mg arm. At Week 144, the proportion increased to 28.6% (95% CI: 16.6%, 43.3%). The PSCR presented additional analyses of HDV RNA response rates using different viral load cutoff levels using the pivotal MYR301 trial data at Week 144. The PSCR noted that the majority (32/49, 65.3%) of patients treated with bulevirtide in MYR301 had a viral load below 930 IU/mL and would have been classified as having “undetectable” HDV RNA by the standards available at the time of the more modern HIDIT-I and HIDIT-II studies (in interferon for treatment of HDV) where improved clinical outcomes were observed for patients with undetectable HDV RNA. The PSCR argued that this supports the claim that HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL from baseline is a good proxy for responses that previously would have been defined as undetectable using less sensitive assays. The ESCs noted that this definition of virological response (viral load below 930 IU/mL) would reduce the proportion of responders from 73.5% to 65.3%.

Table 8: HDV RNA Response Rate at Week 144 by Different Cutoff for HEPCLUDEX 2mg

Proportion responders, n (%); 95% CI	HEPCLUDEX 2mg (N=49)
Cutoff level = 50 IU/mL	25 (51%); 36.3%, 65.6%
Cutoff level = 100 IU/mL	26 (53.1%); 38.3%, 67.5%
Cutoff level = 930 IU/mL	32 (65.3%); 50.4%, 78.3%

Source: Provided in PSCR

- 6.20 Normalisation of ALT at Week 48 occurred in 51.0% (95% CI: 36.3%, 65.6%) of patients in the bulevirtide 2 mg arm and in 11.8% (95% CI: 4.4%, 23.9%) of patients in the delayed treatment arm, with a statistically significant difference between the two arms (difference: 39.3%; 95% CI: 19.9%, 55.8%; $p < 0.0001$). In the bulevirtide 2 mg treatment arm, the proportion of patients achieving ALT normalisation increased from 51.0% at Week 48 to 63.3% (95% CI: 48.3%, 76.6%) at Week 96. However, at Week 144, the proportion decreased to 59.2% (95% CI: 42.2%, 73.0%).
- 6.21 Bulevirtide also resulted in improvements in liver stiffness in the bulevirtide 2 mg treatment arm. A least square mean decrease (improvement) of liver stiffness from baseline by -3.08 kPa (95% CI: -4.70 to -1.46) in treated patients at Week 48 of treatment was observed, while patients receiving no treatment had an increase (worsening) of liver stiffness from baseline by 0.88 kPa (95% CI: -0.80 to 2.56). The difference in the least square means between the two arms was statistically significant (-3.96 kPa; 95% CI: -6.28 to -1.64; $p=0.0010$). Liver stiffness continued to improve in patients receiving bulevirtide 2 mg from Week 48 to Week 96. During this time period, the least square mean change from baseline in this treatment arm decreased further to -4.3 kPa (95% CI: -5.5%, to -3.1%). At Week 144, the least square mean change from baseline decreased further to -5.22 kPa (95% CI: -6.8%, -3.6%).

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6.22 At Week 48, scores for the individual EuroQoL-5 Dimension-3 Level (EQ-5D-3L) domains, EuroQol visual analogue scale (EQ-VAS), Fatigue Severity Scale (FSS), and Hepatitis Quality of Life Questionnaire (HQLQ) were generally similar between the bulevirtide 2 mg treatment arm and the comparator arm, with the exception of the EQ-VAS and some components of the HQLQ (such as role physical, hepatitis-specific limitations and hepatitis-specific health stress), in which there was a significant improvement in the bulevirtide treatment arm compared with the delayed treatment arm. At Week 96, the results for quality-of-life questionnaires were generally consistent with the Week 48 results. From Week 96 to Week 144, further improvement in health-related quality of life measured by EQ-VAS and HQLQ in the bulevirtide 2 mg treatment arm was observed. The quality-of-life data should be interpreted with caution as multiple endpoints were tested, and the study was not sufficiently powered to test these exploratory endpoints. In addition, given the open-label design of the study, neither participants nor the study personnel who collected health-related quality of life data were blinded to the treatment allocation. These subjective patient-reported outcomes are therefore at risk of bias.

Comparative harms

6.23 Table 9 below summarises the overall TEAEs in the bulevirtide 2 mg treatment arm at Week 48, Week 96, and Week 144, as well as in the delayed treatment arm (i.e., BSC) at Week 48 in the MYR301 trial.

Table 9: Summary of overall TEAEs in the MYR301 trial

	Bulevirtide 2 mg (N=49)			Delayed treatment (N=51)
Data cut-off	Week 48	Week 96	Week 144	Week 48
TEAE	41 (83.7%)	47 (95.9%)	48 (98.0%)	39 (76.5%)
TEAE with Grade 3 or higher	5 (10.2%)	9 (18.4%)	12 (24.5%)	4 (7.8%)
TEAE related to study drug	24 (49.0%)	25 (51.0%)	27 (55.1%)	0
TEAE related to study drug with Grade 3 or higher	1 (2.0%)	4 (8.2%)	4 (8.2%)	0
TE serious AE	2 (4.1%)	2 (4.1%)	2 (4.1%)	1 (2.0%)
TE serious AE related to study drug	0	0	0	0
TEAE leading to premature discontinuation of study drug	0	0	0	0
Death	0	0	0	0

Source: Table 2.9-7, p82 of the resubmission

AE = adverse event; SAS = safety analysis set; TE = treatment-emergent; TEAE = treatment-emergent adverse event

Note: Blue shading denotes results presented in the previous submission

6.24 The incidence of drug-related TEAEs was significantly higher in patients treated with bulevirtide 2 mg once daily than in the comparator arm (49.0% vs. 0%) during the first 48 weeks. Continued exposure to the study drug resulted in higher proportions of treated patients experiencing any TEAEs, Grade 3 TEAEs, and drug-related $\geq$ Grade 3 TEAEs.

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- 6.25 The AEs reported in MYR301 in the entire 144 weeks of treatment were mostly Grade 1 (mild) or 2 (moderate) in severity. The incidence of serious TEAEs was low across treatment arms throughout the 144-week treatment period, none of which were considered related to bulevirtide. No cases of premature discontinuation of bulevirtide treatment due to TEAEs, nor deaths were observed in either treatment arm.
- 6.26 The most commonly reported (> 10%) AEs in the bulevirtide 2 mg treatment arm were headache, leukopenia, vitamin D deficiency, pruritus, thrombocytopenia, eosinophilia, and fatigue during the 48 week treatment period. With extended duration of treatment, between Week 96 and Week 144, vitamin D deficiency became the most common AE (44.9%, 22 patients at Week 144 vs. 12.2%, 6 patients at Week 48). Headache, leukopenia, and thrombocytopenia were experienced by 20.4%, 10 patients each. Lymphopenia and neutropenia were experienced by 16.3%, 8 patients each. Arthralgia and fatigue were experienced by 14.3%, 7 patients each. The proportion of patients experiencing pruritus and eosinophilia remained the same at Week 144 compared to Week 48. Increased ALT and anaemia were not commonly reported TEAEs at Week 48. However, at Week 144, these two TEAEs were each experienced by 5 patients (10.2%) in the bulevirtide 2 mg treatment arm. It is noted that there was a > 3-fold increase in the frequency of vitamin D deficiency at Week 144 compared to Week 48 (44.9%, 22 patients vs. 14.3%, 7 patients). The frequency of neutropenia also increased more than 3 times at Week 144 compared to Week 48 (16.3%, 8 patients vs. 4.1%, 2 patients). In general, the frequency of disorders in the blood and lymphatic system increased significantly with continued bulevirtide 2 mg treatment compared to disorders in other systems.
- 6.27 At Week 48, the most frequently reported bulevirtide-related AEs were pruritus (10.2%, 5 patients), eosinophilia (8.2%, 4 patients), nausea and injection site reaction (6.1%, 3 patients each). One patient experienced a Grade 3 bulevirtide-related AE, which was a decrease in neutrophil count. By Week 144, the number of patients experiencing AEs related to bulevirtide treatment were basically unchanged compared to those reported at Week 48. Three additional patients among the 49 treated patients in the bulevirtide arm experienced ≥ Grade 3 bulevirtide related AEs at Week 96 and Week 144.
- 6.28 AEs of special interest (AESIs) in the trial include hepatic flares (presented as increases in ALT, aspartate aminotransferase (AST) and/or blood bilirubin, increased gamma-glutamyl transferase (GGT), hyperbilirubinemia and hepatic pain), eosinophilia and increased eosinophil count, injection site reactions (presented as erythema, haematoma, pain, pruritus or swelling), hypersensitivity or anaphylactoid reactions, skin and subcutaneous disorders (presented as alopecia, angioedema, macular rash, pruritus or night sweats), and increases in bile salt. All AESIs observed in the trial were Grade 1 or 2 in severity and none resulted in discontinuation of treatment.

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Table 10: Summary of results of AESIs of the MYR301 trial

	Bulevirtide 2 mg (N=49)			Delayed treatment (N=51)
	Week 48	Week 96	Week 144	Week 48
Hepatic flares	7 (14.3%) ^a	7 (14.3%) ^a	14 (28.6%) ^b	4 (7.8%) ^c
Eosinophilia and Eosinophil count increased	5 (10.2%)	5 (10.2%)	5 (10.2%)	1 (2.0%)
Injection site reactions	12 (24.5%) ^d	8 (16.3%) ^d	14 (28.6%) ^d	0 (0.0%)
Hypersensitivity/Angioedema/Anaphylactic/Anaphylactoid	3 (6.1%) ^e	1 (2.0%)	5 (10.2%) ^f	0 (0.0%)
Skin and subcutaneous disorders	9 (18.4%) ^h	9 (18.4%) ^g	13 (26.5%) ⁱ	1 (2.0%) ^g
Increases in bile salt	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)

Source: Table 2.9-10, p87 of the resubmission

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; INR = international normalised ratio

^a Increases in ALT, AST and/or blood bilirubin, hyperbilirubinemia, hepatic pain

^b Increases in ALT, AST, GGT, hyperbilirubinemia, increase in INR and urine bilirubin

^c Increases in ALT, AST and GGT

^d Injection site erythema/ haematoma/ pain/pruritus/reaction/swelling/rash

^e Angioedema, injection site rash, rash macular

^f Eczema, angioedema, injection site rash, rash macular, rash

^g Night sweats

^h Alopecia, angioedema, rash macular, pruritus

ⁱ Alopecia, eczema, erythema, night sweats, pruritus, rash, rash macular

Note: Blue shading denotes results presented in the previous submission

6.29 A very low incidence of increased bile salt was reported in the entire 144 weeks of bulevirtide treatment in the trial. This was because isolated and asymptomatic increases in total bile salts, above the ULN considered clinically insignificant by the investigator, was not reported as an AE as per the study protocol. In the bulevirtide 2 mg treatment arm, at Week 144, the reported proportion of patients experiencing renal and urinary AEs was 10.2% (5 patients), and proteinuria occurred in 4 of these 5 patients (8.2%), compared to 3 patients (6.1%) in Week 48. As stated in the approved PI of bulevirtide, one of the very common adverse effects of the drug is increased level of bile salts, which are renally excreted.

6.30 At the March 2024 PBAC meeting, the PBAC considered that the safety data provided in the previous submission was limited due to the small size of the key trial, as well as the limited follow-up period. The PBAC considered that longer-term safety data would be informative to further support the claim that bulevirtide has a manageable safety profile compared to BSC (paragraph 7.11, bulevirtide PSD, March 2024 PBAC meeting). Although the resubmission provided safety data from the key trial covering an additional 48 weeks of treatment, the trial duration (144 weeks) is insufficient to represent the ongoing treatment of bulevirtide that will occur in clinical practice (modelled treatment duration in the economic evaluation: 12.3 years). Furthermore, patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min) were excluded from the trial. However, the proposed PBS restriction for bulevirtide treatment does not restrict by patient's renal function.

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Benefits/ harms

6.31 A summary of the comparative benefits and harms for bulevirtide versus BSC in the MYR301 trial is presented in the table below.

Table 11: Summary of comparative benefits and harms for bulevirtide 2 mg and BSC in the MYR301 trial

Outcome		Bulevirtide 2 mg n/N	BSC n/N	Event rate/100 patients		RD (95% CI)		
				Bulevirtide 2 mg	BSC			
Benefits								
Dichotomous outcomes								
Combined response ^a	Week 48	22/49	1/51	44.9	2.0	42.9 (27.0, 58.5) ^d		
	Week 96	27/49	n/a	55.1	n/a	n/a		
	Week 144	28/49		57.1				
Virological response ^b	Week 48	36/49	2/51	73.5	3.9	69.5 (54.1, 81.9)		
	Week 96	37/49	n/a	75.5	n/a	n/a		
	Week 144	36/49		73.5				
Undetectable HDV RNA	Week 48	6/49	0/51	12.2	0	12.2 (3.7, 24.8)		
	Week 96	10/49	n/a	20.4	n/a	n/a		
	Week 144	14/49		28.6				
ALT normalisation ^c	Week 48	25/49	6/51	51.0	11.8	39.3 (19.9, 55.8)		
	Week 96	31/49	n/a	63.3	n/a	n/a		
	Week 144	29/49		59.2				
Continuous outcome								
		Bulevirtide 2 mg			BSC		Mean difference: Bulevirtide 2 mg vs. BSC (95% CI)	
		n/N	Mean Δ baseline (kPa)	95% CI	n/N	Mean Δ baseline (kPa)		95% CI
Liver stiffness, change from baseline (kPa)	Week 48	48/49	-3.1	(-4.7, -1.5%)	45/51	0.9	(-0.8, 2.6%)	-4.0 (-6.3, -1.6%)
	Week 96	48/49	-4.3	(-5.5, -3.1%)	n/a			n/a
	Week 144	45/49	-5.2	(-6.8, -3.6%)				
Harms								
		Bulevirtide 2 mg n/N	BSC n/N	Event rate/100 patients		RD		
				Bulevirtide 2 mg	BSC			
Adverse event between baseline and Week 48								
TEAE related to study drug	Week 48	24/49	0/51	49.0	0	49.0		
	Week 96	25/49	n/a	51.0	n/a	n/a		
	Week 144	27/49		55.1				
≥ Grade 3 TEAEs	Week 48	5/49	4/51	10.2	7.8	2.4		
	Week 96	9/49	n/a	18.4	n/a	n/a		
	Week 144	12/49		24.5				
Hepatic flares	Week 48	7/49	4/51	14.3	7.8	6.4		
	Week 96	7/49	n/a	14.3	n/a	n/a		
	Week 144	14/49		28.6				
Eosinophilia and eosinophil count increased	Week 48	5/49	1/51	10.2	2.0	8.2		
	Week 96	5/49	n/a	10.2	n/a	n/a		
	Week 144	5/49		10.2				
Injection site reactions	Week 48	12/49	0/51	24.5	0	24.5		
	Week 96	8/49	n/a	16.3	n/a	n/a		
	Week 144	14/49		28.6				
	Week 48	9/49	1/51	18.4	2.0	16.4		

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Outcome		Bulevirtide 2 mg n/N	BSC n/N	Event rate/100 patients		RD (95% CI)
				Bulevirtide 2 mg	BSC	
Skin and subcutaneous disorders	Week 96	9/49	n/a	18.4	n/a	n/a
	Week 144	13/26.5		26.5		

Source: developed during evaluation

ALT = alanine aminotransferase; BSC = best supportive care; HDV = hepatitis D virus; n/a = not applicable; RNA = ribonucleic acid; TEAE = treatment-emergent adverse event

^a Defined as undetectable HDV RNA (HDV RNA < lower limit of detection (LLOD)) or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/ml from baseline and ALT normalisation (i.e., below the central laboratory defined upper limit of normal (ULN))

^b Defined as undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/ml from baseline

^c ALT normalisation: ≤ 31 U/L for females and ≤ 41 U/L for males (Russian sites); ≤ 34 U/L for females and ≤ 49 U/L for males (all other sites)

^d 96% CI was reported for the RD of the primary endpoint of combined response at Week 48 between the two treatment arms, according to the statistical analysis plan.

Note: Blue shading denotes results presented in the previous submission

Note: For the AEs of injection site reactions, the figures not shaded in blue for Week 48 and 96 are the figures that differed from the previous submission (in the previous submission, the figures presented for Week 48 were 8 (16.3%) and the figures presented for Week 96 were 10 (20.4%))

6.32 On the basis of the MYR301 trial presented by the resubmission, for every 100 patients treated with bulevirtide in comparison to BSC and over a treatment duration of 48 weeks:

- Approximately 43 additional patients would achieve a combined response (i.e., undetectable HDV RNA or a reduction of serum HDV RNA viral load $\geq 2 \log_{10}$ IU/mL from baseline, and ALT normalisation) at Week 48.
- Approximately 70 additional patients would achieve either undetectable HDV RNA or a decrease in HDV RNA by $\geq 2 \log_{10}$ IU/ml from baseline at Week 48.
- Approximately 12 additional patients would have undetectable HDV RNA at Week 48.
- Approximately 39 additional patients would have their ALT level return to normal at Week 48.
- Approximately 49 additional patients would have a drug-related TEAE.
- Approximately 2 additional patients would experience TEAEs $\geq$ Grade 3.
- Approximately 6 additional patients would experience AEs indicative of hepatic flare.
- Approximately 8 additional patients would experience AEs indicative of eosinophilia and increased eosinophil counts.
- Approximately 16 additional patients would experience AEs indicative of skin and subcutaneous disorders.

6.33 Based on the longer term results of the MYR301 trial up to 144 weeks presented in the resubmission, continuing treatment is likely to result in additional patients

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achieving a response, and additional TEAEs, however no comparative data are available.

Clinical claim

- 6.34 The resubmission described bulevirtide as superior, in terms of effectiveness compared to current symptomatic management of CHD or BSC. The comparative evidence from the MYR301 trial demonstrated treatment effects associated with bulevirtide over BSC regarding virological response (undetectable HDV RNA or HDV RNA $\geq 2 \log_{10}$ IU/mL reduction from baseline), biochemical endpoint (ALT normalisation) and liver stiffness at Week 48. The ESCs considered that the clinical key issue was that the correlation between the surrogate serum HDV RNA $\geq 2 \log_{10}$ IU/mL reduction from baseline and the magnitude of longer-term clinical benefits of bulevirtide treatment in terms of a reduction in liver decompensation, HCC, liver transplantation, or mortality, remains uncertain.
- 6.35 The resubmission described bulevirtide as having a manageable safety profile compared to symptomatic management of CHD or BSC. The ESCs agreed with the evaluation that this claim was partially supported by the evidence presented. Even though most AEs observed in the MYR301 trial were mild to moderate in severity and no AEs led to withdrawal from the study treatment, the small sample size of the trial (N = 49) is of concern. The longer-term renal safety of bulevirtide treatment in patients with moderate or severe renal impairment is another safety concern as this patient group was not included in the trial but may be eligible for bulevirtide treatment under the proposed listing.
- 6.36 The PBAC reaffirmed its previous advice that the claim of superior comparative effectiveness was reasonable for the outcomes of virologic response and ALT normalisation, however the magnitude of benefit to longer-term and patient-relevant outcomes was uncertain.
- 6.37 The PBAC reaffirmed its previous advice that the claim of manageable safety for bulevirtide compared to symptomatic management of CHD (or BSC) may, on balance, be reasonable, however the PBAC agreed with the ESC that longer term safety data would be informative.

Claim of codependence

- 6.38 The evaluation considered the claim of codependence was reasonable for the initial quantitative HDV RNA PCR testing to establish the presence of chronic HDV infection and for access to treatment with bulevirtide. However, the following issues apply to the role of testing after starting bulevirtide treatment:
- 6.39 The commentary considered that the claim of codependence for quantitative HDV RNA PCR testing for monitoring of response to bulevirtide was not established because no patient had a change in management as a consequence of monitoring HDV

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RNA levels with a PCR test in the key clinical trial, MYR301 and there was limited evidence cited in the resubmission concerning the use of HDV RNA levels (quantitative measurements) to guide patient management. The evidence cited in the resubmission found only 4 patients (in 2 studies) who had a change in therapeutic management due to the monitoring of HDV RNA levels: two changes were in response to an insufficient response to treatment and two due to a sustained response to treatment (clearing of HDV RNA lasting at least 6 months). The ESCs noted that evidence of change in management is limited as HDV is relatively rare and few effective treatments are available.

- 6.40 However, the ESCs identified an Austrian publication, Jachs et al 2022 as providing the most compelling evidence of likely changes in patient management as a result of monitoring quantitative HDV RNA levels in patients treated with bulevirtide. The study reported that interferon treatment was added in eight out of 23 patients who achieved no further decline in HDV-RNA after week 24. This group included 2 viral responders with a $> 2 \log_{10}$ or more reduction in HDV-RNA levels and 6 non-responders. The decision to change treatment by adding interferon for the two responders appeared to be directly related to the quantitative HDV RNA result. However, some non-responders received interferon and some did not and the reason for this discrepancy was not discussed in the study.
- 6.41 On the basis of these considerations, the ESCs advised that a quantitative test was more useful in altering management pathways than a qualitative test. However, the ESCs considered there was no clear consensus on the threshold reduction in viral load that would inform changes in clinical management. The ESCs advised that qualitative testing for monitoring treatment response had limited utility.
- 6.42 The ESCs accepted that the evidence presented in the resubmission, including evidence based on detectable versus undetectable RNA levels, was indicative of the biologically plausible claim that a drop in quantitative HDV viral load levels relative to baseline was indicative of clinical response to treatment insofar as patients with lower detectable viral loads may have a reduced risk of developing liver-related clinical events compared to patients with higher detectable viral loads. However, the ESCs noted that the clinical claim for bulevirtide and the outcomes applied in the economic model were based on a viral load decrease of $2\log_{10}$ IU/mL. Although a reduction in viral load is likely to be clinically relevant, the ESCs considered that there was limited evidence for $2\log_{10}$ IU/mL as the cut-off and it was associated with uncertain prognostic value.

Economic analysis

- 6.43 The resubmission presented an updated modelled economic evaluation based on virological response rates (defined as undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline) reported up to Week 144 in the MYR301 trial that

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compared bulevirtide treatment to BSC (delayed treatment) in patients with HDV RNA positive CHD. The key components of the economic evaluation are summarised in Table 12. The ESCs considered that PBAC's advice that the most appropriate way to manage the substantial uncertainties in the economic model would be to adopt a conservative approach to the model inputs (paragraph 7.14 bulevirtide PSD, March 2024 PBAC Meeting) was not addressed in the resubmission or the PSCR. The ESCs advised that the more conservative approach reflected in the multivariate sensitivity analysis is likely to provide more confidence in the estimated incremental cost-effectiveness ratio (ICER).

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Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Comparison modelled	Bulevirtide with HDV RNA testing to identify one patient eligible for treatment versus BSC. Entry at the point of treatment is the less-preferred approach noted in the 'Product type 4, 37 (O)' (PBAC guidelines (v5.0)).
Time horizon	Lifetime (58 years) in the model base case (versus 144 weeks for bulevirtide and 48 weeks for BSC in the key trial). The PBAC considered this an area of uncertainty. The ESCs considered a time horizon of 10-20 years was more appropriate in the context of economic uncertainties, and would be consistent with previous considerations of chronic HBV treatments (paragraph 6.25 and para 7.12, bulevirtide PSD, March 2024 PBAC meeting).
Outcomes	Quality-adjusted life years.
Methods used to generate results	State-transition Markov model.
Health states	Eleven health states: NC (separated into F0, F1, F2 and F3 states), CC (i.e. F4), DCC, HCC, liver transplantation, post-liver transplantation, dead (liver-related) and dead (background). The NC and CC health states were also separated by responder status, or whether patient had experienced HBsAg seroclearance. Patients enter the model as non-responders distributed across the NC and CC health states (based on MYR301 and Romeo et al. et al 2009). This remains the same as the previous submission. It may be more appropriate to have a single health state representing NC, given the limited data to inform the transitions within the NC health states in patients with CHD.
Cycle length	24 weeks.
Test parameters	Yield of HDV RNA testing modelled was 54.4% based on a weighted average of Australian studies. The resubmission uses the same studies on which the weighted average is based, but the calculation has been corrected according to the previous Evaluation.
Implications of false positive and false negative results	Not modelled in the base case. However, the resubmission presented a scenario analysis to explore the impacts of false results on the ICER for HDV RNA testing used to determine treatment initiation. The structure and the assumptions of the resubmission's scenario analysis were not appropriate. Thus, the result from this analysis is not meaningful. In addition, the resubmission did not examine the implications of false results from testing used to monitor treatment response.
Transition probabilities	Natural history of CHD: Disease progression in non-responders was based on estimates reported in chronic HBV (Bermingham et al. 2015), adjusted for concomitant HBV/HDV infection. HBsAg seroclearance rate based on Zhou et al. 2019. The source used to model the natural history of CHD was uncertain (paragraph 7.12, bulevirtide PSD, March 2024 PBAC meeting). The ESCs noted additional alternative data sources identified during the previous evaluation. Background mortality based on ABS Australian life tables (2020–22). Effect in responders: Reduction in disease progression in responders was based on a meta-analysis published recently (Gish et al. 2024) which investigated the association of HDV with liver morbidity and mortality. Several studies included in the meta-analysis were not relevant to inform the relationship of a reduction in HDV RNA levels on liver-related clinical outcomes. Where relevant comparisons were presented, the definition of the surrogate measure (detectable versus undetectable HDV RNA) was in general narrower than the definition of combined or virological response used in MYR301. In addition, the meta-analysis by Gish et al. missed one relevant study identified by the meta-analysis presented in the previous submission (Palom et al. 2021). Regression in F3 and CC responders based on Marcellin et al. 2013 and Farci et al. 2004, respectively.

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Component	Summary
	Response rate: Virological response rates up to Week 144 reported in MYR301. Extrapolation of virological response rates in the delayed treatment arm of MYR301 at 24 and 48 weeks to 72, 96, 120, and 144 weeks using the non-linear E_{max} function. The definition of virological response applied to the model (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL) was broader than the surrogate measure (undetectable HDV RNA) used to estimate the effect of response on liver-related outcomes. This favours bulevirtide.
Duration of bulevirtide treatment	All patients were assumed to remain on bulevirtide treatment in the model until Week 144, unless they progress or experience HBsAg seroclearance. Non-responders discontinue treatment at 144 weeks. Responders were assumed to continue treatment unless they experience the events noted above, or discontinue due to other reasons. The proposed PBS listing does not specify stopping rules and/or continuation criteria. It is possible that the use of bulevirtide in Australian clinical practice may differ from the bulevirtide treatment modelled in the economic evaluation.
Health related quality of life	NC (0.935) and CC (0.923) utilities in non-responders were derived from baseline utility data in MYR301, applying Australian weights. The health state utilities for NC and CC used in the resubmission lacked face validity and were notably higher than the utilities for NC and CC in the HCV economic model previously considered by the PBAC (daclatasvir PSD, March 2015 PBAC meeting).
	Patients who achieved a response were assumed to have a utility gain of 0.033, based on a Tobit regression model fitted to data from MYR301 at Week 48, using Australian population weights. Both the PBAC and the ESCs considered a utility gain in responders was uncertain (paragraph 6.65, para 6.66, para 7.12, bulevirtide PSD, March 2024 PBAC meeting).
	Utility values in the remaining health states were derived from a meta-analysis of health state utility in chronic HBV.
	Health state utilities were adjusted for age, using Clemens et al. 2014.

Source: Adapted from Table 3.1–1, p101 of the resubmission.

BSC = best supportive care; CC = compensated cirrhosis; CHD = chronic hepatitis D; DCC = decompensated cirrhosis; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; ICER = incremental cost-effectiveness ratio; NC = non-cirrhosis; PSD = public summary document; RNA = ribonucleic acid.

Note: Blue shaded denotes model inputs and data sources unchanged from the previous submission.

6.44 The structure of the model remains unchanged since the previous submission. Patients enter the economic model at the point of treatment, and the cost of testing to identify one patient eligible for bulevirtide therapy is applied on model entry. As in the previous submission, the resubmission's base case analysis assumed 100% sensitivity and 100% specificity for HDV RNA PCR testing. When the March 2024 submission was considered, the MSAC noted that there were numerous and important uncertainties associated with the economic model because it did not take into account false positive and false negative test results, and the pattern of use of testing and retesting (p2 and p7, Application No. 1708 PSD, April 2024 MSAC meeting). The resubmission argued that the clinical evidence showed high performance accuracy for HDV RNA testing and the change in LLoD is unlikely to change the diagnostic accuracy. Therefore, false positives and false negatives were not modelled in the base case. To address the MSAC concern regarding the impact of false negative and false positive results from HDV RNA testing at initial diagnosis, the resubmission presented a scenario analysis comparing bulevirtide with BSC, by assuming 95% sensitivity and 95% specificity for the HDV RNA PCR test. Based on the clinical evidence

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that the qualitative (positive/negative) concordance of the VIDRL in-house test compared with the RoboGene clinical utility standard was |% positive percent agreement and |% negative percent agreement, an additional analysis was performed by assuming |% sensitivity and |% specificity. The ESCs noted that these inputs had only a minor impact on the ICER.

- 6.45 The main changes to model inputs are the use of updated trial data on treatment response rates, the alternative data source for the effect of response, the longer duration of bulevirtide treatment, and the use of Australian preference weights in estimating utility weights for non-cirrhosis (NC) and compensated cirrhosis (CC) health states.
- 6.46 The economic model in the resubmission used the virological response rates up to Week 144 from the MYR301 trial (vs. 96-week data in the previous submission). The hazard ratios (HRs) for disease progression of CHD in responders were derived from a recently published meta-analysis by Gish et al (2024)⁴ (vs. sponsor commissioned meta-analysis in the previous submission). Several studies in this meta-analysis included irrelevant comparisons which limited the applicability to the target clinical benefit of a response in patients with CHD, e.g. comparisons of patients with acute versus chronic HDV infections and comparisons of HBV mono-infection versus HBV/HDV infections. Also, Gish et al.'s meta-analysis missed one relevant study identified by the sponsor-commissioned meta-analysis presented in the previous submission⁵. The evaluation considered the meta-analysis conducted during the previous evaluation, after excluding studies that contained irrelevant comparisons, is a more reasonable data source to model relative reduction in progression in CHD patients who respond to treatment. The PSCR and pre-PBAC response disagreed that the meta-analysis conducted during the previous evaluation was appropriate but noted that its use resulted in only a modest increase to the ICER.
- 6.47 Treatment response as applied in the model (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL) is neither the primary efficacy endpoint in the key trial (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline and ALT normalisation) nor the surrogate measure best supported with the available evidence (detectable vs. undetectable HDV RNA) to estimate the effect of response on liver-related clinical outcomes (refer to paragraphs 6.11-6.13). The PBAC previously agreed with the ESCs that there are likely to be differences in outcomes between patients who are able to clear HDV infection (undetectable HDV RNA) and those who are achieving and/or sustaining virological suppression with ongoing treatment. Whilst there may be improvements in tests over time, the use of

⁴ Gish RG, Wong RJ, Di Tanna GL, et al. Association of hepatitis delta virus with liver morbidity and mortality: A systematic literature review and meta-analysis. *Hepatology* (Baltimore, Md). 2024;79(5):1129-40.

⁵ Palom A, Sopena S, et al. One-quarter of chronic hepatitis D patients reach HDV-RNA decline or undetectability during the natural course of the disease. *Alimentary Pharmacology & Therapeutics*. 2021;54(4):462-9.

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undetectable viral load as the response measure would be more consistent with studies used to quantify the effect of virological response on outcomes (paragraph 7.12, bulevirtide PSD, March 2024 PBAC meeting).

- 6.48 The PSCR and pre-PBAC response maintained that the most appropriate clinically relevant response outcome for CHD for HTA decision making is a $\geq 2 \log_{10}$ decline in HDV RNA from baseline, arguing that it is a standardised definition that has been established to demonstrate improved clinical outcome and is consistently assessed in CHD treatment trials. The ESCs considered that, although a reduction in viral load is likely to be clinically relevant, the correlation between the surrogate HDV RNA $\geq 2 \log_{10}$ IU/mL reduction from baseline and the magnitude of longer-term clinical benefits of bulevirtide treatment in terms of a reduction in liver decompensation, HCC, liver transplantation, or mortality, remains uncertain. The PSCR and pre-PBAC response argued that $\geq 2 \log_{10}$ IU/mL reduction from baseline is a good proxy for responses that were previously would have been defined as undetectable using less sensitive assays, however the ESCs noted that use of the lower threshold for “undetectable” (viral load below 930 IU/mL) would reduce the proportion of bulevirtide virological responders from 73.5% to 65.3%.
- 6.49 The resubmission assumed that all patients in the bulevirtide arm receive 144 weeks of bulevirtide treatment, unless they experience HBsAg seroclearance, disease progression (DCC or HCC) or death. After Week 144, non-responders were assumed to cease treatment. Responders were assumed to continue treatment unless they experience the events noted above or discontinue due to other reasons. Over the 58-year time horizon of the model, the average duration of bulevirtide treatment was estimated to be 12.3 years (compared with 8.8 years in the previous economic evaluation). The TGA-approved product information states that bulevirtide treatment should be continued as long as it is associated with clinical benefit. The proposed PBS restrictions, however, do not specify stopping rules and/or treatment continuation criteria. The decision to continue or cease treatment, based on virological response, is likely to be a matter of clinical judgement and the available evidence suggests that changes in management are not consistently exercised on the basis of changes in HDV RNA levels. In addition, the extended treatment duration is likely to be associated with an increased risk of AEs, which may potentially impact on patient’s and clinician’s willingness to continue treatment indefinitely. The ESCs noted that the economic model assumed that patients would undergo HDV RNA testing every 6 months while on bulevirtide treatment and that although this is consistent with the proposed MBS item descriptor, the model was limited because the only change in management modelled due to the inclusion of HDV RNA monitoring was to cease treatment in non-responders at Week 144. The ESCs considered it may be informative to provide a sensitivity analysis assuming stopping of treatment at 48 weeks without demonstrated viral load response as patients may be unlikely to continue therapy

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without evidence of a response (especially given daily SC injections are required). The ESCs noted that this resulted in a 1% decrease in the ICER as both costs and QALYs were reduced.

- 6.50 The model maintained a lifetime horizon (58 years) in the model base case. The PBAC previously considered that the choice of a 58 year time horizon was a source of uncertainty for the modelled outcomes. The ESCs previously considered a time horizon of 10-20 years was more appropriate in the context of economic uncertainties, and would be consistent with previous considerations of chronic HBV treatments (paragraph 6.25 and 7.12, bulevirtide PSD, March 2024 PBAC meeting). The PSCR and pre-PBAC response argued that HDV is a chronic and progressive disease with significant long-term health and economic consequences and a shorter time horizon cannot fully capture the benefits associated with bulevirtide treatment. Overall, the ESCs considered it remained unclear whether the treatment duration, and, consequently, the treatment response and health outcomes, modelled in the economic evaluation would reflect clinical practice.
- 6.51 Health state utilities for non-responders in the NC and CC health states were based on the EQ-5D-3L data at baseline in patients enrolled in the MYR301 trial, by applying Australian population weights (vs. UK preferences used in the previous submission). The derived utility weights in NC and CC patients (0.935 for NC and 0.923 for CC in non-responders) lack face validity, as these values are higher than the average utility score for general Australian population in the age category containing the starting age of the modelled patients (0.85 for the age category of 45-54 years)⁶. The resubmission's estimated utilities for NC and CC health states are also substantially higher than the utility weights in the HCV model previously considered by the PBAC (daclatasvir PSD, March 2015 PBAC meeting) (utility values of 0.77 for mild NC, 0.66 for moderate NC and 0.55 for CC, based on Wright (2006)⁷. In addition, the minimal difference between NC and CC health states assumed in the bulevirtide economic model (0.012) appears unreasonable and is not consistent with the difference between these health states in the previous HCV economic model (0.11-0.22). The PSCR argued the values based on Wright (2006) were not applicable to the analysis given the study is outdated, it was conducted in an HCV population with different baseline patient and disease characteristics compared to the MYR301 trial population and the utility weights were derived using UK tariffs. The ESCs acknowledged the limitations regarding the Wright et al. utilities. However, the health state utility for NC from Wright (2006) appears more reasonable than the revised NC utility proposed in the PSCR which assumed that the quality of life (QoL) of NC patients who do not

⁶ Redwood L, Currow D, *et al.* Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Qual Life Res.* 2024;33(3):721-33.

⁷ Wright M, Grieve R, *et al.* Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess.* 2006;10(21):1-113, iii.

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respond to treatment is identical to the QoL in general Australian population (0.85), with QoL in responders being better than the general population. The ESCs noted the utilities from Wright (2006) were used in the stepped multivariate analyses presented in the previous evaluation and considered by the PBAC at the March 2024 meeting. Using these utilities in univariate and multivariate sensitivity analyses helped to explore whether the model was sensitive to health state utilities inputs, and, along with other assumptions, forms a “conservative” scenario to address economic uncertainties identified.

- 6.52 As in the previous submission, the resubmission assumed a lower treatment compliance rate in the economic model than observed in the trial (90% vs. 96.75%). While treatment compliance in clinical practice may be lower than the trial setting, it was not appropriate to adjust treatment costs for the anticipated reduction in compliance but not adjust the anticipated clinical outcomes (i.e. response rates). This has introduced bias in favour of bulevirtide.
- 6.53 Other major areas of economic concern in the previous submission as previously noted by the PBAC (paragraph 7.12, bulevirtide PSD, March 2024 PBAC meeting) are outlined below. These model inputs essentially remain unchanged and the evaluation considered their continued use was not adequately justified in the resubmission. However, these inputs were updated in pre-PBAC response as noted below:
- The source used to model the natural history of CHD (a UK economic evaluation of HBV mono-infection⁸, adjusted for an increased risk in patients with HBV/HDV concomitant infection). The pre-PBAC response proposed natural history CHD data to inform transition probabilities reflective of direct CHD evidence per Goyal and Murray (used in its entirety).
 - The assumption of a utility gain in responders. The pre-PBAC response reverted back to original values.
 - The compliance to bulevirtide treatment (90%, lower than the trial data). The pre-PBAC response used compliance rate reflective of the trial data.
- 6.54 A summary of the key drivers of the model is presented in Table 13.

⁸ Bermingham SL, Hughes R, *et al.* Cost-effectiveness analysis of alternative antiviral strategies for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in the United Kingdom. *Value Health*. 2015 Sep;18(6):800-9.

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Table 13: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$115,000/QALY gained.
Definition of response	Virological response (defined as undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL)	High, favours bulevirtide. Using rates where undetectable HDV RNA was achieved increases the ICER to \$135,000/QALY gained. Using the outcome of combined response increases the ICER to \$135,000/QALY gained.
Natural history of CHD infection	Based on a UK economic evaluation of HBV mono-infection, adjusted for an increased risk in patients with HBV/HDV infection	High, favours bulevirtide. Using probabilities (except HBsAg seroclearance) from Goyal and Murray (2016) ^a increases the ICER to \$135,000/QALY gained. Using chronic HBV probabilities from Xiao (2020) ^b increases the ICER to \$135,000/QALY gained.
Time horizon	58 years.	High, favours bulevirtide. Decreasing the time horizon to 20 years increases the ICER to \$135,000/QALY gained. Using 10 years increases the ICER to \$135,000/QALY gained.
Health state utilities, NC and CC	0.935 and 0.923, respectively.	Moderate, favours bulevirtide. Using utility values consistent with Wright et al. (2006) ^c (F0-2: 0.77, F3: 0.66 and CC: 0.55) increases the ICER to \$135,000/QALY gained.
Utility increment in responders	0.033, based on Tobit regression model fitted to MYR301 data at Week 48, using Australian weights.	Moderate, favours bulevirtide. Excluding the utility increment in responders increases the ICER to \$135,000/QALY gained.
Compliance to treatment	90.0% (assumed).	Moderate, favours bulevirtide. Increasing the compliance to 96.75% ^d increases the ICER to \$135,000/QALY gained.
HRs for disease progression in responders	HRs were estimated from a meta-analysis by Gish et al. (2024) of the relationship of undetectable HDV RNA on any liver event (HR = 0.38); HCC (HR = 0.34); DCC (HR = 0.26) and liver-related death (HR = 0.26).	Moderate, favours bulevirtide. Using HRs derived from the revised meta-analysis in the previous Commentary after excluding studies that contained irrelevant comparisons (any liver event, HR = 0.51; HCC, HR = 0.39; DCC, HR = 0.35; and liver-related death, HR = 0.29) increases the ICER to \$135,000/QALY gained.

Source: Compiled during the evaluation.

CC = compensated cirrhosis; CHD = chronic hepatitis D; DCC = decompensated cirrhosis; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HDV = hepatitis D virus; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; NC = non-cirrhosis; QALY = quality-adjusted life year; RNA = ribonucleic acid.

^a Goyal A and Murray JM. Cost-effectiveness of peg-interferon, interferon and oral nucleoside analogues in the treatment of chronic hepatitis B and D infections in China. Clin Drug Investig. 2016 Aug;36(8):637-48.

^b Xiao Y, Howell J, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526-36.

^c Wright M, Grieve R, et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess. 2006 Jul;10(21):1-113, iii.

^d Compliance rate at Week 144 in MYR301.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$135,000 to < \$155,000

³ \$115,000 to < \$135,000

⁴ \$155,000 to < \$255,000

6.55 The results of the stepped economic evaluation are presented in Table 14. The stepped analyses presented in the resubmission combined a number of transformations of the trial data to the proposed clinical setting from Steps 3 to Step 4, including the transformation of the surrogate outcome of response into effect on disease progression, assumption of reduced compliance to bulevirtide treatment expected in practice and extrapolation of costs and outcomes over the 58-year time horizon.

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Table 14: Results of the stepped economic evaluation

Step and component	Bulevirtide	BSC	Increment
Step 1: Trial-based costs and outcomes (48 weeks)			
Trial-based analysis at 48 weeks. Cost of testing to identify one patient with detectable HDV RNA included (assuming 54.4% positivity rate). Compliance with bulevirtide treatment was 99.55% based on MYR301 trial compliance at 48 weeks (equivalent to 5.57 scripts per patient per 48 weeks).			
Costs	\$1	\$0	\$1
Virological response ^a at 48 weeks	73.5%	3.9%	69.5%
Incremental cost/additional responder			1
Step 2: Trial-based costs and outcomes to 144 weeks, with extrapolation of comparator outcomes			
Trial-based analysis at 144 weeks, assuming extrapolation of virological response in the comparator arm. Compliance with bulevirtide treatment was 96.75% based on MYR301 trial compliance at 144 weeks (equivalent to 16.25 scripts per patient per 144 weeks).			
Costs	\$1	\$0	\$1
Virological response ^a at 144 weeks	73.5%	4.4%	69.1%
Incremental cost/additional responder			\$2
Step 3: Transformation of virological response into QALYs			
A utility increment of 0.033 × 2.00 years (i.e. 144 weeks) was applied per patient with virological response at 144 weeks.			
Costs	\$1	\$0	\$1
QALY gained	0.067	0.004	0.063
Incremental cost/extra QALY gained			\$2
Step 3a: Transformation of the surrogate outcome of virological response into effect on disease progression			
Differences in disease progression were modelled across responders and non-responders based on the estimated relationship between virological response and liver-related outcomes. While the cost of testing was unchanged from the steps prior, the cost of bulevirtide treatment was reduced due to disease progression or HBsAg seroclearance. Costs of managing AEs, monitoring costs and other health state costs (disease management, liver transplantation and liver-related death) were included. Utility weights were applied according to the time spent in each health state and disutility due to AEs was included.			
Costs	\$1	\$15,160	\$1
LY gained	2.43	2.39	0.04
QALY gained	2.24	2.12	0.12
Incremental cost/extra QALY gained			\$3
Step 3b: Adjustment of compliance to bulevirtide treatment			
Costs and outcomes as per Step 3a, except bulevirtide costs were adjusted for reduced compliance (90%)			
Costs	\$1	\$15,160	\$1
LY gained	2.43	2.39	0.04
QALY gained	2.24	2.12	0.12
Incremental cost/extra QALY gained			\$4
Step 4: Extrapolation over 58 years			
Cost of testing and costs and outcomes due to AEs were unchanged from previous steps. All other costs and outcomes were extrapolated over 58-year time horizon.			
Costs	\$1	\$71,803	\$1
LY gained	11.38	8.47	2.91
QALY gained	10.06	7.11	2.95
Incremental cost/extra QALY gained (base case)			\$5

Source: Table 3.8-1, p142 of the of the resubmission.

AE = adverse event; BSC = best supportive care; HBsAg = hepatitis B surface antigen; HDV = hepatitis D virus; LYs = life years; QALYs = quality adjusted life years; RNA = ribonucleic acid.

Note: Analyses in italics were conducted during the evaluation.

^a Defined as undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

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² \$155,000 to < \$255,000

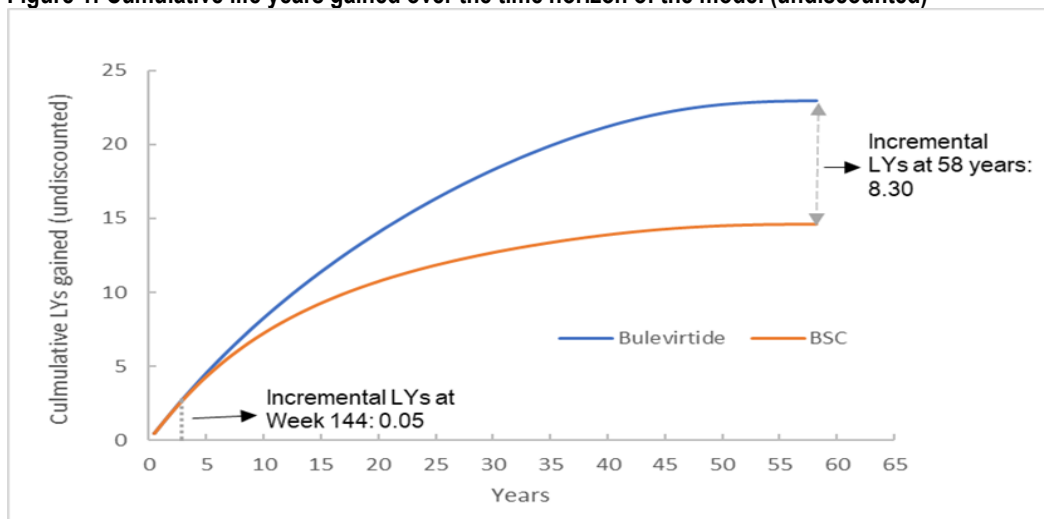
³ \$755,000 to < \$855,000

⁴ \$655,000 to < \$755,000

⁵ \$95,000 to < \$115,000

- 6.56 The incremental cost-effectiveness ratio (ICER) from the resubmission's base case analysis was estimated to be \$95,000 to < \$115,000 /quality-adjusted life year (QALY) gained. When the previous submission was reviewed, the PBAC recalled that other antivirals for chronic viral hepatitis have previously been considered cost-effective with ICERs less than \$35,000 to < \$45,000/QALY, although the PBAC noted that the frequency of CHD infection in Australia is much lower than for HBV or hepatitis C, treatment options for CHD are limited, and the TGA granted orphan drug designation to bulevirtide (paragraph 7.14, bulevirtide PSD, March 2024 PBAC meeting).
- 6.57 As depicted in Figure 1, 99.4% of the incremental life years (LYs) gained were accrued during the extrapolated period. The modelled duration of treatment was 12.3 years, and ongoing treatment is required to maintain viral suppression. In this context, the undiscounted LYs gain estimated in the model, i.e. 8.3 years, appears implausible.

Figure 1: Cumulative life years gained over the time horizon of the model (undiscounted)



Source: Constructed during the evaluation, based on "Attachment 17 - Hepcludex HDV Section 3A Cost-Eff Model Resubmission_vfinal.xlsm" Excel workbook.
BSC = best supportive care; LY = life year.

- 6.58 The number of liver-related events experienced across model arms over the extrapolated time horizon is presented in Table 15. Results show that while bulevirtide treatment is associated with reduced DCC, HCC, liver transplantation and death due to liver-related disease (which are consistent with modelled benefit associated with response to treatment), the number of compensated cirrhosis events increases with bulevirtide, due to the modelled assumptions regarding regression from cirrhosis in responders.

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Table 15: Total proportion of patients who experience liver-related events over the model time horizon

Event	Bulevirtide	BSC	Difference
Cirrhosis (compensated)	0.360	0.337	0.023
Decompensated cirrhosis	0.237	0.331	-0.094
Hepatocellular carcinoma	0.339	0.402	-0.063
Liver transplantation	0.021	0.028	-0.007
Death, due to liver-related disease	0.647	0.841	-0.194

Source: Constructed during the evaluation, based on "Attachment 17 - Hepcludex HDV Section 3A Cost-Eff Model Resubmission_vfinal.xlsm" Excel workbook.

BSC = best supportive care.

Note: A patient could experience more than one event.

6.59 Results of the key sensitivity analyses presented by the submission and additional analyses conducted during the evaluation are summarised in Table 16.

Table 16: Sensitivity analyses

	Inc. costs (\$)	Inc. QALYs	ICER	% change
Base case		2.95		
Time horizon (base case: 58 years)				
• 30 years		2.59	1	%
• 20 years (#3)		1.97	2	%
• 10 years		0.88	3	%
Discounting rate (base case: 5%)				
• 0%		7.84	4	%
• 3.50%		3.81	5	%
Distribution of F0-F3 stage at baseline (base case: Romeo et al. 2009)				
• MYR301		2.86	1	%
• Assuming all NC patients enter model as F3		3.43	5	%
HDV natural disease progression (base case: chronic HBV probabilities from Bermingham, adjusted for HBV/HDV)				
• Xiao et al. (2020), adjusted for HBV/HDV as in resubmission		2.35	6	%
• Goyal and Murray (2016) (using base case probability of HBsAg seroclearance estimate) (#4)		2.07	2	%
HBsAg seroclearance (base case: 1.13% annually)				
• 0.25% (Romeo et al. 2009)		3.04	1	%
• 6.7% (Goyal and Murray 2016)		2.43	5	%
Definition of response (base case: virological response defined as undetectable HDV RNA or reduction in RNA level $\geq 2\log_{10}$ IU/mL from baseline)				
• Combined (virological response and ALT normalisation)		2.13	1	%
• Undetectable HDV RNA (#2)		1.06	6	%
HRs of HDV disease progression in responders (base case: meta-analysis by Gish et al. 2024)				
• PBAC suggested HRs (Table 11, bulevirtide PSD, March 2024 PBAC meeting) (#1)		2.63	1	%
Annual fibrosis regression probability (base case: F4 to F3: 8.8% (Farci et al, 2004); F3 to F2: 13.3% (Marcellin et al. 2013))				
• F4 to F3 regression, 0%		2.41	1	%
• F3 to F2 regression, 0%		2.71	1	%
• Exclude regression		2.25	2	%
Treatment stopping rule in non-responders (base case: Week 144)				
• Week 96		2.96	5	%
• Week 48		2.79	5	%
• None applied ^a		2.95	2	%

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	Inc. costs (\$)	Inc. QALYs	ICER	% change
Base case		2.95	1	
Treatment discontinuation (base case: 2.26% per year (MYR301 data at Week 144))				
• 14.4% annually (MYR203 permanent discontinuers at Week 48)		1.43	1	%
Health state utility weights (base case: MYR301, Australian weights for NC and CC; HBV meta-analysis utilities for DCC to PLT)				
• MYR301, UK weights for NC and CC ^b		2.72	1	%
• Wright et al. 2006 for NC and CC ^c		2.29	2	%
• Wright et al. 2006 for all health states ^d (#5)		2.30	2	%
Utility increment in responders (base case: 0.033)				
• 0 (#6)		2.75	1	%
Bulevirtide drug acquisition cost (no price reduction over time; compliance of 90%)				
• Price reduction of % beyond 10 years		2.95	5	%
• Compliance, 96.75% (MYR301 data at Week 144) (#7)		2.95	1	%
Multivariate analyses				
#1 AND #2		0.95	3	%
#1, #2 AND #3		0.62	3	%
#1, #2, #3 AND #4		0.40	7	%
#1, #2, #3, #4 AND #5		0.32	8	%
#1, #2, #3, #4, #5 AND #6		0.27	8	%
#1, #2, #3, #4, #5, #6 AND #7^e		0.27	9	%
As above, with input #2 revised to combined definition of response		0.60	7	%
As above, with pre-PBAC proposed price for bulevirtide (\$ AEMP)		0.60	7	%

Source: Table 3.9-2, of the resubmission and "Attachment 17 - Hepcludex HDV Section 3A Cost-Eff Model Resubmission_vfinal.xlsm" Excel workbook.

ALT = alanine aminotransferase; BSC = best supportive care; CC = compensated cirrhosis; DCC = decompensated cirrhosis; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HDV = hepatitis D virus; HR = hazard ratio; ICER = incremental cost effectiveness ratio; NC = non-cirrhosis; PLT = post-liver transplantation; PSD = public summary document; QALY = quality adjusted life year; RNA = ribonucleic acid.

Notes: Analyses in italics were conducted during the evaluation.

^a Assuming no effect on response rates

^b F0-F3: 0.813, CC: 0.812. A utility increment of 0.057 is applied to responders.

^c F0-2: 0.77, F3: 0.66, CC: 0.55. The utility increment in responders remains the same as in the base case (0.033).

^d F0-2: 0.77, F3: 0.66, CC: 0.55, DCC: 0.45, HCC: 0.45, LT: 0.45 and PLT: 0.67. The utility increment in responders remains the same as in the base case (0.033).

^e Multivariate analysis reflects cumulative changes for consistency with previous PBAC decision making (time horizon, source for health state utilities and exclusion of utility increment in responders), internal consistency (definition of response and treatment compliance) and where the inclusion of studies was inadequately justified in the resubmission (source for transition probabilities and studies included in the meta-analyses demonstrating the effect of response on liver-related outcomes).

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$115,000 to < \$135,000

³ \$155,000 to < \$255,000

⁴ \$55,000 to < \$75,000

⁵ \$75,000 to < \$95,000

⁶ \$135,000 to < \$155,000

⁷ \$255,000 to < \$355,000

⁸ \$355,000 to < \$455,000

⁹ \$455,000 to < \$555,000

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- 6.60 Results of the univariate sensitivity analyses show that the ICER is very sensitive to the definition of response, the source used to model CHD disease progression, and time horizon. Changes in health state utilities for NC and CC, utility increment in responders, compliance of treatment, and HRs for disease progression in responders moderately affect the result. These were areas of uncertainties previously noted by the PBAC and by the current evaluation. In addition, variables such as discounting rate, HBsAg seroclearance rate, and fibrosis regression rate in responders also have a big impact on the ICER.
- 6.61 When the previous submission was considered, the PBAC agreed with the ESC that it would likely be a long time before the patient-relevant impacts of bulevirtide treatment are well-characterised, and considered there remains uncertainty regarding how bulevirtide is likely to be used in clinical practice. As such, the PBAC considered the most appropriate way to manage the substantial uncertainties would be to adopt a conservative approach to the model inputs and advised that a revised economic model would be required (paragraph 7.14, bulevirtide PSD, March 2024 PBAC meeting). Results from stepped multivariate analyses demonstrate that the ICER is highly sensitive to cumulative changes in the model, increasing from \$95,000 to < \$115,000/QALY gained in base case to \$455,000 to < \$555,000/QALY gained when a number of model inputs are revised for consistency with previous PBAC decision making (time horizon, source for health state utilities and exclusion of utility increment in responders), internal consistency (definition of response and treatment compliance). When the definition of response was changed to the combined outcome the ICER for this multivariate analysis was reduced to \$255,000 to < \$355,000 per QALY.
- 6.62 The ESCs noted that the PSCR presented alternative multivariate sensitivity analyses, but considered that the selected inputs for these analyses were not well-justified. The pre-PBAC also presented an alternative base case with revisions to the source used to model natural history of CHD, revised utility values, and increased compliance (see paragraph 6.53) and a reduced cost for bulevirtide (\$1 AEMP). This resulted in an ICER of \$75,000 to < \$95,000 per QALY. The pre-PBAC response argued that other changes to the model inputs were not justified.

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Drug cost/patient/course

Table 17: Drug cost per patient for bulevirtide

	Trial dose and duration	Model	Financial estimates
Mean dose	2 mg per day Average compliance 96.75%	2 mg per day Average compliance 90%	2 mg per day Average compliance 90%
Mean duration	139.8 weeks (2.7 years) (15.8 scripts) ^a	641.7 weeks (12.3 years) (67.4 scripts) ^a	312 weeks (6 years) (32.87 scripts) ^b
Cost per script	\$ ^c	\$ ^c	\$ ^c
Cost/patient/course	\$	\$	\$

Source: Compiled during the evaluation from the 'Attachment 10 - Hepcludex HDV Section 3A Cost-Eff Model_vfinal.xlsm' and 'Attachment 14 - HEPCLUDEX HDV CoDep Section 4_final.xlsm' files included with the submission.

^a Duration of treatment (years) x compliance x (52 x 7) days per year / 60 days per script

^b Duration of treatment (years) x compliance / 60 days per script. However, discontinuation is applied consistent with the model, 47.7% of patients discontinue by year 6.

^c Weighted dispensed price by assuming 80% of the scripts will be dispensed in a private/community setting and the remaining 20% in a public setting.

6.63 The cost per course of bulevirtide treatment modelled is \$ [REDACTED] (undiscounted). This was based on an average duration of treatment of 12.3 years (equivalent to 67.4 scripts)⁹ assuming 90% compliance and a weighted cost per script of \$ [REDACTED].

Estimated PBS usage & financial implications

6.64 The resubmission was not considered by DUSC. The sponsor retained the epidemiological approach taken in the submission considered at the March 2024 PBAC meeting. A summary of the data sources and parameter values used to estimate the utilisation and financial implications associated with the listing of HDV RNA testing and bulevirtide treatment for chronic HDV is presented below in Table 18.

Table 18: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Population projections, 2025–2030	27,970,435 in 2025, increasing to 29,931,725 in 2030	ABS Australian population projections, ages 0–100+	The reported HBV prevalence estimates also applied across all ages, so this population is appropriate, however the resubmission does not consider that bulevirtide is proposed in adults only.
Prevalent population – known HDV			
Prevalence of chronic HBV in 2023	0.77%	Nguyen 2024, MacLachlan 2024	In line with the DUSC estimate, this updated value was taken from the same data source as the March 2024 submission but updated to use most recent 2002 prevalence evidence.
Prevalent chronic HBV diagnosed	72.1%		

⁹ 12.34 years x 90% compliance x (52 x 7) days per year / 60 days per script

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Data	Value	Source	Comment
Prevalent chronic HBV patients diagnosed & engaged in care	35.4%		In considering the March 2024 submission, the PBAC noted more recent estimates are somewhat higher (35.9% of diagnosed patients in MacLachlan 2023) than the value provided (30.9%).
Chronic HBV patients tested for anti-HDV prior to bulevirtide listed	35.0%	UK NICE submission, confirmed by clinicians	While local clinicians were consulted, the DUSC considered the proportion of CHB patients tested for anti-HDV antibodies prior to bulevirtide being available was likely a substantial overestimate as it would only occur when clinically indicated. The resubmission noted that no alternative sources had been suggested during the March 2024 PBAC submission process and the value remains unchanged.
Chronic HBV patients tested who are anti-HDV positive	4.21%	Weighted average from Coghill et al, Jackson et al. (2018) and Shadur et al. (2013)	Based on the DUSC estimate of weighted value from Coghill, Jackson and Shadur.
Uptake of RNA testing in anti-HDV positive patients prior to bulevirtide listed	44.4%		Given that only a small number of labs currently provide HDV RNA testing, it is unclear whether the estimates derived from these studies apply across the country.
Prevalent population – unknown HDV			
Prevalent chronic HBV patients who are engaged in care that are tested for anti-HDV after bulevirtide listed	Year 1: █% × █% Year 2: █% × █% Year 3: █% × █% █%	Assuming 80% uptake in those not previously tested for anti-HDV testing, over the first three years of listing	Assumes unchanged overall 80% uptake as March 2024 submission but distribution amended for higher uptake in Year 1.
Uptake of RNA testing in anti-HDV positive patients after bulevirtide listed	█% in Year 1 increasing to █% from Year 3	Assumption, supported by clinician discussions.	As described in Table 16, Bulevirtide, PBAC PSD March 2024, the uptake in the initial years has been increased.
Prevalent patients not currently engaged in care	64.6%	100% - 35.4% (% diagnosed and engaged in care)	As described in Table 16, Bulevirtide, PSD March 2024, the uptake accounts for prevalent patients not currently being treated.
Prevalent patients not currently engaged in care	1.00%	Nguyen 2024, page 14, Table 4	As described in Table 16, Bulevirtide, PSD March 2024, the uptake accounts for prevalent patients not currently being treated. This population is currently diagnosed prevalent patient who re-engage with care.
Incident population			
Incidence of chronic HBV	0.0198%	Communicable Diseases Dashboard for 2023 ^a	Previously accepted source, updated to 2023 evidence.

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Data	Value	Source	Comment
Incident chronic HBV patients diagnosed & engaged in care	90.0%	Assumption	As this was an assumption, there is likely to be uncertainty around this estimate.
Incident chronic HBV patients tested for anti-HDV after bulevirtide listed	████% in Year 1 increasing to █████% from Year 3	Assumption	As this was an assumption, there is likely to be uncertainty around this estimate.
HDV RNA positive	54.4%	Section 3 Economic model	Updated as suggested during evaluation of the March 2024 submission.
Proportion HDV RNA positive patients eligible for bulevirtide	82.0%	MYR301	The DUSC considered the proportion of HDV RNA positive patients being eligible for bulevirtide may be overestimated. The Pre-PBAC response clarified the intended population is patients with Child Pugh Class A disease (no restriction on liver fibrosis), therefore the requested PBS population is aligned with the MYR301 trial.
Treatment utilisation			
Uptake rate	████% in Year 1, increasing to █████% from Year 4	Assumptions based on discussions with clinicians	Updated as suggested during evaluation of the March 2024 submission.
Proportion of patients remaining on treatment per year	Year 1: 93.8% Year 2: 86.3% Year 3: 76.9% Year 4: 59.3% Year 5: 55.7% Year 6: 52.3%	Section 3 economic model	Updated to reflect the Section 3 economic model.
Scripts dispensed per patient per year	5.48	6.09 scripts per year (365.25/60), assuming 90% compliance	DUSC considered 90% may be an overestimate of compliance for PBS utilisation - a real-world retrospective cohort study (2019-2021) by De Ledingham V et al suggested 91% at 6 months, 88% at 12 months and 78% at 24 months.
Costs			
Bulevirtide	Effective prices (DPMQ) \$████ public \$████ private	Proposed Section 100 HSD Public /Private and Community Access DPMQ	Updated to be consistent with Section 3 which assumed 20% of scripts would be dispensed in a public hospital.
Patient copayment	\$24.44	PBS items 10310P, 11142K and 11155D, assuming only PBS copayments	This was appropriate.
MBS costs			
HDV RNA PCR testing	\$129.30	Proposed MBS item fee, assuming 85% benefit	Considered reasonable in the March 2024 submission.
Anti-HDV antibody testing	\$13.35	MBS item 69475, assuming 85% benefit	Considered reasonable in the March 2024 submission.

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Source: Table 4.1–1, pp150–3 of the resubmission.

DCC = decompensated cirrhosis, HBV = hepatitis B virus, HDV = hepatitis D virus; RNA = ribonucleic acid.

^a <https://nindss.health.gov.au/pbi-dashboard/>

Blue shaded rows are unchanged from the previous submission.

6.65 The table below summarises the service volumes and financial impact on the MBS and PBS/RPBS of the listing of the HDV RNA test and bulevirtide. The overall impact presented in the March 2024 submission is also presented for comparison.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of the HDV RNA test						
Number of patients tested	¹	²	²	²	²	²
Number of patients likely to receive a positive test result (54.4%)	²	²	²	²	²	²
Estimated extent of use of bulevirtide						
Number of patients likely to be treated with proposed drug	²	²	²	²	²	²
Number of scripts dispensed ^a	¹	¹	¹	¹	¹	¹
Estimated financial implications of the HDV RNA test to the MBS						
Cost to the MBS @ 85% benefit ^b	³	³	³	³	³	³
Estimated financial implications of bulevirtide to the PBS/RPBS						
Cost to PBS/RPBS less copayments – published ^c	⁴	⁵	⁶	⁶	⁶	⁶
Cost to PBS/RPBS less copayments – effective ^c	³	⁷	⁷	⁷	⁷	⁴
Estimated financial implications for anti-HDV testing to the MBS						
Cost to MBS	³	³	³	³	³	³
Net financial implications						
Net cost to PBS/RPBS - effective	³					⁴
Net cost to MBS	³	³	³	³	³	³
Net cost to PBS/RPBS/MBS ^c	³	⁷	⁷	⁷	⁷	⁴
Previous submission March 2024						
Net cost to PBS/RPBS ^d	³	⁷	⁷	⁷	⁷	⁷

Source: Table 64 to Table 76 of the evaluation

Note: Blue shaded rows denote information unchanged from the previous submission.

^a Assuming 6.09 scripts at 90% compliance – 5.48 scripts per year as estimated by the submission.

^b Includes HDV RNA testing for eligibility testing and on-going monitoring of treated patients.

^c Includes revised corrected copayment amount. The resubmission incorrectly applied a 20% reduction to the patient copayments, increasing the overall cost to the PBS/RPBS.

^d Includes revisions made to the submission during the evaluation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ \$0 to < \$10 million

⁴ \$20 million to < \$30 million

⁵ \$30 million to < \$40 million

⁶ \$40 million to < \$50 million

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⁷ \$10 million to < \$20 million

- 6.66 The total cost to the PBS/RPBS of listing bulevirtide was estimated to be \$20 million to < \$30 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing.
- 6.67 The resubmission addressed the issues raised by DUSC and PBAC in the March 2024 submission where there were alternative or suggested data sources. The resubmission introduced a new patient population to address concerns that there was a prevalent pool of patients who were not currently engaged in treatment. The PBAC previously considered the likely uptake of both testing and treatment, and utilisation and duration of therapy with bulevirtide, to be highly uncertain in practice. In addition, persistence is uncertain noting that most patients would likely have no or limited symptoms of hepatic disease and given the onerous administration requirements of daily and ongoing injections (paragraph 7.15, bulevirtide PSD, March 2024 PBAC meeting).
- 6.68 The resubmission aligned the financial estimates with the economic modelling as requested following the March 2024 submission. The financial estimates mirror the HDV RNA testing regimen during treatment that is presented in the economic model. This may overestimate the cost of HDV RNA testing if it is not conducted as frequently as every 6 months.

Quality use of medicines

- 6.69 The quality use of medicines factors presented by the resubmission are unchanged from the March 2024 submission.

Financial management – risk sharing arrangements

- 6.70 Consistent with the March 2024 submission, the resubmission stated that a Risk Sharing Arrangement (RSA) was not proposed due to the small number of patients expected to be commencing treatment with bulevirtide (< 500 patients annually).

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation for the listing of bulevirtide for treatment of chronic hepatitis delta virus (CHD) infection. While the PBAC was of a mind to recommend bulevirtide, the PBAC noted that an integrated codependent submission for the MBS listing of Hepatitis D ribonucleic acid polymerase chain reaction testing for CHD would be considered at the April 2025 MSAC meeting. The PBAC acknowledged that hepatitis D virus (HDV) is relatively rare in Australia, but there is a need for effective treatments. The PBAC reaffirmed its view that whilst the evidence indicates that bulevirtide is effective for some patients in terms of achieving

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a significant reduction in viral load and/or improvement in liver enzymes, the longer-term and patient-relevant benefits were highly uncertain. The PBAC noted that the resubmission included a small reduction in the proposed price for bulevirtide and revised some inputs in the economic analysis as requested, but a number of optimistic assumptions that were likely to have underestimated the incremental cost-effectiveness ratio remained. Overall, the PBAC considered that bulevirtide would be cost-effective with a further substantial price reduction, to address the remaining uncertainties in the economic model and bring the ICER into an acceptable range. The PBAC also considered the proposed utilisation of bulevirtide was uncertain but the estimates presented in the submission appeared to be reasonable.

- 7.2 The PBAC noted that hepatitis D virus (HDV) is relatively rare in Australia, and reaffirmed its view that there is a high clinical need for effective therapies for CHD infection as current treatments for CHD (such as peg-interferon alfa-2a (PEG-IFN- α)) were not effective or not tolerable for many patients. The PBAC noted that Hepatitis B (which is required for infection with HDV) is vaccine-preventable, and elimination of Hepatitis B as a public health threat should remain a priority.
- 7.3 The PBAC noted the input from 2 consumer group/organisations which supported the listing of bulevirtide and highlighted the long-term impacts of CHD infection.
- 7.4 The PBAC considered a Section 100 Highly Specialised Drugs Program Streamlined Authority listing in Public and Private Hospital and Community Access for bulevirtide is reasonable and aligns with PBS listings for chronic hepatitis B (CHB). The PBAC noted this would facilitate patients who are engaged with hospital hepatology units to be prescribed bulevirtide alongside community practice managed patients. The PBAC considered that the proposed maximum quantities and repeats were reasonable. With regard to the requested listing and restrictions, the PBAC reaffirmed its view on the following (as per paragraphs 7.5-7.7 bulevirtide PSD, March 2024 PBAC meeting):
 - Given the rarity of CHD in Australia, and the potential access issues for patients in rural and remote communities, it was appropriate for prescribing to be in consultation with physicians with experience in the management of viral hepatitis. The PBAC noted that access to specialists is likely to be difficult for many patients with CHD and requested that the MSAC consider allowing GPs to order initial testing, in consultation with specialists.
 - The proposed restriction was reasonable for the purposes of initiating treatment and generally reflected the patient population included in the key clinical trial for bulevirtide (patients with no or well-compensated liver disease i.e. Child Pugh Class A).
 - It was appropriate that the restriction criteria be age agnostic rather than specifying patients must be over 18 years.

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- Clinical criteria should include “prior to commencing treatment with bulevirtide” for criteria relating to detectable viral load and elevated serum alanine transaminase (ALT), to allow continuation of bulevirtide treatment.
 - An explicit stopping rule was not appropriate because of the risk of viral breakthrough should treatment be ceased. The PBAC previously noted the decision to continue or cease treatment, based on response, was a matter of clinical judgement.
 - The PBAC considered it would not be appropriate to require use of PEG-INF prior to bulevirtide given PEG-INF is not commonly used in Australian practice.
- 7.5 The PBAC noted that the role of ongoing testing to monitor HDV RNA levels was somewhat uncertain as there are no clear guidelines on patient management and decisions to continue or cease treatment are likely to be patient specific. Although the PBAC did not recommend continuation criteria based on ongoing testing, the Committee considered that such testing was likely to be of use in guiding treatment decisions regarding continuation of bulevirtide.
- 7.6 The PBAC reaffirmed its view that the nominated comparator of symptomatic management of CHD (also referred to as BSC) was reasonable.
- 7.7 The PBAC noted the key trial (MYR301) presented as the basis for comparative effectiveness of bulevirtide, was unchanged from the previous submission. In the resubmission, effectiveness and safety data covering Week 96 to Week 144 of the treatment period of the trial were presented, in addition to the data that were presented in the previous submission (the first 96 weeks of the study). The PBAC maintained its view that the trial was reliable in terms of assessing virologic response (i.e. decrease in HDV RNA by $\geq 2 \log_{10}$ IU/ml from baseline), undetectable HDV RNA, ALT normalisation, change in liver stiffness and key safety outcomes.
- 7.8 The PBAC noted that the resubmission presented additional evidence addressing the correlation between viremia and clinical outcomes. The PBAC agreed with the ESCs that the evidence presented in the resubmission, including evidence based on detectable versus undetectable RNA levels, was supportive of the biologically plausible claim that a drop in HDV viral load levels relative to baseline was indicative of clinical response to treatment insofar as patients with lower viral loads may have a reduced risk of developing liver-related clinical events compared to patients with higher viral loads. However, no studies provided conclusive evidence to support that the $\geq 2 \log_{10}$ IU/mL decline in HDV RNA level, as a surrogate marker by itself, is correlated with improved long-term liver-related health outcomes. The PBAC acknowledged the sponsor’s arguments regarding the assays used to quantify HDV RNA in older CHD studies. Studies that reported improved clinical outcomes due to the viral load declining to a level reported as “undetectable” were based on testing

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with LLoD levels that are substantially higher (less sensitive) than the assay used in the pivotal MYR301 trial, making comparisons problematic.

- 7.9 The PBAC reaffirmed its previous advice that the available evidence demonstrates bulevirtide is effective for the treatment of CHD in terms of the composite endpoint (including its components), as well as for achieving undetectable HDV RNA. Therefore, the PBAC considered there is a likely to be a benefit to CHD patients from treatment with bulevirtide. However, the PBAC maintained its previous view that that there were substantial uncertainties in the translation of surrogate measures to target clinical outcomes and that given viral suppression requires ongoing treatment with bulevirtide, assumptions around duration of treatment would impact on long-term outcomes (paragraph 7.9, bulevirtide PSD, March 2024 PBAC meeting).
- 7.10 The PBAC reaffirmed its previous advice that the claim bulevirtide has a manageable safety profile compared to symptomatic management of CHD or BSC may, on balance, be reasonable. However, the PBAC considered that longer term safety is uncertain, particularly with respect to vitamin D deficiency, which appeared to have a cumulative effect over time with additional follow-up.
- 7.11 The PBAC noted that the resubmission included a small reduction in the proposed price for bulevirtide and made the following changes to the model as previously requested: the use of updated trial data on treatment response rates, the alternative data source for the effect of response, a longer duration of bulevirtide treatment, and the use of Australian preference weights in estimating utility weights for non-cirrhosis (NC) and compensated cirrhosis (CC) health states. However, a number of optimistic assumptions that were likely to have underestimated the incremental cost-effectiveness ratio (ICER) remained unchanged in the resubmission model.
- 7.12 The PBAC noted the treatment response as applied in the model (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL) is neither the primary efficacy endpoint in the key trial (undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline and ALT normalisation) nor the best supported surrogate measure based on the available evidence (detectable vs. undetectable HDV RNA) to estimate the effect of response on liver-related clinical outcomes (refer to paragraphs 6.11-6.13). The PSCR and pre-PBAC response maintained that the most appropriate clinically relevant response outcome for CHD is a $\geq 2 \log_{10}$ decline in HDV RNA from baseline, arguing that it is a standardised definition that has been established to demonstrate improved clinical outcome and is consistently assessed in CHD treatment trials. The PBAC noted the ESCs' advice that, although a reduction in viral load is likely to be clinically relevant, the correlation between the surrogate HDV RNA $\geq 2 \log_{10}$ IU/mL reduction from baseline and the magnitude of longer-term clinical benefits of bulevirtide treatment in terms of a reduction in liver decompensation, HCC, liver transplantation, or mortality, remains uncertain. The PBAC noted that using "undetectable HDV RNA" results for treatment response was a conservative approach,

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acknowledging the sensitivity of testing has increased, and noting comparison of “undetectable HDV RNA” across different studies was problematic. The PBAC considered it would be reasonable to include the combined response outcome (virological response defined as undetectable HDV RNA or reduction in RNA level $\geq 2\log_{10}$ IU/mL from baseline and ALT normalisation) as this was the primary outcome in the pivotal trial.

- 7.13 The PBAC again considered it would likely be a long time before the patient-relevant impacts of bulevirtide treatment are well-characterised and considered there remains uncertainty regarding how bulevirtide is likely to be used in clinical practice. The PBAC noted the results from stepped multivariate analyses demonstrated that the ICER is highly sensitive to cumulative changes in the model, increasing from \$95,000 to < \$115,000/QALY gained in the base case to \$455,000 to < \$555,000/QALY gained when a number of model inputs are revised for consistency with previous PBAC advice (time horizon, source for health state utilities and exclusion of utility increment in responders), and internal consistency (definition of response and treatment compliance). The PBAC noted the sponsor’s arguments regarding the inputs applied in this multivariate analysis (see paragraphs 6.46, 6.48 and 6.50). However, with the exception of the definition of response, the PBAC reaffirmed its view that the conservative approach that was adopted during the evaluation by revising model inputs/assumptions was required to address the main areas of uncertainty. The PBAC noted that using the multivariate analysis in the evaluation, but with the definition of response revised to the combined response outcome, the ICER was \$255,000 to < \$355,000 per QALY at the price proposed in the pre-PBAC response. The PBAC considered that the ICER remained unacceptably high and considered that bulevirtide would be considered cost effective at a price that resulted in an ICER of no more than \$35,000 to < \$45,000 per QALY using this revised multivariate analysis. The PBAC noted that this was consistent with its considerations of the cost-effectiveness of other antivirals for chronic viral hepatitis which have previously been considered cost-effective with ICERs less than \$35,000 to < \$45,000/QALY.
- 7.14 The PBAC noted the resubmission retained the epidemiological approach taken in the submission considered at the March 2024 PBAC meeting which was appropriate. The financial model was updated to account for the changes requested following the March 2024 submission including the introduction of a new patient population to address concerns that there was a prevalent pool of patients who were not currently engaged in treatment. The PBAC recalled its previous concern that the likely uptake of both testing and treatment, and utilisation and duration of therapy with bulevirtide, to be highly uncertain in practice. In addition, persistence is uncertain noting that most patients would likely have no or limited symptoms of hepatic disease, and given the onerous administration requirements of ongoing daily injections. The PBAC considered that the level of uncertainty with regard to these factors remained high,

however the overall financial impact of listing bulevirtide would be limited due to the small number of Australian patients impacted by CHD.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Gilead welcomes the PBAC's deferral of the decision, with a mind to recommend bulevirtide for the treatment of chronic hepatitis delta (CHD) virus, noting no decision had been made regarding the integrated codependent submission for the MBS listing of Hepatitis D ribonucleic acid polymerase chain reaction (HDV RNA PCR) testing for CHD by the Medical Services Advisory Committee (MSAC). Gilead intends to work with the Department of Health for PBS access that recognises the value of bulevirtide.

Addendum to the March 2025 PBAC PSD:

14.06 BULEVIRTIDE

Powder for injection 2 mg

Hepcludex®

Gilead Sciences Pty Ltd

10 Background

- 10.1 At its March 2025 meeting, the PBAC deferred making a recommendation for the listing of bulevirtide for treatment of chronic hepatitis delta virus (hepatitis D). While the PBAC was of a mind to recommend bulevirtide, the PBAC noted that an integrated codependent submission for the Medicare Benefits Schedule (MBS) listing of ribonucleic acid (RNA) polymerase chain reaction testing (PCR) for chronic hepatitis D would be considered at the April 2025 MSAC meeting (see paragraph 7.1).
- 10.2 At its April 2025 meeting, the MSAC supported the creation of a new MBS item for the quantitation of Hepatitis D viral (HDV) RNA using PCR testing to i) determine eligibility for treatment with bulevirtide and ii) monitor the efficacy of bulevirtide treatment in patients with chronic HDV infection with compensated liver disease. The MSAC considered that there is a high clinical need for treatments for chronic HDV infection as it is a rare and aggressive condition with limited treatment options that is more common in socially vulnerable groups.

11 PBAC Outcome

- 11.1 The PBAC recommended the listing of bulevirtide for the treatment of chronic hepatitis D (CHD) in patients positive for hepatitis D virus (HDV) RNA as detected by PCR, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program: Public and Private Hospital and Community Access). The PBAC noted that the MSAC supported MBS listing of HDV RNA PCR testing to determine eligibility for treatment with bulevirtide and to monitor the response to treatment.
- 11.2 The PBAC is satisfied that bulevirtide provides, for some patients, a significant improvement in efficacy over symptomatic management of CHD (also referred to as BSC). The PBAC recalled that it had previously considered that whilst the evidence indicates that bulevirtide is effective for some patients in terms of achieving a significant reduction in viral load and/or improvement in liver enzymes, the longer-term and patient-relevant benefits were highly uncertain compared BSC.

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- 11.3 The PBAC recalled that the resubmission included a small reduction in the proposed price for bulevirtide and revised some inputs in the economic analysis as requested, but a number of optimistic assumptions that were likely to have underestimated the incremental cost-effectiveness ratio remained. The PBAC considered that the ICER remained unacceptably high and considered that bulevirtide would be considered cost effective at a price that resulted in an ICER of no more than \$35,000 to < \$45,000 per QALY using the revised multivariate analysis outlined in paragraph 7.13. The PBAC noted that this was consistent with its considerations of the cost-effectiveness of other antivirals for chronic viral hepatitis which have previously been considered cost-effective with ICERs less than \$35,000 to < \$45,000/QALY.
- 11.4 The PBAC also recalled in its previous consideration that it considered the proposed utilisation of bulevirtide was uncertain but the estimates presented in the submission appeared to be reasonable.
- 11.5 The PBAC reaffirmed its views regarding the Section 100 Highly Specialised Drugs Program (Public and Private Hospital and Community Access) Streamlined Authority listing for bulevirtide for the treatment of CHD infection (as per paragraph 7.4). The PBAC noted the resubmission requested a grandfather restriction and noted that there are currently 10 patients accessing bulevirtide. The PBAC considered a separate grandfather restriction was not necessary as grandfathered patients would be able to meet the clinical criteria at the time of treatment initiation under the recommended listing.
- 11.6 The PBAC advised that bulevirtide is suitable for prescribing by nurse practitioners for continuation of therapy.
- 11.7 The PBAC recommended that bulevirtide should not be treated as interchangeable on an individual patient basis with any other drugs under Section 101 (3BA) of the *National Health Act 1953*. The PBAC considered bulevirtide is the only targeted therapy currently proposed for hepatitis D infection, and there are no comparable direct acting anti-viral agents for other forms of hepatitis that have similar mechanisms of action (as an entry inhibitor for hepatitis B/D virus).
- 11.8 The PBAC advised that bulevirtide should not be exempt from the Early Supply Rule as it currently applies to anti-viral therapies for chronic hepatitis B.
- 11.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation bulevirtide:
- 1) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies. Although the MYR301 trial demonstrated a benefit in terms of virologic response, longer-term patient-relevant clinical benefits of bulevirtide treatment (reduction in liver decompensation, HCC, liver transplantation, or mortality) remain uncertain
 - 2) The treatment is not expected to address a high and urgent unmet clinical need

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- 3) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

11.10 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

12 Recommended listing

12.1 Add new medicinal product:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BULEVIRTIDE						
Bulevirtide acetate 2 mg injection, 30 vials		NEW	2	60	5	HEPCLUDEX®
Restriction Summary [new1] / Treatment of Concept: [new1A]						
Concept ID	Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) / Community Access (CA)					
	Prescriber type: ☒ Medical Practitioners ☒ Nurse Practitioners					
	Restriction type: ☒ Authority Required (Streamlined) [new]					
	Authority type: ☒ Non-complex Authority Required (non-CAR)					
Prescribing rule level	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
		Episodicity: Chronic				
		Condition: Hepatitis D infection				
		Indication: Chronic Hepatitis D infection				
		Clinical criteria:				
		Patient must have detectable hepatitis delta virus (HDV) RNA levels prior to commencing treatment with bulevirtide				
		AND				
		Clinical criteria:				
		Patient must have elevated serum alanine transaminase (ALT) level prior to commencing treatment with bulevirtide				
		AND				
		Clinical criteria:				
		Patient must not have current or previous (within last 2 years) decompensated liver disease				

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	AND
	Treatment criteria:
	Must be initiated in consultation with a physician experienced in the management of patients with viral hepatitis if treatment is being initiated or continued
	OR
	Treatment criteria:
	Must be treated by a medical practitioner if treatment is being continued;
	OR
	Treatment criteria:
	Must be treated by a nurse practitioner in consultation with a medical practitioner if treatment is being continued.
	Administrative Advice: Treatment can be as monotherapy for chronic hepatitis D virus or in co-administration with another therapy for Hepatitis B virus infection.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.

Addendum to the July 2025 PBAC PSD:

14.06 BULEVIRTIDE

Powder for injection 2 mg

Hepcludex®

Gilead Sciences Pty Ltd

11 Background

- 11.1 At its July 2025 meeting, the PBAC recommended the section 100 (s100) Highly Specialised Drugs (HSD) Program (Public and Private Hospital and Community Access) Authority Required (STREAMLINED) listing of bulevirtide for the treatment of chronic hepatitis delta virus (hepatitis D) in patients positive for hepatitis D virus (HDV) ribonucleic acid (RNA) as detected by polymerase chain reaction (PCR). The PBAC noted that at its April 2025 meeting, the Medical Services Advisory Committee (MSAC) supported the Medicare Benefits Schedule (MBS) listing of HDV RNA PCR testing for chronic hepatitis D to determine eligibility for treatment with bulevirtide and to monitor the response to treatment (see paragraph 9.1).
- 11.2 The basis for the PBAC's recommendation in terms of the appropriate s100 HSD listing for bulevirtide was the Committee's initial consideration in March 2025 (as noted at paragraph 7.4) that a s100 HSD Program Streamlined Authority listing under Public and Private Hospital and Community Access arrangements was reasonable and aligned with PBS listings for chronic hepatitis B. At this time, the PBAC noted that this would facilitate patients who are engaged with hospital hepatology units being prescribed bulevirtide alongside community practice-managed patients.
- 11.3 This recommendation however is not consistent with the PBS listing of medicines for the treatment of chronic hepatitis B infection, which are listed on the s100 HSD Program under Community Access (CA) arrangements only.
- 11.4 The application of s100 HSD CA arrangements to relevant s100 HSD listings is given effect via the definition of a 'community access medication' in the s100 legislative instrument for the HSD Program, the [National Health \(Highly Specialised Drugs Program\) Special Arrangement 2021](#) (HSD legislative instrument). This definition operates "by exception" by carving out CA listings as applicable (i.e. at drug level or lower) from the application of the standard (more restrictive) rules around HSD prescribing and supply that would otherwise apply. As such, it is not possible for a listing to be defined as both CA and non-CA in the HSD legislative instrument.

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12 PBAC Outcome

- 12.1 The PBAC noted that the listing of bulevirtide as both an s100 HSD Public/Private Hospital and s100 HSD CA benefit (per the Committee's July 2025 recommendation) is:
- 1) not readily implementable within the HSD legislative instrument, in which a given listing is either legally defined as a 'community access medication' or it is not; and
 - 2) not necessary to achieve the intent of the recommendation, being to facilitate prescribing of bulevirtide for patients who are engaged with hospital hepatology units alongside community practice-managed patients. This is because s100 HSD CA listings can also be accessed in hospital settings.
- 12.2 The PBAC recommended that its July 2025 recommendation for the listing of bulevirtide for the treatment of chronic hepatitis D infection should be amended to listing as a s100 HSD CA benefit only. The PBAC noted that this s100 HSD listing type is accessible to eligible patients and prescribers in both hospital and community settings. No other changes to the restrictions recommended at the July 2025 PBAC were to be made.
- 12.3 The PBAC noted that an amendment to the s100 HSD legislation will be required to implement the listing of bulevirtide.

13 Recommended Listing

- 13.1 Add new medicinal product:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BULEVIRTIDE						
Bulevirtide acetate 2 mg injection, 30 vials		NEW	2	60	5	HEPCLUDEX®
		Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) / Community Access (CA)				
		Prescriber type: ☒ Medical Practitioners ☒ Nurse Practitioners				
		Restriction type: ☒ Authority Required (Streamlined) [new]				
		Authority type: ☒ Non-complex Authority Required (non-CAR)				
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
		Administrative Advice: No increase in the maximum number of repeats may be authorised.				
		Administrative Advice: Special Pricing Arrangements apply.				
		Episodicity: Chronic				

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	Condition: Hepatitis D infection
	Indication: Chronic Hepatitis D infection
	Clinical criteria:
	Patient must have detectable hepatitis delta virus (HDV) RNA levels prior to commencing treatment with bulevirtide
	AND
	Clinical criteria:
	Patient must have elevated serum alanine transaminase (ALT) level prior to commencing treatment with bulevirtide
	AND
	Clinical criteria:
	Patient must not have current or previous (within last 2 years) decompensated liver disease
	AND
	Treatment criteria:
	Must be initiated in consultation with a physician experienced in the management of patients with viral hepatitis if treatment is being initiated or continued
	OR
	Treatment criteria:
	Must be treated by a medical practitioner if treatment is being continued;
	OR
	Treatment criteria:
	Must be treated by a nurse practitioner in consultation with a medical practitioner if treatment is being continued.
	Administrative Advice: Treatment can be as monotherapy for chronic hepatitis D virus or in co-administration with another therapy for Hepatitis B virus infection.

		Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Community Access (CA)
		Prescriber type: ☒ Medical Practitioners ☒ Nurse Practitioners
		Restriction type: ☒ Authority Required (Streamlined) [new]
		Authority type: ☒ Non-complex Authority Required (non-CAR)
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Episodicity: Chronic
		Condition: Hepatitis D infection
		Indication: Chronic Hepatitis D infection
		Clinical criteria:
		Patient must have detectable hepatitis delta virus (HDV) RNA levels prior to commencing treatment with bulevirtide
		AND

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	Clinical criteria:
	Patient must have elevated serum alanine transaminase (ALT) level prior to commencing treatment with bulevirtide
	AND
	Clinical criteria:
	Patient must not have current or previous (within last 2 years) decompensated liver disease
	AND
	Treatment criteria:
	Must be initiated in consultation with a physician experienced in the management of patients with viral hepatitis if treatment is being initiated or continued;
	OR
	Treatment criteria:
	Must be treated by a medical practitioner if treatment is being continued;
	OR
	Treatment criteria:
	Must be treated by a nurse practitioner in consultation with a medical practitioner if treatment is being continued.
	Administrative Advice: Treatment can be as monotherapy for chronic hepatitis D virus or in co-administration with another therapy for Hepatitis B virus infection.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor's Comment

The sponsor had no comment.