

5.06 BULEVIRTIDE

Powder for injection 2 mg, Hepcludex[®], Gilead Sciences Pty Ltd.

1 Purpose of submission

- 1.1 An integrated codependent submission requesting 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 adult patients positive for hepatitis D virus (HDV) RNA as detected by PCR.
- 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.
- 1.3 The sponsor also argued that the Rule of Rescue criteria are satisfied on the following basis:
 - no nonpharmacological or pharmacological interventions currently registered or reimbursed for HDV patients;
 - CHD results in significant morbidity and premature mortality;
 - CHD is a rare disease and bulevirtide has been designated as an orphan drug by TGA; and
 - bulevirtide study results indicate unprecedented improvements in efficacy compared with best supportive care which will translate into significant reductions in liver complications and have a substantial positive impact on reducing premature death.

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) Drug: Patients with positive CHD with detectable polymerase chain reaction (PCR) results for serum/plasma HDV ribonucleic acid (RNA) ^a
Intervention	Test: HDV RNA PCR on serum or blood Drug: Bulevirtide 2 mg once daily subcutaneous injection
Comparator	Test: No HDV RNA testing Drug: Symptom management of CHD
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 < lower level 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 level of normal (ULN). - Secondary endpoints at Week 48 of: - Undetectable HDV RNA at Week 48 - ALT normalisation at Week 48 - Proportions of patients across the treatment arms achieving HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL (exploratory endpoint) - Quality of life using EuroQol 5-Dimensions (EQ-5D), Fatigue Severity Scale (FSS) and Hepatitis Quality of Life Questionnaire (HQLQ) - Safety (adverse events, physical examinations, laboratory findings)
Clinical claim	In adults with chronic HDV infection, bulevirtide is superior in efficacy 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 bulevirtide for the diagnosis and the treatment of chronic HDV will result in superior health outcomes compared to no testing and no access to bulevirtide.

Source: Table 1.1-1 p5 of the submission

^a The eligible population for bulevirtide is further restricted to patients with elevated serum alanine aminotransferase (ALT) level and patients with compensated liver disease in the requested PBS listing.

2 Background

Registration status

- 2.1 *TGA status at time of PBAC consideration:* the Delegate's Overview was not available, with a mutual stop clock applied to the TGA processes at most recent update. Bulevirtide was granted Priority Review Determination and Orphan Drug Designation on 15 March 2023 for the treatment of chronic HDV infection. The submission was made under the TGA/PBAC Parallel Process. In the Clinical Evaluation Report, it was concluded that, overall, there is no safety concern with bulevirtide treatment in CHD infection. The Clinical Evaluation Report noted that the major uncertainty with bulevirtide treatment in CHD was about the consistent recurrence of HDV infection and loss of efficacy after stopping the treatment.

Previous PBAC consideration

- 2.2 The PBAC has not previously considered bulevirtide for the proposed indication. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

3 Requested listing

- 3.1 Secretariat suggesting wording is shown below, with suggested additions in italics and deletions in strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer	
BULEVIRTIDE Bulevirtide acetate 2 mg injection, 30 vials	NEW	2	60	5	Hepcludex®	Gilead Sciences Pty Limited
Category/Program:	Section 100 – Highly Specialised Drugs Program (Community Access [CA]) Section 100 – Highly Specialised Drugs Program (Public Hospital) Section 100 – Highly Specialised Drugs Program (Private Hospital)					
Prescriber type:	☒ Medical Practitioners					
Restriction type:	☒ Authority Required – Streamlined					
Administrative Advice:	<i>No increase in the maximum quantity or number of units may be authorised.</i>					
Administrative Advice:	<i>No increase in the maximum number of repeats may be authorised.</i>					
Administrative Advice:	<i>Special Pricing Arrangements apply.</i>					
Episodicity:	Chronic					
Condition:	Hepatitis D infection					
PBS indication:	Chronic hepatitis D infection					
Treatment phase:	Not applicable					
Treatment criteria:	Treatment should <i>must</i> be initiated only by <i>in consultation with</i> a physician experienced in the treatment of patients with HDV infection <i>experienced in the management of patients with viral hepatitis</i>					
Clinical criteria:	Patient must have detectable <i>hepatitis delta virus</i> (HDV) RNA levels, AND Patient must have confirmed elevated serum alanine transaminase level, AND Patient must not have current or previous (within last 2 years) decompensated liver disease					
Population criteria:	Patient must be <i>at least 18 years of age</i> an adult					
Prescribing Instructions:	Treatment can be as monotherapy for chronic hepatitis D virus or in co-administration with another therapy for Hepatitis B virus infection					
Administrative Advice:						

- 3.2 The submission proposed a Special Pricing Arrangement (SPA). The requested effective dispensed prices for maximum quantity (DPMQs) (2 mg x 60 vial) were \$~~1~~ for public hospital and \$~~1~~ for private hospital and community access.
- 3.3 The requested amount of 2 mg x 360 vials of bulevirtide (one original script plus 5 repeats) will cover approximately one year of treatment, with the proposed dosing being bulevirtide 2 mg once daily.
- 3.4 The ESCs considered the prescriber restriction should be amended to a 'physician experienced in the management of patients with viral hepatitis' as there are likely to be few clinicians experienced in the management of HDV infection (specifically). The

PBAC considered that there may be access barriers for patients in remote areas and advised that this criterion should read “Treatment must be initiated in consultation with a physician experienced in the management of patients with viral hepatitis”.

- 3.5 The proposed restriction was assumed to be for both initiation and continuation of bulevirtide treatment. No continuing treatment restriction has been proposed. Therefore, once a patient finishes a 12-month treatment course, under the proposed restriction they would need to satisfy all clinical criteria again, in order to qualify for continuous treatment. As written, if the patient no longer has detectable HDV RNA or an elevated ALT level (both are signals of clinical benefit), the patient would not be eligible for ongoing treatment. This conflicts with what is suggested in the draft Product Information (PI): “Treatment should be continued as long as associated with clinical benefit”. The Pre-Sub-Committee Response (PSCR) clarified the intent of the restrictions is not to require a patient to satisfy clinical criteria again to qualify for ongoing treatment.
- 3.6 The ESC noted that the submission and PSCR identified that the proposed restriction was consistent with the restrictions for treatments for CHB (e.g. entecavir), which also do not include specific criteria for ongoing treatment in patients who may not meet the criteria in terms of detectable HBV levels. The ESC considered that there was a lack of clarity regarding ongoing treatment under the restrictions for CHB treatments and advised that there may be issues with interpretation of the restriction which may preclude continuing treatment where it is clinically indicated. The PBAC considered the restriction, as proposed, may inappropriately cause some patients to become ineligible if they achieved an undetectable HDV RNA level and/or achieved ALT normalisation. The Committee agreed the intent of the listing as described by the Sponsor was reasonable, but considered that the wording of the restriction needed changes to accurately reflect this intent.
- There was no information presented in the submission to provide guidance on when bulevirtide treatment should be ceased, or when – and for how long – to continue with treatment. In a randomised clinical trial of bulevirtide (MYR202), 13 out of the 15 responders’ HDV RNA levels had rebounded by Week 48 after discontinuation of bulevirtide at Week 24¹. The draft PI states that treatment should be continued as long as associated with clinical benefit, and that consideration to discontinue bulevirtide in patients with CHD should be given when there is sustained (6 months) hepatitis B surface antigen (HbsAg) seroconversion. However, it is unclear when in clinical practice clinicians and patients can decide there is no more clinical benefit to justify ongoing bulevirtide treatment. The PSCR clarified that ongoing treatment is required to maintain viral suppression and the intention of the proposed restriction is to allow ongoing

¹ Wedemeyer H et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. *Lancet Infectious Diseases*. 2023; 23:117-129.

treatment for patients with clinical benefit. The ESC considered the lack of long term data for efficacy and safety create significant uncertainties for estimating the likely duration of therapy, which has implications for the economic model and financial estimates.

- In the requested listing, non-responders were not defined and the timing of stopping bulevirtide treatment in non-responders was not specified. This was not consistent with the economic evaluation (patients receive bulevirtide for 96 weeks, thereafter, non-responders will discontinue treatment). For bulevirtide, the proportion of patients who achieved combined response in the bulevirtide 2 mg treatment arm of the key trial was reported to be 34.7% at Week 24, 44.9% at Week 48, and 55.1% at Week 96. The ESCs considered an enforceable discontinuation rule may be required if the use of bulevirtide is to be consistent with the modelled economic evaluation. However, the ESCs considered that such a rule may not be clinically justified as there is evidence that late response to treatment is relatively common for both partial responders and non-responders².
- The evaluation considered the proposed listing allows use of bulevirtide in patients with compensated liver disease (including Child-Pugh Class A and some Child-Pugh Class B cirrhosis based on clinician's judgement), and patients infected with HDV of all genotypes. However, in the key trial presented, only patients with Child-Pugh Class A cirrhosis and HDV genotype A infection were included. The PSCR clarified the listing of bulevirtide is intended for patients with compensated liver disease and Child Pugh Class B and C are excluded. The PBAC noted that the proposed restriction specifies that patients must not have decompensated liver disease and considered that this would ensure the patient population is consistent with the key trial in terms of Child-Pugh class. The PSCR also stated the antiviral activity of bulevirtide has been studied in vitro in the 8 HDV genotypes, as determined by sequencing, demonstrating broad spectrum antiviral activity against HDV-1 to -8 with across the 8 HBV genotypes, supporting the broad coverage of bulevirtide across HDV genotypes, which is reflected in the recently released European Association for the Study of the Liver (EASL) HDV Guidelines.
- The submission requested a grandfather restriction. The Sponsor noted three patients are currently receiving bulevirtide compassionately and an intent to allow further access ahead of an anticipated PBS listing. The PBAC noted that a separate listing for patients transitioning from non-PBS to PBS-subsidised supply would be required.

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

² Lampertico et al. Results from an integrated analysis at week 96: continued treatment of early virologic non-responders or partial responders with bulevirtide monotherapy for chronic hepatitis delta leads to improvement in virologic and biochemical responses. 2023 AASLD November 2023.

4 Population and disease

- 4.1 HDV is a defective virus in that the hepatitis D virion comprises an RNA genome and a single HDV encoded antigen but relies on a lipoprotein envelope provided by HBV to complete virion assembly and secretion in its life cycle³. Concomitant infection of HDV and HBV can either be a coinfection (i.e., an individual is infected simultaneously with HBV and HDV), or a superinfection (i.e., a chronic HBV carrier subsequently infected with HDV). In approximately 95% of patients who have acute HDV-HBV coinfection, the infection is followed by clearance of both viruses and the disease course is usually transient and self-limited, although there is a higher risk of fulminant hepatitis and acute liver failure with acute HDV-HBV coinfection, compared with acute HBV infection alone. However, in more than 90% of the patients who are chronic HBV carriers and have HDV superinfection, the infection becomes chronic⁴. Superinfection of HDV in chronic HBV carriers is associated with a more aggressive disease course compared with HBV mono-infection and is associated with an increased risk of development of acute hepatic failure, cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). The 5-year mortality from HDV/HBV superinfection is twice that of HBV mono-infection. In Fattovich et al (2000) study, after adjustment for clinical and serological differences at baseline, the estimated 5-year survival probability in Child-Pugh Class A patients was 90% and 95% for anti-HDV positive/HbeAg negative and anti-HDV negative/HbeAg negative, respectively⁵.
- 4.2 In Australia, CHD is predominantly prevalent in groups with risk factors, including intravenous drug users, men who have sex with men, and people from migrant communities and backgrounds where CHB and CHD are endemic.
- 4.3 Currently, CHD is diagnosed by a positive serum anti-HDV antibody test. There is no TGA approved treatment specifically for CHD and the standard of care 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 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. NTCP has been found to be a starting point for hepatocyte uptake of the viruses. The PSCR noted that as a result of this mechanism of action the HDV viral load can decrease over

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

⁴ 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.

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 Fattovich G et al. Influence of hepatitis delta virus infection on morbidity in compensated cirrhosis type B. *Gut*. 2000; 46:420-426.

a longer period of time than is expected for direct antivirals since the immune system slowly eliminates currently infected hepatocytes over time with bulevirtide effectively inhibiting new infection. Therefore, ongoing treatment with bulevirtide (similar to antivirals for CHB treatment) is required to continue inhibiting the entry of HDV into the hepatocytes, thus suppressing the virus. On rare occasions, HDV will clear the cells due to the spontaneous clearance of HBV infection (approx. 1%). Bulevirtide is proposed to be used for treatment of patients diagnosed with CHD who have tested positive for HDV RNA detected by PCR, having compensated liver disease as well as elevated ALT level. Patients receiving bulevirtide treatment will simultaneously receive management for the underlying HBV infection as clinically appropriate.

- 4.5 The ESCs noted that bulevirtide is not a curative therapy and ongoing treatment is required to maintain viral suppression of HDV. The ESCs considered there was a possibility the availability of bulevirtide may alter clinical management of CHD in Australian practice. While acknowledging that use of PEG-IFN- α is very limited for viral hepatitis in Australian practice and response rates are typically low, the availability of an additional viral suppressive agent has the potential to lead to changes in the management and treatment goals of CHD in the future, especially if there is the potential for achieving viral clearance. The ESCs noted that there was a phase 2 trial evaluating the efficacy of bulevirtide administered with PEG-INF- α as a potential finite curative treatment strategy in patients with CHD (MYR204), however only limited results from this trial have been published. The ESCs noted PEG-IFN- α has unrestricted listings on the PBS (11037X, 11416W).

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

5 Comparator

- 5.1 The nominated comparator for the proposed HDV RNA PCR testing on the MBS is no HDV RNA PCR testing and the nominated comparator for bulevirtide on the PBS is symptomatic CHD management (or BSC). The main argument provided in support of this nomination was that, currently, there is no TGA approved therapy specifically for the treatment of CHD in Australia. Symptom management of CHD and long-term follow up by a liver specialist is current standard of care in Australia for CHD patients with compensated liver disease.
- 5.2 Pegylated interferons (PEG-IFNs) have been used as an off-label treatment for CHD in Australia, but CHD is not a TGA-approved indication for PEG-IFNs. The virologic response of CHD patients to PEG-INFs treatment is around 30%⁶. PEG-IFN is associated with an unfavourable adverse event (AE) profile and recurrence of the disease after treatment ceases. In addition, PEG-IFNs are contraindicated in many HDV patients including those with advanced cirrhosis, psychiatric conditions and autoimmune diseases. All the above reasons prevent PEG-INFs from being widely used for CHD

⁶ Abdrakhman A et al, Effectiveness of pegylated interferon monotherapy in the treatment of chronic hepatitis D virus infection: a meta-analysis. *Antiviral Research*. 2021;185: 104995.

treatment. The ESCs noted that the UK National Institute for Health and Care Excellence (NICE) recommendation is for bulevirtide treatment to be an option where a patient's hepatitis has not responded to PEG-INF or they cannot have PEG-INF based therapy⁷. However, the ESCs considered that PEG-INF is used less frequently in Australian practice and it would not be appropriate to require use of PEG-INF prior to bulevirtide.

- 5.3 Overall, the evaluation and ESCs considered symptom management of chronic HDV is the appropriate comparator. In addition, PEG-INF may be replaced by bulevirtide (if listed) in some patients with CHD, and, thus, could be considered as a relevant comparator. However, as noted above, PEG-INF may also be used prior to or in combination with bulevirtide.

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 health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals described bulevirtide as an effective treatment for CHD which may have long term benefits such as preventing decompensated disease, which is associated with reduced risk of liver fibrosis, hepatocellular carcinoma and need for liver transplant. The comments also described the favourable, albeit short-term, data supporting the safety of bulevirtide, and the limitations of Peg IFN treatment. Health care professionals noted the requirement for daily injections will be inconvenient for patients.
- 6.3 The PBAC noted the comments from the organisations Hepatitis Australia and LiverWELL described CHD as more aggressive than CHB leading to more rapid progression of liver disease than HBV alone, and the need for effective treatment options such as bulevirtide. The comments from Hepatitis Australia also noted Peg IFN- α has shown some efficacy but the proportion of patients achieving a sustained virologic response was low. The PBAC also noted the comments from consumer organisation, LiverWELL, highlighted that in the Victorian community, prevalence of CHB and CHD is strongly linked to areas of disadvantage, and these conditions disproportionately affect migrant refugee and communities from regions where HDV is endemic.

⁷ <https://www.nice.org.uk/guidance/TA896/chapter/1-Recommendations>

Overview of the evidence base

- 6.4 The approach taken in the submission is 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 2).

Table 2: Summary of the linked evidence approach

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Used in modelled evaluation
Accuracy and performance of the test (cross-sectional accuracy)	Concordance with clinical utility standard.	☒ k=1 concordance study n=35	High	No
Prognostic evidence (longitudinal accuracy)	Comparison of outcomes in patients receiving usual care, conditioned on the presence or absence of HDV RNA at baseline	☒ k=5 retrospective cohorts n=1896	High	No
	Comparison of outcomes in patients receiving usual care, conditioned on the reduction of HDV RNA	☒ k=7 retrospective cohorts n=1687	High	Yes
Change in patient management	Evidence to show that HDV RNA guides decisions about stopping treatment (due to response or lack of response) or intensifying treatment (due to limited response)	☒ k=2 uncontrolled before/after study n=129	High	No
Health outcomes (clinical utility)	No evidence presented.	☐ k=0 n=0	Low	Yes
Predictive effect (treatment effect variation)	No evidence presented.	☐ 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		

Source: developed during the evaluation

CHD = chronic hepatitis D, HDV = hepatitis D virus, k=number of studies, n=number of patients, NA=not applicable, PCR = polymerase chain reaction; RNA = ribonucleic acid

- 6.5 The populations, tests and treatment regimens were not always transferrable across the evidence linkages in terms of patient selection criteria, testing methodology and timing, and duration of treatment, as they varied considerably.
- 6.6 The submission included a single key trial of bulevirtide versus symptom management in the proposed patient population (first-line treatment for CHD patients with positive HDV RNA detected by PCR, confirmed elevated serum ALT level and compensated liver disease) (MYR301).

Table 3: Data availability to inform comparisons

Proposed test vs no test	No evidence presented.	
Proposed test vs alternative test	Concordance between test used in Australia and clinical utility standard: 1 study	
	Bulevirtide	No active treatment
Biomarker test positive	MYR301	MYR301
Biomarker test negative	No evidence presented	

Source: Developed during the evaluation

- 6.7 The risk of bias was considered high for the studies which inform accuracy and performance of the test, prognostic value of HDV RNA and change in patient management. The risk of bias in the key trial in the submission (MYR301), was considered generally low. However, the study was open-label, with patients and investigators not blinded to the treatment group assignment. The risk of bias was considered low for assessment of the efficacy endpoints (i.e., HDV RNA level and liver function), as these were objective outcomes and 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.

Claim of codependence

- 6.8 The ESCs considered the claim of codependence was reasonable for HDV RNA PCR testing to establish the presence of chronic HDV infection and for access to treatment with bulevirtide (thereby influencing treatment management decisions). The ESCs considered that the risk that acute HDV infections would be diagnosed with a positive RNA PCR test was small because of the short incubation period of acute HDV infection.
- 6.9 However, the claim of codependence was not properly addressed in the submission for HDV RNA PCR testing for monitoring of response to bulevirtide. The submission did not address how the presence/absence or level of detectable HDV RNA would impact on management, incremental to ALT levels. It was not clear how monitoring HDV RNA levels would influence bulevirtide use as no continuation or discontinuation criteria based on HDV RNA levels were proposed for the PBS restrictions and none are defined in the draft PI.

Clinical trial on the effectiveness and safety of bulevirtide

- 6.10 The submission was based on one ongoing head-to-head, Phase 3, multicentre, open-label trial that assessed the effectiveness and safety of bulevirtide in patients diagnosed with CHD who had detectable serum/plasma HDV RNA by PCR and compensated liver disease (n=150) (MYR301 trial). In this trial, patients were randomly assigned to three treatment groups: 1) bulevirtide 2 mg group (bulevirtide 2 mg once daily for 144 weeks) (N=49); 2) bulevirtide 10 mg group (bulevirtide 5 mg twice daily for 144 weeks) (N = 50); and 3) delayed treatment group (symptom management of CHD or BSC for the first 48 weeks, followed by bulevirtide 10 mg daily for 96 weeks) (N=51). Effectiveness and safety data presented in the submission covered the first 96 weeks of the trial.

- 6.11 In the trial, patients randomised into the two bulevirtide treatment groups would receive bulevirtide therapy for up to 144 weeks, regardless of their response status. This is not consistent with the draft PI, which suggests continued treatment as long as associated with clinical benefit, nor with the economic model, which assumed that non-responders would discontinue treatment after 96 weeks.
- 6.12 The recommended dosing of bulevirtide in the submission was 2 mg once daily administered subcutaneously (SC). This is consistent with the draft PI. Overall, bulevirtide 2 mg showed comparable effectiveness to bulevirtide 10 mg (daily dose) for treatment in patients with CHD in terms of combined response⁸ (response rate at Week 96: 55.1% vs. 56.0%), virologic response⁹ (response rate at Week 96: 75.5% vs. 82.0%), and normalisation of ALT (response rate at Week 96: 63.3% vs. 64.0%). The incidence of Grade 3 or higher treatment-related treatment-emergent adverse events (TEAEs) at Week 96 was slightly lower in patients receiving bulevirtide 2 mg compared with those receiving bulevirtide 10 mg (8.2% vs. 10.0%). In addition, it is expected that bulevirtide 2 mg treatment could be associated with better drug compliance as it requires SC self-injection once daily, compared to bulevirtide 10 mg treatment which requires SC self-injection twice daily. 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 below.
- 6.13 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). Use of interferons (INFs) within 6 months before screening was an exclusion criterion in the trial and no study participant received PEG-INFs concomitantly with bulevirtide during the trial.
- 6.14 The primary efficacy endpoint of the MYR301 trial was a combined response at Week 48. The combined response was defined as simultaneous achievement of:
- Undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline, and
 - ALT normalisation.

Outcomes such as undetectable HDV RNA, ALT normalisation and virologic response defined as HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL or undetectable HDV RNA were also reported in the MYR301 trial. The Food and Drug Administration (FDA) has suggested that the use of the combined virologic response (i.e. undetectable serum HDV RNA level or serum HDV RNA load decline $\geq 2 \log_{10}$ IU/mL) and biochemical response (i.e. normalisation of ALT) as a surrogate measure can predict clinical benefit of HDV antiviral treatment. The PSCR argued the aim of CHD treatment is to prevent the development of complications of liver disease (cirrhosis, cancer, the requirement for

⁸ In the MYR301 trial, combined response was defined as HDV RNA decrease by $\geq 2 \log_{10}$ IU/ml from baseline or undetectable HDV RNA and ALT normalisation

⁹ Virologic response defines as HDV RNA decrease by $\geq 2 \log_{10}$ IU/ml from baseline or undetectable HDV RNA)

liver transplant and death) but that these are inappropriate and/or impractical to measure in clinical trials, hence the reliance on virological and histological outcomes as surrogate markers to predict clinical benefit.

- 6.15 There is some clinical evidence indicating an increased risk of liver-related events in CHD patients who are anti-HDV positive and have detectable HDV RNA compared to those with undetectable HDV RNA¹⁰. However, in patients with viral hepatitis, liver injury is considered 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. It is usually used as an indicator to measure the severity of liver disease. In patients with CHB or CHD, however, decompensated cirrhosis may present with normal ALT levels.
- 6.16 Uncertainty remains regarding how to quantify the surrogate relationship between virologic response or ALT normalisation and patient-relevant outcome. Although the submission presented a systematic review and meta-analysis to support the relationship of HDV RNA reduction or undetectability or ALT normalisation on chronic HDV progression, the evaluation and ESC noted the submission did not explicitly use the framework in the PBAC guidelines for translating the comparative treatment effects of the proposed surrogate measure to target clinical outcomes (Appendix 5, PBAC guidelines (v5.0)). For further discussion, see Paragraphs 6.32-6.34.
- 6.17 Details of the trial presented in the submission are provided in the table below.

¹⁰ Farci P et al. Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology*. 2004; 1740-1749.

Table 4: 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.	13 September 2023
	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.	<i>Digestive and Liver Disease</i> 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.	<i>Digestive and Liver Disease</i> 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.	<i>Hepatology International</i> 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.	<i>Journal of Hepatology</i> 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.	<i>Journal of Hepatology</i> 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.	<i>Journal of Gastroenterology and Hepatology</i> 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.	<i>Hepatology</i> 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.	<i>Hepatology</i> 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.	<i>Hepatology</i> 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.	<i>Zeitschrift für Gastroenterologie</i> 2023; 61(01): e45-6
	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.	<i>Official journal of the American College of Gastroenterology</i> 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.	<i>Zeitschrift für Gastroenterologie</i> 2023; 61(01): e47-.

Source: Table 2.7-2, pp86-87 of the submission.

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

Table 5: 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 Ongoing	Patient with CHD, compensated liver disease, positive HDV RNA detected PCR and elevated serum ALT level	Primary efficacy endpoint: combined response defined as virologic response ^b and ALT normalisation Key secondary and exploratory efficacy endpoints: • Undetectable HDV RNA • Virologic 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	Virologic response ^b , EQ-5D, and ≥ Grade 3 TEAEs

Source: Table 2.9-5, pp101-102 of the submission

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 arms were not presented.

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

Comparative effectiveness

6.19 A summary of the 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 for this treatment arm and the differences between the bulevirtide 2 mg arm and the delayed treatment arm at Week 96 are not presented.

Table 6: 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	1
	Proportion responders, % (95% CI)	44.9 (30.7, 59.8)	2.0 (0.0, 10.4)
	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	n/a
	Proportion responders, % (95% CI)	55.1 (40.2, 69.3)	n/a

Endpoint		Bulevirtide 2 mg (N=49)	Delayed treatment (N=51)
Virologic response ^b	Week 48 (additional endpoint)		
	Number of responders	36	2
	Proportion responders, % (95% CI)	73.5 (58.9, 85.1)	3.9 (0.5, 13.5)
	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	n/a
	Proportion responders, % (95% CI)	75.5 (61.1, 86.7)	n/a
Undetectable HDV RNA	Week 48 (key secondary endpoint)		
	Number of responders	6	0
	Proportion responders, % (95% CI)	12.2 (4.6, 24.8)	0.0 (0.0, 7.0)
	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	n/a
	Proportion responders, % (95% CI) (bulevirtide 2 mg vs delayed treatment)	20.4 (10.2, 34.3)	n/a
ALT normalisation ^c	Week 48 (secondary endpoint)		
	Number of responders	25	6
	Proportion responders, % (95% CI)	51.0 (36.3, 65.6)	11.8 (4.4, 23.9)
	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	n/a
	Proportion responders, % (95% CI)	63.3 (48.3, 76.6)	n/a
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)	-4.0 (-5.6, -2.5)	n/a

Source: Table 2.10-1, p104; Table 2.10-3, p107; Table 2.10-4, p10, and Table 2.10-5, p110 of the submission

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 level 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 level 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 presentation nor is the difference between the delayed treatment arm and the 2 mg arm at this timepoint.

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

6.20 The primary combined response (achieving both virologic 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. 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.

- 6.21 At Week 48, virologic response (defined as HDV RNA decrease by $\geq 2 \log_{10}$ IU/mL from baseline or undetectable HDV RNA) was achieved in 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 virologic response rate between the two arms was 69.5% (95% CI: 54.1%, 81.9%). From 48 weeks to 96 weeks, the virologic response rate in the bulevirtide 2 mg treatment arm increased by 2.0% to 75.5% (95% CI: 61.1%, 96.7%).
- 6.22 Six of the 49 patients (12.2%; 95% CI: 4.6%, 24.8%) treated with bulevirtide 2 mg once daily 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 treatment arm.
- 6.23 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 comparator arm, with 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 percentage of patients achieving ALT normalisation increased from 51.0% at Week 48 to 63.3% (95% CI: 48.3%, 76.6%) at Week 96.
- 6.24 Bulevirtide also resulted in 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, 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 groups 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 LS change from baseline decreased further to -4.0 kPa (95% CI: -5.6%, to -2.5%) in the bulevirtide 2 mg treatment arm.
- 6.25 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 delayed treatment 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. The evaluation considered 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 trial design, neither participants nor the study personnel who collected health-related quality of life data were blinded to the treatment allocation. These patient-reported outcomes are subject to a high risk of bias.

Comparative harms

6.26 Table 7 below summarises the overall TEAEs in the bulevirtide 2 mg treatment arm at Week 48 and Week 96 and in the delayed treatment arm (i.e., BSC) at Week 48 in the MYR301 trial.

Table 7: 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 48
TEAE	41 (83.7%)	47 (95.9%)	39 (76.5%)
TEAE with Grade 3 or higher	5 (10.2%)	9 (18.4%)	4 (7.8%)
TEAE related to study drug	24 (49.0%)	25 (51.0%)	0
TEAE related to study drug with Grade 3 or higher	1 (2.0%)	4 (8.2%)	0
TE serious AE	2 (4.1%)	2 (4.1%)	1 (2.0%)
TE serious AE related to study drug	0	0	0
TEAE leading to premature discontinuation of study drug	0	0	0
Death	0	0	0

Source: Table 2.10-7, p118 of the submission

AE = adverse event; SAS = Safety Analysis Set; TE = treatment-emergent; TEAE = treatment-emergent adverse event

6.27 During the first 48 weeks, the proportion of patients experiencing at least one TEAE was comparable between the bulevirtide 2 mg treatment group and the delayed treatment group (83.7% vs. 76.5%). The incidence of drug-related TEAEs, however, was significantly higher in patients treated with bulevirtide 2 mg once daily, compared with those receiving BSC (49.0% vs. 0%). The AEs reported in MYR301 were mostly Grade 1 (mild) or 2 (moderate) in severity, with TEAEs of $\geq$ Grade 3 reported in 10.2% and 7.8% of patients in the bulevirtide 2 mg arm and in the delayed treatment arm, respectively (all Grade 3 AEs). Grade 3 TEAEs were not related to the study drug in all patients except for one (2.0%) patient in the bulevirtide 2 mg treatment group. The incidence of serious TEAEs was low across treatment arms (4.1% in the bulevirtide arm vs. 2.0% in the delayed treatment arm), none of which were related to the study drug. No cases of treatment-related serious AEs, premature discontinuation of study drug due to TEAEs, or deaths were observed in either treatment arms.

6.28 It is noted that the blood and lymphatic system disorders accounted for most TEAEs in the first 48 weeks in both treatment arms (36.7% vs. 29.4%). Of the most common AEs, headache (18.4% vs. 0%), pruritus (12.2% vs. 0%), eosinophilia (10.2% vs. 0%), fatigue (10.2% vs. 2.0%) occurred more frequently in the bulevirtide 2 mg treatment arm than in the delayed treatment arm. Grade 3 TEAEs which occurred in more than

one patient in both treatment arms included thrombocytopenia (1 (2.0%) participant in the bulevirtide 2 mg group and 3 (5.9%) participants in the delayed treatment group) and neutropenia (0 participants in the bulevirtide 2 mg group and 2 (3.9%) participants in the delayed treatment group).

- 6.29 For the bulevirtide 2 mg treatment group, longer exposure through Week 96 resulted in higher proportions of participants who experienced any TEAEs (95.9% vs. 83.7%), Grade 3 TEAEs (18.4% vs. 10.2%), and drug-related $\geq$ Grade 3 TEAEs (8.2% vs. 2.0%), compared with Week 48. The incidence of serious TEAEs was the same for both time periods (4.1%). The most commonly reported AEs in the bulevirtide 2 mg treatment group which showed an increased incidence of $\geq$ 5% from Week 48 to Week 96 were vitamin D deficiency (30.6% vs. 12.2%), neutropenia (12.2% vs. 4.1%), lymphopenia (14.3% vs. 8.2%), arthralgia (12.2% vs. 6.1%) and COVID-19 (8.2% vs. 2.0%).
- 6.30 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 eosinophil count increased, injection site reactions (presented as erythema, haematoma, pain, pruritus or swelling), hypersensitivity or anaphylactoid reactions, skin and subcutaneous disorders (presented as alopecia, angioedema, rash macular, 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.

Table 8: Summary of results of AESIs of the MYR301 trial

	Bulevirtide 2 mg (N=49)	Delayed treatment (N=51)	Bulevirtide 2 mg (N=49)
	Week 48	Week 48	Week 96
Hepatic flares	7 (14.3%)	4 (7.8%)	10 (20.4%)
Eosinophilia and Eosinophil count increased	5 (10.2%)	1 (2.0%)	5 (10.2%)
Injection site reactions	8 (16.3%)	0 (0.0%)	10 (20.4%)
Hypersensitivity/Angioedema/ Anaphylactic/Anaphylactoid	1 (2.0%)	0 (0.0%)	4 (8.2%)
Skin and subcutaneous disorders	9 (18.4%)	1 (2.0%)	10 (20.4%)
Increases in bile salt	1 (2.0%)	0 (0.0%)	1 (2.0%)

Source: Table 2.10-10, p123 of the submission, pp166-173 of the Interim Week 96 CSR

- 6.31 It was reported that through to Week 96, only one patient (2.0%) in the bulevirtide 2 mg treatment arm had increases in bile salt. Very low incidence of increases in bile salt was reported up to Week 96 in the trial. This was because isolated and asymptomatic increase of total bile salts above the ULN that was considered to be clinically insignificant by investigator was not reported as an AE as per the study protocol. However, increase in bile salt is the most commonly reported bulevirtide-related adverse event in “real-world” bulevirtide studies.

Benefits/harms

- 6.32 A summary of the comparative benefits and harms for bulevirtide versus BSC at Week 48 in the key trial is presented in the table below.

Table 9: 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 at Week 48 ^a	22/49	1/51	44.9	2.0	42.9 (27.0, 58.5) ^d		
Virologic response at Week 48 ^b	36/49	2/51	73.5	3.9	69.5 (54.1, 81.9)		
Undetectable HDV RNA at Week 48	6/49	0/51	12.2	0	12.2 (3.7, 24.8)		
ALT normalisation at Week 48 ^c	25/49	6/51	51.0	11.8	39.3 (19.9, 55.8)		
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 to Week 48 (kPa)	49 ^e	-3.1	(-4.7, -1.5%)	51 ^e	0.9	(-0.8, 2.6%)	-4.0 (-6.3, -1.6%)
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	24/49	0/51	49.0	0	49.0		
≥ Grade 3 TEAEs	5/49	4/51	10.2	7.8	2.4		
Hepatic flares	7/49	4/51	14.3	7.8	6.4		
Eosinophilia and eosinophil count increased	5/49	1/51	10.2	2.0	8.2		
Injection site reactions	8/49	0/51	16.3	0	16.3		
Skin and subcutaneous disorders	9/49	1/51	18.4	2.0	16.4		

Source: Table 2.10-1, p104; Table 2.10-2, p105; Table 2.10-3, p107; Table 2.10-4, p108; Table 2.10-7, p118; Table 2.10-10, p123 of the submission

ALT = alanine aminotransferase; BSC = best supportive care; HDV = hepatitis D virus; RNA = ribonucleic acid; TEAE = treatment-emergent adverse event

^a Defined as undetectable HDV RNA (HDV RNA < lower level 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 level 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.

^e The number of participants in analysis of liver stiffness at Week 48 was 48 in the bulevirtide arm and 45 in the delayed treatment arm.

6.33 On the basis of the MYR301 trial presented by the submission, 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 any drug-related TEAEs.
- Approximately 2 additional patients would experience TEAEs of $\geq$ Grade 3.
- Approximately 6 additional patients would experience AEs indicative of hepatic flare.

Surrogate measures to target clinical outcomes

- 6.34 Surrogate endpoints in chronic HDV have not been previously considered by the PBAC. The submission presented a systematic review and meta-analysis to support the relationship of HDV RNA reduction or undetectability or ALT normalisation on chronic HDV progression but did not explicitly use the framework in the PBAC guidelines for translating the comparative treatment effects of the proposed surrogate measure to target clinical outcomes (Appendix 5, PBAC guidelines (v5.0)). Briefly:
- The proposed surrogate measure applied in model was virologic response (i.e. undetectable RNA or HDV RNA decline by $\geq 2 \log_{10}$ IU/mL). In the trial this was measured using the Robogene assay, which has a lower limit of detection (LloD) of 6 IU/mL.
 - The target clinical outcome was reduced progression or regression of liver-related events (CC, DCC, HCC or liver-related mortality) in chronic HDV.
 - The biological plausibility of the relationship between the proposed surrogate measure and the target clinical outcome was that detectable RNA is indicative of an actively replicating virus, which contributes to hepatitis disease progression. Therefore reducing levels of RNA may indicate a suppression of viral activity, which may slow or reverse liver-related disease progression.
- 6.35 The comparisons presented in a number of the studies are unlikely to be applicable to inform the relationship between response as observed in the MYR301 trial and liver-related outcomes in patients with chronic HDV. Some studies presented a comparison of outcomes in patients with acute versus chronic HDV infections or compared outcomes in HBV mono-infection versus HBV/HDV infection. Some studies did not test patients for RNA.
- 6.36 Where relevant comparisons were presented, in general, the definition of the surrogate measure (detectable versus undetectable RNA) used was narrower than the definition of virologic response used in MYR301. Only one study was identified that presented comparisons consistent with the definition of virologic response in MYR301 (undetectable RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline), though the LloD in this study was noted to be higher than the test used in the trial (100 IU/mL versus 6 IU/mL). After excluding studies that contained irrelevant comparisons, revised meta-analyses presented show an increased risk of liver-related events in chronic HDV patients with anti-HDV positive who have detectable HDV RNA

compared to those with undetectable HDV RNA. Therefore use of response rates from MYR301 defined as undetectable RNA may be more consistent with the studies included in the meta-analyses. However, heterogeneity was also observed across the studies in terms of the LLoD of the tests applied and in general differed to the LLoD of the test used in the MYR301 trial. It is unclear what impact differences in LLoD have on the transformation of the surrogate to clinical outcomes. The Pre-PBAC response argued the assays used to quantify HDV RNA had improved over time and a test able to detect HDV RNA to a level of 6 IU/mL did not become available until approximately 2017. Furthermore, the Pre-PBAC response argued therefore it is not appropriate to use 'undetectable HDV RNA' as a singular outcome as the benchmark for detection has changed with improving tests over time; therefore the use of an alternate measure such as a reduction in HDV RNA was more appropriate, and the threshold of a $-2 \log_{10}$ reduction has previously been associated with clinical benefit in Farci 2004.

- 6.37 The PSCR argued that persistent HDV RNA viraemia is the strongest predictor factor of cirrhosis, liver decompensation, HCC and death (Roulot et. al., 2020). The PSCR also argued this is consistent with well-established surrogacy of viraemia and adverse liver outcomes in CHB, and therefore the most appropriate endpoint for clinical management and prognostic purposes is a virologic response/suppression. The Pre-PBAC response argued the primary endpoint of combined response, which includes ALT normalisation, provides evidence of both a decline in viral load and an improvement in associated liver inflammation to predict clinical benefit.
- 6.38 The ESCs considered that the correlation between the achievement and maintenance of surrogate endpoints and long-term clinical benefits remains uncertain (see also paragraph 6.38).

Clinical claim

- 6.39 The submission described bulevirtide as superior, in terms of effectiveness, compared with current symptomatic management of CHD or BSC. The comparative evidence from the MYR301 trial showed treatment effects associated with bulevirtide over BSC regarding virologic response (undetectable HDV RNA or HDV RNA $\geq 2 \log_{10}$ IU/mL reduction from baseline), biochemical endpoint (ALT normalisation) and clinical parameter (liver stiffness) at Week 48. The key issues were:
- it is difficult to quantify the magnitude of patient-relevant benefit (i.e., reduction in liver decompensation, HCC, liver transplantation or mortality) from bulevirtide based on the surrogate outcomes observed in the clinical trial; and
 - recurrence of HDV infection after treatment discontinuation.
- 6.40 The ESCs noted that the evidence presented to transform the surrogate of virologic response into liver-related outcomes, in general, reflected outcomes in patients with detectable versus undetectable HDV RNA and as such was based on viral clearance (either spontaneous or IFN-induced) rather than suppression. As such, the relevance of the trial outcomes to patient-relevant outcomes in this context is uncertain. Overall,

the ESCs accepted that bulevirtide demonstrates virologic suppressive activity of HDV and reduces biochemical evidence of hepatitis for some patients while on therapy, but considered that the level of clinical benefit associated with virological suppression was uncertain. The ESCs also noted that virological suppression requires ongoing treatment with bulevirtide, and considered that the duration of treatment and therefore longer-term patient-relevant outcomes for bulevirtide were uncertain.

- 6.41 The submission described bulevirtide as having a manageable safety profile compared to symptomatic management of CHD or BSC. This claim was partially supported by the evidence presented. Although the vast majority of the AEs were of mild to moderate intensity and no AEs led to permanent withdrawal the main areas of concern are: 1) the small sample size of the trial (N=49 in the bulevirtide 2 mg group of MYR301); and 2) the limited follow-up period (safety data from the key trial covered up to 96 weeks of bulevirtide treatment) whereas patients may receive ongoing treatment as long as associated with clinical benefit. The PSCR stated the MYR-301 study will continue for up to 144 weeks of bulevirtide treatment and thus longer term safety data will become available in the future. The ESCs considered longer term safety data would be informative, when available.
- 6.42 The PBAC considered that the claim of superior comparative effectiveness was reasonable for the outcomes of virologic response and ALT normalisation, however considered the magnitude of benefit to longer-term and patient-relevant outcomes was uncertain.
- 6.43 The PBAC considered 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 agreed with the ESC that longer term safety data would be informative.

Economic analysis

- 6.44 The submission presented a modelled economic evaluation based on virologic response rates (defined as undetectable HDV RNA or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline) reported in the MYR301 trial which compared bulevirtide treatment to BSC (delayed treatment) in patients with HDV RNA positive chronic HDV.
- 6.45 The key components of the economic evaluation are summarised in Table 10.

Table 10: 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 not the preferred approach for modelling codependent technologies (Product type 4, 37 (O)', PBAC guidelines (v5.0)).
Time horizon	Lifetime (58 years) in the model base case (versus 96 weeks for bulevirtide and 48 weeks for BSC in the key trial). A time horizon of 20 years (with sensitivity analyses noted using 10 years) has previously been considered by the PBAC in the context of chronic HBV treatment (lamivudine, March 1999 PBAC meeting, and telbivudine PSD, March 2008 PBAC meeting).
Outcomes	Quality-adjusted life years.

Component	Summary
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 2009 ^a). While the health states included are consistent with the existing literature, limited data are available in chronic HDV to model progression within the NC health states. It may be more appropriate to have a single health state representing NC disease.
Cycle length	24 weeks.
Test parameters	The positivity rate of HDV RNA testing modelled was 56.2% based on a weighted average of Australian studies. ^{b,c,d} Test performance assumed was 100% and was not explicitly modelled. The approach to weighting the Australian data may have resulted in an overestimate as the submission applied the proportion of positives (50%) from the randomly tested sample in Jackson 2018) ^c (n = 20) to the denominator for the sample where PCR testing had been requested (n = 63, where 46% were positive). An estimate of 54.4% was derived during the evaluation. All patients identified with detectable RNA were assumed to be eligible and receive treatment. This may not be reasonable given that use is excluded in patients with normal ALT or who have decompensated disease. However the analysis is not sensitive to changes in the proportion of patients tested who receive bulevirtide treatment.
Implications of false positive and false negative results	Not modelled. The submission stated that low levels of FP or FN patients would have minimal impact on the overall cost-effectiveness results. The impact of false results may differ depending on whether testing is used to determine treatment initiation or for monitoring. False positives at initiation may falsely appear to respond to treatment and so could be considered to benefit from ongoing treatment.
Natural history of chronic HDV	Disease progression in non-responders was based on estimates reported in chronic HBV ^e , adjusted for concomitant HBV/HDV infection. ^{f,g,h} HbsAg seroclearance rate based on Zhou (2019) ⁱ . Background mortality based on ABS Australian life tables (2019–21). The sources used to model the natural history of chronic HDV were inadequately justified, given that additional sources ^{a,h,j} report outcomes directly in HBV/HDV patients, and because an Australian Markov model of chronic HBV progression is available. ^k
Effect in responders	Relative reduction in progression in responders was based on a meta-analysis of liver disease progression in HDV RNA negative versus HDV RNA positive patients (Attachment 11 of the submission). Regression in F3 and CC responders was also included. A number of the studies included in the meta-analysis were not relevant to inform the relationship of a reduction in HDV RNA levels on liver-related outcomes. Where relevant comparisons were presented, the definition of the surrogate measure (detectable versus undetectable RNA) was in general narrower than the definition of virologic response used in MYR301.
Response rate	Virologic response reported in MYR301. The use of response defined as undetectable RNA may be more consistent with the studies translating the comparative treatment effects of the proposed surrogate measure to target clinical outcomes. Extrapolation of virologic response rates in the delayed treatment arm of MYR301 to 72 and 96 weeks using an E _{max} function. While the fitted E _{max} model did not appear to be a good predictor of response to treatment at earlier time points, the ICER is not sensitive to plausible changes in BSC response
Duration of bulevirtide treatment	All patients were assumed to remain on bulevirtide treatment in the model until Week 96, unless they progress or experience HbsAg seroclearance. After Week 96, only those patients who achieved a response were assumed to continue. This was inconsistent with the use in the trial (all patients receive 144 weeks of treatment) and with the proposed PBS restriction (which may preclude use in patients with undetectable RNA or normal ALT levels, and may allow continued use in non-responders).

Component	Summary
Health related quality of life	NC (0.813) and CC (0.812) utilities in non-responders were derived from baseline utility in MYR301. Little difference in utility was observed in patients with and without cirrhosis at baseline, which is inconsistent with differences previously considered by the PBAC (para 6.38, daclatasvir PSD, March 2015 PBAC meeting). Patients who achieved a response were assumed to have a utility gain of 0.057, based on a Tobit regression model fitted to data from MYR301 at Week 48. A utility gain in responders may not be reasonable in chronic HDV as this was considered uncertain in chronic HCV, where SVR is an accepted surrogate for a cure (para 6.33, daclatasvir PSD, March 2015 PBAC meeting). Utility values in the remaining health states were derived from a sponsor-commissioned meta-analysis of health state utility in chronic HBV.

Source: Adapted from Table 3.1–1, p134 of the submission.

ALT = alanine transaminase; BSC = best supportive care; CC = compensated cirrhosis; DCC = decompensated cirrhosis; FN = false negative; FP = false positive; 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-cirrhotic; SVR = sustained virologic response.

^a Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. 2009 May;136(5):1629-38.

^b Coghill S, McNamara J, Woods M, Hajkiewicz K. Epidemiology and clinical outcomes of hepatitis delta (D) virus infection in Queensland, Australia. *Int J Infect Dis*. 2018 Sep;74:123-7.

^c Jackson K, MacLachlan J, Cowie B, Locarnini S, Bowden S, Higgins N, et al. Epidemiology and phylogenetic analysis of hepatitis D virus infection in Australia. *Intern Med J*. 2018 Nov;48(11):1308-17.

^d Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000-2009. *Intern Med J*. 2013 Oct;43(10):1081-7.

^e Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, P TK, 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.

^f Da BL, Heller T, Koh C. Hepatitis D infection: from initial discovery to current investigational therapies. *Gastroenterol Rep (Oxf)*. 2019 Aug;7(4):231-45.

^g Alfaiate D, Clement S, Gomes D, Goossens N, Negro F. Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. *J Hepatol*. 2020 Sep;73(3):533-9.

^h Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi 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 Mar;46(3):420-6.

ⁱ Zhou K, Contag C, Whitaker E, Terrault N. Spontaneous loss of surface antigen among adults living with chronic hepatitis B virus infection: a systematic review and pooled meta-analyses. *Lancet Gastroenterol Hepatol*. 2019 Mar;4(3):227-38.

^j Goyal A, 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.

^k Xiao Y, Howell J, van Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. *J Viral Hepat*. 2020 May;27(5):526-36.

6.46 Alternate scenarios of test/treatment provision were not explored in the submission.

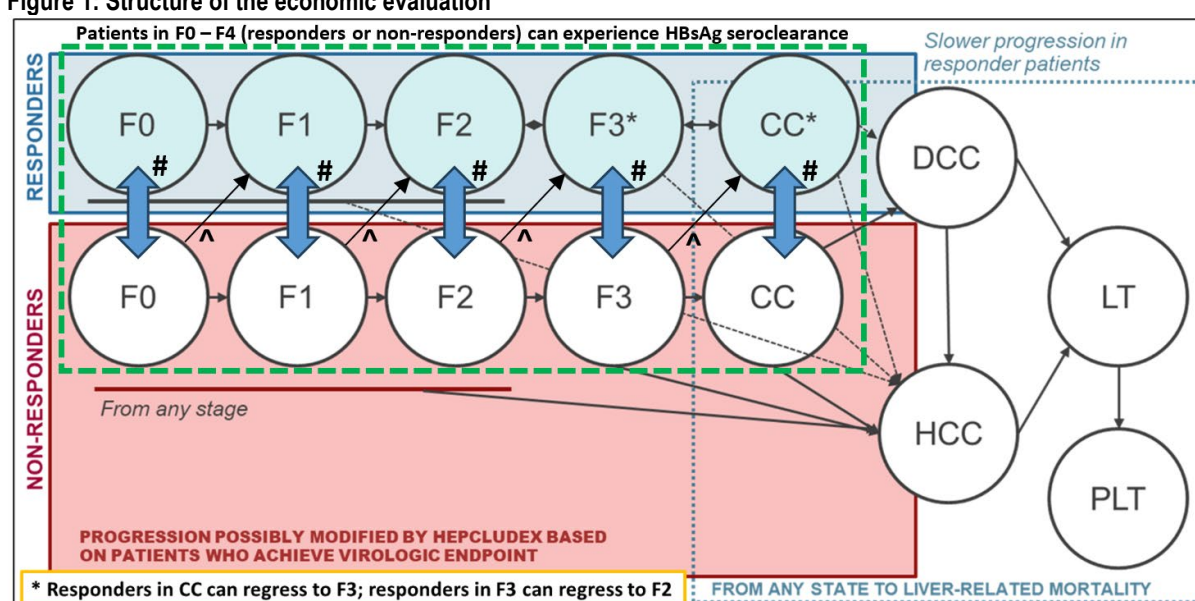
6.47 Patients enter the model at the point of treatment, and so the cost of testing in order to find one patient eligible for treatment was applied at model entry. Under the submission's assumption of the rate of HDV RNA positivity (56.2%) and 100% test performance, the cost of testing applied on model entry was \$270.64¹¹. Entry at the point of treatment is not the approach preferred for codependent technologies (Product type 4, 37 (O), PBAC guidelines (v5.0)), as this does not explicitly allow the impact of false-positive and/or false-negative results to be explored. The submission stated that if in practice there are low levels of false positives or false negatives due to uncertainty in the sensitivity and specificity of the proposed HDV RNA PCR testing, this will have minimal impact on the overall cost-effectiveness results. At treatment initiation, the impact of a false negative result may be limited to foregone potential benefit from bulevirtide treatment (i.e. cost of testing incurred, without benefit from treatment), though this would likely have been captured in the yield data used. The impact of a false positive result may not be insignificant – these patients may appear

¹¹ $1 \div \text{yield [56.2\%]} \times \text{the cost per test [\$152.10]}$

to falsely respond to bulevirtide treatment, and depending on the continuation criteria for treatment, may receive ongoing treatment for no benefit. False results may have different effects when the test is used for monitoring. False negatives may appear to respond to treatment, whereas false positives would not. These may affect decisions to continue or cease treatment, depending on bulevirtide continuation and stopping rules.

- 6.48 The structure of the economic evaluation included eleven distinct health states: non-cirrhosis (separated into F0, F1, F2 and F3 states), compensated cirrhosis (CC) (i.e. F4), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplantation, post-liver transplantation, dead (liver-related) and dead (background) (Figure 1).

Figure 1: Structure of the economic evaluation



Source: Adapted from Figure 3.2–1, p143 of the submission.

CC = compensated cirrhosis; DCC = decompensated cirrhosis; HbsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; LT = liver transplantation; PLT = post-liver transplantation.

Until Week 96, patients can move between non-responders and responders. After Week 96, responders can discontinue treatment (transitioning to non-responder status), but non-responders no longer receive treatment and so are unable to achieve a response.

^ Patients could progress and respond within the same cycle until Week 96

All health states are also subject to background mortality

- 6.49 While the model presented was similar to models in chronic hepatitis previously presented to the PBAC, no data were identified to inform progression within the non-cirrhotic health states (i.e. F0 to F3). The submission used a probability of developing cirrhosis in non-cirrhotic patients to approximate fibrosis stage progression, which may not be appropriate. The incremental cost-effectiveness ratio (ICER) is sensitive to changes in transition probabilities applied within the fibrosis health states. Simplifying the model structure to include one non-cirrhotic health state may be more appropriate.

- 6.50 Patients eligible for bulevirtide treatment include those with non-cirrhotic or CC disease. Therefore patients entering the model were distributed across these health

states, as non-responders. Within each model cycle (24 weeks), patients in either treatment arm could respond to treatment (up to 96 weeks only) and/or progress. Responding to treatment was assumed to reduce further disease progression, and allowed regression of F3 (to F2) and CC (to F3) disease. The modelled benefit for bulevirtide was therefore mediated through an increase in the proportion of responders, who were assumed to have slower disease progression and higher quality of life.

- 6.51 A lifetime time horizon (i.e. until 100 years of age) was assumed, based on the claim that an improvement in response delays, potentially avoiding, sequelae that result in substantial excess mortality. Given an average age of 42 years on model entry, the time horizon was therefore 58 years. This was substantially longer than the trial (96 weeks for bulevirtide, 48 weeks for BSC) and longer than previously considered by the PBAC in the context of chronic HBV treatment (20 years) (lamivudine, March 1999 PBAC meeting, and telbivudine Public Summary Document (PSD), March 2008 PBAC meeting). The model is sensitive to changes in the time horizon (see Table 14).
- 6.52 The PSCR argued the time horizon of 58 years was reasonable because HDV is a chronic and progressive disease and bulevirtide treatment significantly extends survival; therefore, many patients will have a normal life expectancy. The PSCR also reiterated the base case model predicts 85% and 70% of the bulevirtide and BSC cohorts (respectively) are still alive after 30 years, and the approach is consistent with the PBAC Guidelines. The ESCs considered the claim of an overall survival benefit was speculative and not directly supported by the available (shorter term) evidence and the uncertainty was further increased by the surrogate to final outcome approach used. Furthermore, the ESCs noted that patients were treated for a modelled average of 8.8 years and as patients only experience benefit while on treatment the duration of response and disease outcomes over the extended time horizon are highly uncertain. Overall, the ESCs considered a time horizon of 10-20 years was more appropriate in the context of these uncertainties, and would be consistent with previous considerations of chronic HBV treatments. The Pre-PBAC response argued a shorter time horizon would not allow the model to capture future benefits associated with treatment (as per PBAC guidelines).
- 6.53 The general approach to model chronic HDV disease progression used probabilities reported for disease progression with HBV mono-infection, adjusted for an increased risk in patients with HBV/HDV concomitant infection. The evaluation identified additional sources^{12,13,14} that report outcomes directly in HBV/HDV patients. These may provide a more reasonable basis for deriving the transition probabilities for use

¹² Goyal A, 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.

¹³ Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. 2009 May;136(5):1629-38.

¹⁴ Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi 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 Mar;46(3):420-6.

in the economic model and the ICER was noted to be sensitive to using these probabilities, where applicable. The primary source for the HBV mono-infection transition probabilities was an economic evaluation of alternate treatment options for chronic HBV conducted in the United Kingdom (UK)¹⁵. The submission did not justify the selection of this source, nor were alternate sources considered.

- 6.54 The benefit of bulevirtide was modelled through increasing the proportion of patients who respond to treatment. The MYR301 trial reported response rates to Week 96 for patients treated with 2 mg bulevirtide, and to Week 48 for those who received BSC in the delayed treatment arm. While the primary outcome of the trial was combined response defined as undetectable RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline and ALT normalisation, the definition of response applied in the model was that of virologic response defined as undetectable RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline (noted to be an additional efficacy end point of MYR301).
- 6.55 The PSCR argued a HDV RNA decrease of $\geq 2 \log_{10}$ IU/mL from baseline, was an appropriate measure of virologic response to define a responder because:
- It represents a clinically significant reduction in viral load, as the associated percentage reduction in baseline HDV viral load for a $\geq 2 \log_{10}$ IU/mL decrease from baseline is >99%;
 - ALT normalisation can fluctuate over time due to various factors, as noted by the evaluators; and
 - Undetectable HDV RNA is a function of test LLoD, which has significantly reduced over time based on assay improvements, and is difficult to achieve with modern testing.
- 6.56 The ESCs were concerned that the benefits of viral suppression in the economic evaluation were modelled based on extrapolation of sustained viral immune clearance (either spontaneous or associated with interferon treatment) and considered there are likely to be differences in outcomes between patients who are able to clear HDV infection (and are essentially cured) and those who are achieving and/or sustaining virologic suppression with ongoing treatment. Therefore, the ESCs considered the surrogate outcomes measured in the MYR-301 study were likely not translated to patient relevant liver-related outcomes appropriately. The ESCs agreed with the evaluation and considered that 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.
- 6.57 All patients who enter the intervention arm of the model receive 96 weeks of bulevirtide treatment, unless they experience HbsAg seroclearance, disease

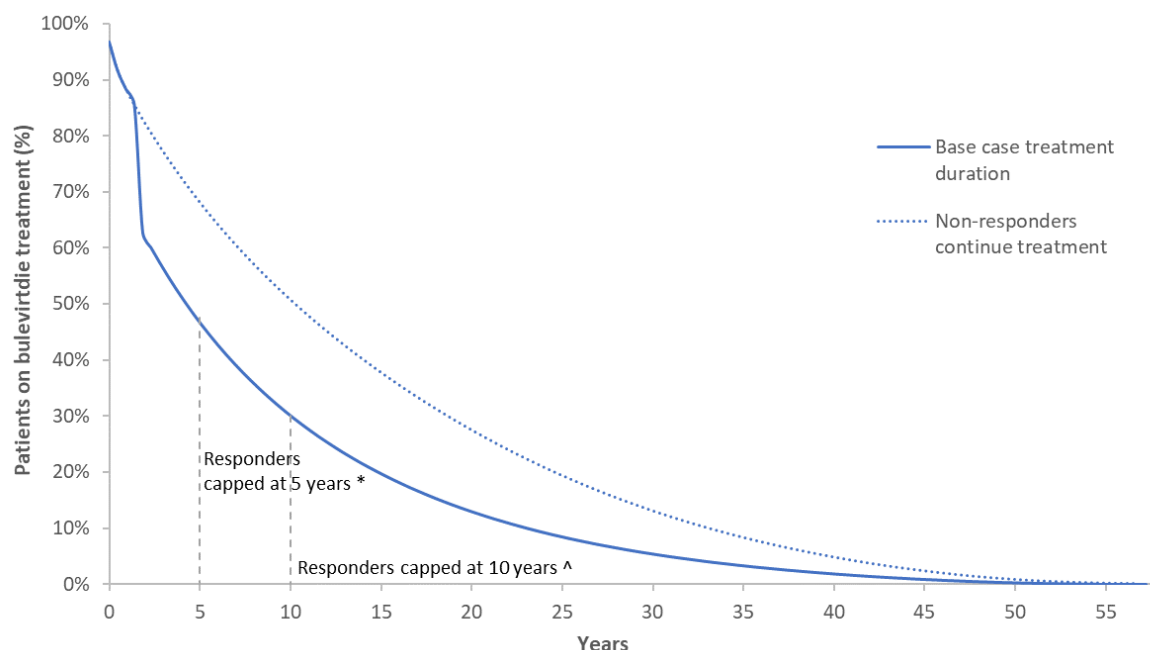
¹⁵ Bermingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, P TK, et al. Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom. *Value Health*. 2015 Sep;18(6):800-9.

progression (DCC or HCC) or die. The proportion of patients remaining in the F0–4 health states was not based on the MYR301 trial, but rather on external sources. In the first four model cycles, the average duration of treatment applied was 87.0 weeks, which was lower than the average duration reported in MYR301 to 96 weeks (94.4 weeks) in patients randomised to 2 mg bulevirtide.

- 6.58 After Week 96, non-responders were assumed to cease treatment. The basis for this assumption was not clear, given that patients enrolled in MYR301 will receive bulevirtide treatment up to 144 weeks, regardless of response, and that the proposed PBS restriction does not include a stopping rule in non-responders. While the proposed PI suggests that treatment should be continued as long as associated with clinical benefit, it is unclear when in clinical practice it would be decided that there was no longer a possibility for clinical benefit to be realised, or whether treatment would continue. The PSCR noted week 144 data was not available at time of submission, however argued it was likely to have a minor impact on the model results because the potential incremental cost due to the use of 96 weeks compared to 144 weeks affects cost calculations for only two cycles and for less than 25% of patients. The PSCR stated a scenario analysis performed assuming no increase in response to week 144 but with a treatment duration of the same, the ICER increased by 1% to \$95,000 to < \$115,000 per Quality-Adjusted Life Year (QALY). The ESCs considered, given the restriction is not intended to be prescriptive around continuation of therapy it was unclear whether the model appropriately captured how bulevirtide is likely to be used in practice. The Pre-PBAC Response reiterated the week 144 data was not available at time of submission and the results of the scenario analysis undertaken for the PSCR.
- 6.59 Responders were modelled to continue bulevirtide treatment beyond Week 96 unless they experience the events noted above, or discontinue due to other reasons. An annual probability of discontinuation (implemented as a loss of response and cessation of treatment) (5.07%) was applied based on the proportion of patients who permanently discontinued treatment to Week 48 across the bulevirtide 2 mg treatment arms of MYR301 and MYR203. The submission did not consider whether the reasons for treatment discontinuation in the trial were due to lack of response. As the submission has applied this estimate in responders only and this estimate did not change over time in the model, the applicability of the estimate as applied is uncertain and does not seem reasonable.
- 6.60 Over the 58-year time horizon, the average duration of bulevirtide treatment was estimated to be 8.8 years (Figure 2). Given issues noted above, the modelled duration of bulevirtide treatment is uncertain. The evaluation considered the plausibility of these estimates was uncertain, as the proportion of patients completing 10 years of treatment (30%) was similar to studies of chronic HBV treatment (32%)¹⁶.

¹⁶ Marcellin P, Wong DK, Sievert W, Buggisch P, Petersen J, Flisiak R, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. *Liver Int.* 2019 Oct;39(10):1868-75.

Figure 2: Proportion of patients remaining on bulevirtide treatment



Source: Constructed during the evaluation from the 'Attachment 10 – Hepcludex HDV Section 3A Cost-Eff Model_vfinal.xlsm' file included with the submission.

BSC = best supportive care; LYG = life years gained.

* Average duration of treatment with 5-year cap in responders (maintaining Week 96 cap in non-responders) is 3.5 years

^ Average duration of treatment with 10-year cap in responders (maintaining Week 96 cap in non-responders) is 5.4 years

- 6.61 The submission assumed six-monthly HDV RNA testing while patients remained on treatment. While this was consistent with the proposed MBS item, the only change in management modelled due to the inclusion of HDV RNA monitoring was to cease treatment in non-responders at Week 96, which does not seem reasonable.
- 6.62 The weighted DPMQ applied in the model per script was \$[REDACTED], assuming 80% of scripts dispensed in a private hospital or community access, and the remaining 20% in a public hospital. After assuming a relative dose intensity of 90%, the cost per 24-week model cycle applied was \$[REDACTED]¹⁷. The submission did not justify the relative dose intensity applied. Average compliance in patients randomised to bulevirtide 2 mg at Week 96 in MYR301 was 98.1% (Table 32, Study MYR301 Interim Week 96 Clinical Study Report). The submission adjusted drug cost for the lower adherence to treatment expected in practice, but such adjustment was not made for estimates of response. This was not reasonable. Increasing the adherence to treatment in the estimation of bulevirtide treatment cost had a moderate effect on the ICER.
- 6.63 The PSCR argued it was reasonable to assume longer term compliance would be reduced with a daily injection despite a motivated population and noted a French real world retrospective cohort study (Loustaud-Ratti et al 2023¹⁸) of bulevirtide found

¹⁷ No. days in each 24-week cycle [168] ÷ no. days each script lasts [60] × compliance [90.0%] × \$[REDACTED]

¹⁸ Loustaud-Ratti, E. G., H. Fontaine, E. Maugain, M. Lemaître, C. Lacueille, E. Benabadji Baro-Delta: données d'observance et de persistance en vraie vie des patients traités par Bulevirtide 2mg à partir des données du SNDS. (2023).

compliance was 91% at 6 months 88% at 12 months and 78% at 24 months. The ESCs acknowledged that compliance was likely to be lower than observed in the clinical trial given the daily injections required and the lack of a clear relationship between treatment and patients' improvement in quality of life. However, the ESCs agreed with the evaluation that assumptions regarding compliance should be aligned with the trial to be consistent with assumptions regarding ongoing benefit.

- 6.64 Health state utilities for non-responders in the non-cirrhotic and CC health states were based on EQ-5D-3L data at baseline in patients enrolled in the MYR301 trial, estimated using UK preferences. Limited information was provided in the submission on how these estimates were generated, including the number of patients these were based on. Very little difference in utility was observed between patients with (0.812) and without (0.813) cirrhosis at baseline, which is not consistent with differences between these health states previously considered by the PBAC (para 6.38, daclatasvir PSD, March 2015 PBAC meeting) (utility values in mild non-cirrhosis, moderate non-cirrhosis and CC of 0.77, 0.66 and 0.55, respectively, from Wright et al. 2006).¹⁹
- 6.65 Responders were assumed to gain additional utility of 0.057 based on a Tobit regression model fitted to data at Week 48 from MYR301. The 95%CI for this estimate (-0.103, 0.218) suggested that the utility increment estimated was not statistically significant, and so it may not be reasonable to assume higher utility in patients who respond. Further, while a utility increment of 0.05 in patients who achieved an SVR with chronic HCV treatment had previously been assumed in submissions presented to the PBAC (para 6.33, daclatasvir PSD, March 2015 PBAC meeting), this was considered to be a source of uncertainty. Given the differences in the surrogacy claims in chronic HCV versus HDV, the application (and magnitude) of any utility increment in chronic HDV is uncertain.
- 6.66 The PSCR noted the use of the utility increment for composite responders (0.057, 95% CI: -0.103, 0.218 p=0.477), as used in the submission, was more conservative than that observed for virologic responders (0.075, 95% CI: -0.059, 0.207 p=0.27) and argued the lack of significance was likely due to the small sample size. The ESCs noted the results were not statistically significant and considered it was not clear whether a utility gain in week 48 responders was plausible or appropriately applied throughout the model. The ESCs further noted that treatment effect was mediated through an assumed avoidance of liver-related events and disease progression, therefore health-related quality of life gains are realised in the model in other ways and the approach may double count quality of life gains.
- 6.67 A summary of the key drivers of the model are presented in Table 11.

¹⁹ Wright M, Grieve R, Roberts J, Main J, Thomas HC, Investigators UKMHCT. 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.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ /QALY gained.
Definition of response	Virologic response ^a .	High, favours bulevirtide. Using combined response ^b rates increases the ICER to \$ ² /QALY gained and using rates where undetectable RNA was achieved increases the ICER to \$ ³ /QALY gained.
Natural history of chronic HDV	Birmingham (2015) ^c adjusted for increased risk with HBV/HDV infection.	High, favours bulevirtide. Using chronic HBV probabilities from Xiao (2020) ^d increases the ICER to \$ ⁴ /QALY gained, whereas using probabilities (except HBsAg seroclearance) from Goyal and Murray (2016) ^e , increases the ICER to \$ ² /QALY gained.
Time horizon	58 years.	Moderate, decreasing the time horizon to 20 years increases the ICER to \$ ⁴ /QALY gained. Using 10 years increases the ICER to \$ ³ /QALY gained.
Utility increment in responders	0.0574, based on Tobit regression model fitted to MYR301 data at Week 48.	Moderate, favours bulevirtide. Excluding the utility increment in responders increases the ICER to \$ ² /QALY gained.
Health state utilities, NC and CC	0.813 and 0.812, respectively.	Moderate, using utility values consistent with Wright et al. (2006) ^f (F0–2: 0.77, F3: 0.66 and CC: 0.55), increases the ICER to \$ ² /QALY gained.
Compliance to treatment	90.0% (assumed).	Moderate, favours bulevirtide. Increasing the compliance to 98.1% increases the ICER to \$ ² /QALY gained.
HRs for disease progression in responders	HRs were estimated from a meta-analysis of the relationship of undetectable HDV RNA on any liver event (HR = 0.42); HCC (HR = 0.34); DCC (HR = 0.26) and liver-related death (HR = 0.22).	Moderate, favours bulevirtide. Using HRs derived 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) increased the ICER to \$ ² /QALY gained.

Source: Compiled during the evaluation.

CC = compensated cirrhosis; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; ICER = incremental cost-effectiveness ratio; NC = non-cirrhosis; QALY = quality-adjusted life year; RNA = ribonucleic acid.

^a Virologic response defined as undetectable HDV RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL

^b Combined response defined as virologic response (*i.e.* undetectable RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline) and ALT normalisation

^c Birmingham SL, Hughes R, Fenu E, Sawyer LM, Boxall E, P TK, 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.

^d Xiao Y, Howell J, van Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. *J Viral Hepat*. 2020 May;27(5):526-36.

^e Goyal A, 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.

^f Wright M, Grieve R, Roberts J, Main J, Thomas HC, Investigators UKMHCT. 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.

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 \$135,000 to < \$155,000

6.68 The results of the stepped economic evaluation are presented in Table 12. The stepped analyses presented in the submission 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.

Additional steps (3a and 3b) were included during the evaluation to allow the effect of each of these transformations to be distinguished from one another.

Table 12: 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 56.2% positivity rate), based on a weighted average from Coghill et al. (2018) ^a , Jackson et al. (2018) ^b and Shadur et al. (2013) ^c . Compliance to bulevirtide was 99.6% based on MYR301 trial compliance at 48 weeks (equivalent to 5.57 scripts per patient per 48 weeks).			
Costs	\$	\$0	\$
Virologic response ^d at 48 weeks	73.5%	3.9%	69.6%
Incremental cost/additional responder			\$ ¹
Step 2: Trial-based costs and outcomes to 96 weeks, with extrapolation of comparator outcomes			
Trial-based analysis at 96 weeks, assuming extrapolation of virologic response in the comparator arm. Compliance to bulevirtide was 98.1% based on MYR301 trial compliance at 96 weeks (equivalent to 10.98 scripts per patient per 96 weeks).			
Costs	\$	\$0	\$
Virologic response ^d at 96 weeks	75.5%	4.2%	71.3%
Incremental cost/additional responder			\$ ²
Step 3: Transformation of virologic response into QALYs			
A utility increment of 0.0574×1.84 years (i.e. 96 weeks) was applied per patient with virologic response at 96 weeks.			
Costs	\$	\$0	\$
QALY gained	0.080	0.004	0.075
Incremental cost/extra QALY gained			\$ ³
Step 3a: Transformation of the surrogate outcome of response into effect on disease progression			
Differences in disease progression were modelled across responders and non-responders based on the estimated relationship between 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	\$	\$8,688	\$
LY gained	1.688	1.674	0.015
QALY gained	1.396	1.323	0.074
Incremental cost/extra QALY gained			\$ ⁴
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	\$	\$8,688	\$
LY gained	1.688	1.674	0.015
QALY gained	1.396	1.323	0.074
Incremental cost/extra QALY gained			\$ ⁵
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	\$	\$68,278	\$
LY gained	10.851	8.462	2.389
QALY gained	8.548	6.327	2.221
Incremental cost/extra QALY gained (base case)			\$ ⁶

Source: Adapted from Table 3.8–1, p171 of the of the submission and Attachment 13 - Hepcludex HDV Section 3A Stepped Evaluation.

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

Note: Analyses in Step 3a and 3b text were conducted during the evaluation.

^a Coghill S, McNamara J, Woods M, Hajkovicz K. Epidemiology and clinical outcomes of hepatitis delta (D) virus infection in Queensland,

Australia. Int J Infect Dis. 2018 Sep;74:123-7.

^b Jackson K, MacLachlan J, Cowie B, Locarnini S, Bowden S, Higgins N, et al. Epidemiology and phylogenetic analysis of hepatitis D virus infection in Australia. Intern Med J. 2018 Nov;48(11):1308-17.

^c Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000-2009. Intern Med J. 2013 Oct;43(10):1081-7.

^d 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

² \$115,000 to < \$135,000

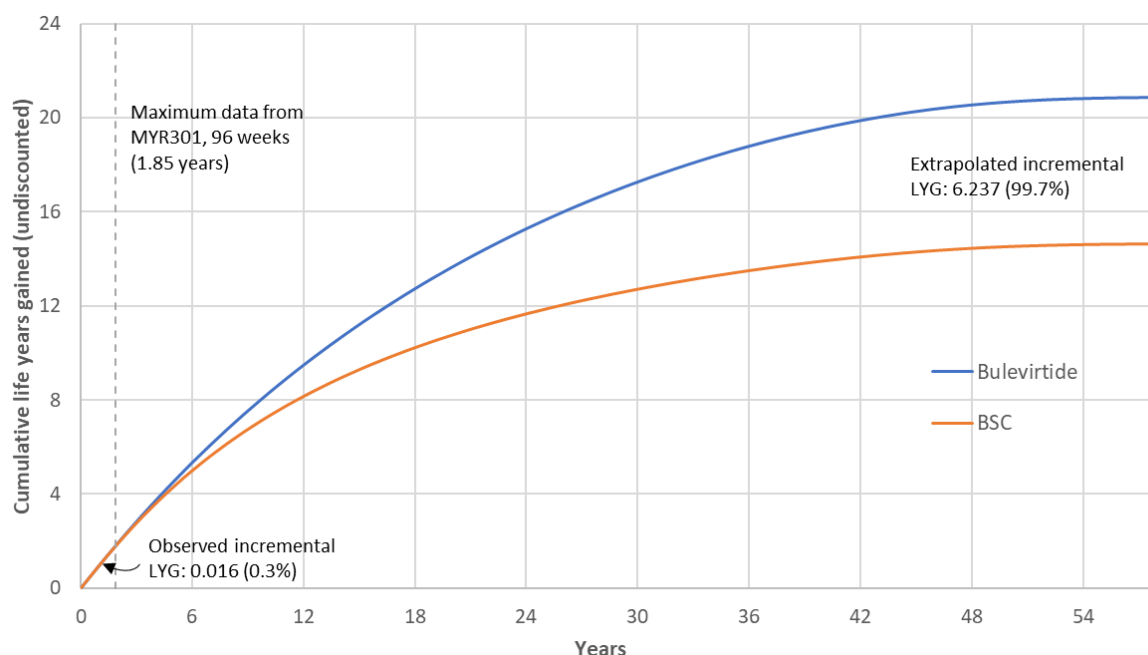
³ > \$1,055,000

⁴ \$955,000 to < \$1,055,000

⁵ \$855,000 to < \$955,000

⁶ \$95,000 to < \$115,000

- 6.69 Each of the steps included in the submission's stepped analysis had a substantial effect on the estimate of incremental cost-effectiveness. Extending the trial-based costs and outcomes from 48 to 96 weeks the ICER, due to the doubling of the cost of treatment, for little incremental benefit in terms of additional responders.
- 6.70 The ICER expressed as \$ per QALY (Step 3) was observed to be numerically much larger than when expressed as \$ per responder (Step 2), due to the small utility increment applied per year in responders (0.0574). As above, the evaluation considered the application of a utility gain in responders may not be reasonable as this was not statistically significant and because a similar gain for responders was considered uncertain in chronic HCV (para 6.33, daclatasvir PSD, March 2015 PBAC meeting). Furthermore, the submission assumed that the additional utility due to response would apply across the 96-week time horizon of the analysis, which does not account for the time in the model before patients achieved a response.
- 6.71 Modelling disease progression, adjustment for bulevirtide compliance and extrapolation over a lifetime time horizon (58 years) led to a substantial reduction in the ICER.
- 6.72 As only limited liver-related outcomes were reported in MYR301, with the primary and key secondary and additional efficacy endpoints being surrogate outcomes, the economic evaluation is completely reliant on modelling and assumptions regarding the durability of a response to bulevirtide treatment and the relationship between the response and chronic HDV disease progression. As depicted in Figure 3, the majority of the life years gained (6.237 years, 99.7%) were accrued in the extrapolated period. Given that estimates of life years gained were informed by a transformation of surrogate outcomes, extrapolated over a very extended time horizon relative to the trial data, the evaluation considered the modelled benefit quantified is inherently uncertain. The ESCs agreed with the evaluation and considered the resulting undiscounted life year gain of ~6.3 years to be highly implausible, given the model assumes only 8.8 years of treatment (paragraph 6.60) and the mechanism of action suppresses HDV only with ongoing treatment. Therefore the ESCs considered the modelled survival gain was extremely optimistic.

Figure 3: Cumulative life years gained over the time horizon of the model (undiscounted)

Source: Constructed during the evaluation from Attachment 10 - Hepcludex HDV Section 3A Cost-Eff Model_vfinal.

BSC = best supportive care; LYG = life years gained.

6.73 The number of liver-related events experienced across model arms over the extrapolated time horizon is presented in Table 13. These were based on published chronic HBV transition probabilities adjusted for HDV/HBV coinfection, with HRs for reduced progression in responders applied, sourced from meta-analyses investigating the effect of undetectable RNA on liver-related events. Issues were noted above regarding both the source of transition probabilities for chronic HDV disease progression and the HRs applied in patients who achieved a response. While bulevirtide treatment was associated with fewer DCC, HCC, liver transplantation and death due to liver-related disease (which were consistent with modelled benefit associated with response to treatment), the number of compensated cirrhosis events was increased with bulevirtide. This was due to the modelled assumptions regarding regression from cirrhosis. However, once a patient had regressed, the risk of developing cirrhosis was unchanged (and so patients could experience another cirrhotic event).

Table 13: Total proportion of patients who experience liver-related events over the model time horizon

Event	Bulevirtide	BSC	Difference
Cirrhosis (compensated)	0.397	0.339	0.058
Decompensated cirrhosis	0.274	0.331	-0.057
Hepatocellular carcinoma	0.374	0.402	-0.028
Liver transplantation	0.024	0.028	-0.004
Death, due to liver-related disease	0.725	0.842	-0.117

Source: Constructed during the evaluation from the 'Attachment 10 - Hepcludex HDV Section 3A Cost-Eff Model_vfinal.xlsm' file included with the submission.

BSC = best supportive care.

Note: A patient could experience more than one event.

- 6.74 Romeo et al. (2009)³¹ reported long-term outcomes in patients with chronic HDV over a mean observation period of 233 months (19.4 years). While modelled estimates over 20 years in the BSC arm were similar to those observed for a diagnosis of cirrhosis during the follow-up period (28.6% estimated in the model, compared to 27.4% observed), the model predicted a higher incidence of DCC (29.8% vs 18.1%) and HCC (35.3% vs 15.4%). The ESCs considered that the modelled DCC and HCC events appeared to be more frequent than would be expected in practice and noted that this favoured bulevirtide.
- 6.75 The PSCR argued long term data for HDV are limited and the approach taken to model the natural history of chronic HDV was reasonable. The PSCR argued that whilst the Xiao 2020 study (as used in the sensitivity analyses) is an Australian-specific hepatitis B model, the inputs are not necessarily Australian specific as they appeared to use data from East Asian countries, therefore the use of epidemiological data from that paper may not be reliable. The ESCs noted additional alternative data sources were raised during the evaluation (such as Goyal and Murray 2016). The pre-PBAC Response argued there are also significant applicability issues with the Goyal and Murray 2016 study to the Australian context, as the epidemiological inputs are derived from a cohort of Chinese CHB patients and use predominately Chinese publications to source epidemiological data and transition probabilities. The PBAC considered the approach taken to the natural history of chronic HDV added uncertainty as the ICER was sensitive to the source used.
- 6.76 Results of the key sensitivity analyses presented by the submission and additional analyses conducted during the evaluation are summarised in Table 14. The results of the univariate sensitivity analyses conducted during the evaluation show that the ICER is sensitive to the definition of response and the source used to model chronic HDV disease progression. The results are also sensitive to assumptions around utility values modelled (e.g. source for health state utilities and inclusion of utility increment in responders), some specific transition probabilities (e.g. fibrosis stage progression, HBsAg seroclearance and regression), time horizon and discount rate applied.

Table 14: Sensitivity analyses

	Inc. cost (\$)	Inc. QALYs	ICER (\$)	% change
Base case		2.221	1	
Time horizon (base case: 58 years)				
• 30 years		2.021	2	%
• 20 years (#3)		1.621	3	%
• 10 years		0.805	4	%
Discount rate (base case: 5%)				
• 0%		5.331	5	%
• 3.50%		2.791	1	%
Distribution of stage at baseline (base case: Romeo et al. 2009)				
• MYR301		2.145	2	%
• Assuming all non-cirrhotic patients enter model as F3 (#8)		2.589	6	%
Transition probabilities (base case: chronic HBV probabilities from Bermingham (2015), adjusted for HBV/HDV)				
• Xiao et al. (2020), adjusted for HBV/HDV as in submission		1.906	3	%

Public Summary Document – March 2024 PBAC Meeting

	Inc. cost (\$)	Inc. QALYs	ICER (\$)	% change
- Goyal and Murray (2016) - Goyal and Murray (2016) (using base case probability of HBsAg seroclearance) (#4)		1.499	1	– %
		1.639	2	%
F _x to F _{x+1} (base case: 15.07%, 5.3% with RR of 3 applied) ^a				
3.91% (Romeo et al. 2009) 4.1% (Goyal and Murray 2016)		2.024	2	%
		2.029	2	%
HBsAg seroclearance (base case: 1.13%) ^a				
0.25% (Romeo et al. 2009) (#9) 6.7% (Goyal and Murray 2016)		2.245	2	%
		1.960	6	– %
Definition of response (base case: virologic)				
- Combined - Undetectable RNA (#2)		1.308	2	%
		0.640	4	%
Treatment discontinuation, 14.4% ^b (base case: 5.07%) ^a		1.323	2	%
HRs in responders, evaluation revised estimates that exclude studies presenting irrelevant comparisons (#1)		1.997	2	%
Regression in responders ^a				
- F3 to F2 regression, 0% (base case: 13.3%) - F4 to F3 regression, 0% (base case: 8.8%) - Exclude regression		2.052	2	%
		1.879	2	%
		1.766	2	%
Health state utility values (base case: MYR301 for non-cirrhotic and CC, and Attachment 12 of the submission)				
- Non-cirrhotic and CC values as per Wright et al. (2006) ^c - All as per Wright et al. (2006) (#5) ^d		1.957	2	%
		1.965	2	%
Utility increment in responders (base case: 0.057)				
0 (#6) 0.207		1.941	2	%
		2.854	6	– %
No treatment discontinuation applied in non-responders ^e (base case: cease at Week 96)		2.221	4	%
Bulevirtide treatment cap (base case: none)				
5 years ^f 10 years ^f		2.221	5	– %
		2.221	6	– %
Compliance, 98.1% (base case: 90.0%) (#7)		2.221	2	%
Multivariate analyses				
#1 AND #2		0.575	4	%
#1, #2 AND #3		0.575	4	%
#1, #2, #3 AND #4		0.415	7	%
#1, #2, #3, #4 AND #5		0.288	7	%
#1, #2, #3, #4, #5 AND #6		0.264	8	%
#1, #2, #3, #4, #5, #6 AND #7 ^g		0.205	9	%
#1, #2, #3, #4, #5, #6, #7 AND #8 ^h		0.265	8	%
#1, #2, #3, #4, #5, #6, #7 AND #9 ^h		0.211	9	%

Source: Table 3.9–2, p175 of the submission and the attached 'Attachment 10 - Hepcludex HDV Section 3A Cost-Eff Model_vfinal.xlsm' file.

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; LT = liver transplantation; PLT = post-liver transplantation; QALY = quality adjusted life year; RNA = ribonucleic acid.

^a Annual transition probability reported. This was converted in the model to reflect a probability per 24-week cycle.

^b Permanent discontinuers in MYR203 at Week 48

^c F0–2: 0.77, F3: 0.66, CC: 0.55

^d F0–2: 0.77, F3: 0.66, CC: 0.55, DCC: 0.45, HCC: 0.45, LT: 0.45 and PLT: 0.67

^e Assuming no effect on response rates

^f Assuming no subsequent retreatment or changes in disease progression in responders

^g 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 submission (source for transition probabilities and studies included in the meta-analyses demonstrating the effect of response on liver-related outcomes).

^h Additional sensitivity analysis around the MV #1-#7 ICER

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$115,000 to < \$135,000

³ \$135,000 to < \$155,000

⁴ \$155,000 to < \$255,000

⁵ \$55,000 to < \$75,000

⁶ \$75,000 to < \$95,000

⁷ \$255,000 to < \$355,000

⁸ \$355,000 to < \$455,000

⁹ \$455,000 to < \$555,000

- 6.77 Multivariate analyses were conducted during the evaluation in a stepped manner to reflect changes in the model 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 submission (source for transition probabilities and studies included in the meta-analyses demonstrating the effect of response on liver-related outcomes). The ICER was highly sensitive to cumulative changes in the model.
- 6.78 After accounting for these, the remaining areas of uncertainty include the approach to modelling the non-cirrhotic health state – in terms of distribution and progression between fibrosis stage – and the probability of HBsAg seroclearance. Assuming all non-cirrhotic patients enter the model in the F3 health state (which may be more consistent with the source applied for the transition probability) led to a substantial reduction in the ICER. A small increase in the ICER was observed when instead the probability of HBsAg seroclearance was reduced to 0.25%, as per Romeo et al. (2009)³¹.
- 6.79 The ESCs considered the sensitivity analyses highlighted the sensitivity of the ICER to a number of key sources of uncertainty in the economic model, including the time horizon, source of transition probabilities, definition of response (and strength of the surrogate to final claim), and utility gains in responders and considered the multivariate analyses that explored these (#1-#6 and #1-#7) demonstrated the impact of more conservative inputs on the model results. The ESCs acknowledged it would likely be a long time before the patient-relevant impacts of bulevirtide treatment are well-characterised, and advised the most appropriate way to address uncertainties now was to adopt a conservative approach to the effectiveness assumptions for the economic evaluation. Given that there was inadequate evidence to support the surrogate to final outcomes modelled in the economic evaluation, the natural history data used were highly uncertain (Table 11), a highly implausible life year gain was modelled (paragraph 6.65) and there were significant uncertainties with the likely use of bulevirtide in practice, the ESCs were of the view the issues with the model were complex and would likely require re-evaluation.

Drug cost/patient/course

Table 15: Drug cost per patient for bulevirtide

	Trial dose and duration	Model	Financial estimates
Mean dose	2 mg per day average compliance 98.1%	2 mg per day average compliance 90.0%	2 mg per day average compliance 90.0%
Mean duration	96 weeks (1.8 years) (11.0 scripts) ^a	8.8 years (48.0 scripts) ^a	3.9 years ^b (21.2 scripts)
Cost per script	\$	\$	\$
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) × compliance × (52 × 7) days per year / 60 days per script

^b Average over first six years of treatment

6.80 The cost per course of bulevirtide treatment modelled was \$ (undiscounted). This was based on an average duration of treatment of 8.8 years (equivalent to 48 scripts)²⁰ assuming 90% compliance and a weighted cost per script of \$.

6.81 The weighted cost per script applied in the submission was inconsistent across the economic and financial analyses. While all scripts were assumed to be dispensed through the Section 100 HSD Private/Community Access program in the financial estimates, some dispensing in public hospitals (20%) was assumed in the economic model.

Estimated PBS & financial implications

6.82 This submission was considered by DUSC. An epidemiological approach was used to estimate the use and cost of HDV RNA testing and bulevirtide treatment.

6.83 The key inputs in the financial analysis are summarised in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population – known HDV		
Prevalence of chronic HBV in 2023	0.87% (McCulloch 2021) ^a	While this source was reasonable, the cited prevalence was reported for 2020. Prevalence in 2023 was estimated to be 0.82%. DUSC considered the most recent estimate of prevalence should be used.
Proportion diagnosed	73.0% (McCulloch 2021) ^a	DUSC noted that more recent estimates were consistent with this value (MacLachlan 2023) ⁹
Proportion of diagnosed patients engaged in care	30.9% (McCulloch 2021) ^a	The Pre-PBAC response clarified the figure of 22.6% in McCulloch is for all patients living with CHB (including those undiagnosed). The PBAC noted more recent estimates are somewhat higher (35.9% of diagnosed patients in MacLachlan 2023 ⁹).

²⁰ Average treatment duration [8.8 years] × compliance [90.0%] × (52 × 7) days per year / 60 days per script

Public Summary Document – March 2024 PBAC Meeting

Parameter	Value applied and source	Comment
Proportion tested for anti-HDV prior to bulevirtide listed	35.0% (UK NICE submission, confirmed by local clinicians)	While local clinicians were consulted, this estimate remains uncertain. 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 Pre-PBAC Response noted EASL 2023 HDV guidelines recommend testing for anti-HDV antibodies in all hepatitis B antigen positive individuals at least once and argued an assumption of a lower testing rate was unreasonable.
Prevalent population – unknown HDV		
Prevalent chronic HBV patients who are engaged in care that are tested for anti-HDV after bulevirtide listed	Year 1: 65% × █ % Year 2: 65% × █ % Year 3: 65% × █ % Assuming █ % uptake in those not previously tested for anti-HDV testing, over the first three years of listing	Given the limited treatment options, the evaluation considered it's plausible that the distribution of testing uptake could shift to earlier years. The submission has not assumed any change in testing in prevalent patients who are currently not engaged in care (69% of prevalent chronic HBV cases). The PBAC considered these estimates were uncertain.
Incident population		
Incidence of chronic HBV	0.02056% (Communicable Diseases Dashboard for 2022) ^b	DUSC considered this was reasonable.
Incident chronic HBV patients diagnosed & engaged in care	90.0% (assumption)	DUSC considered it was unclear why this was much higher than the estimated proportion of prevalent patients diagnosed and engaged in care. The pre-PBAC response noted it is assumed that most newly diagnosed patients will remain engaged in care for a period of time following diagnosis.
Incident chronic HBV patients tested for anti-HDV after bulevirtide listed	█ % in Year 1 increasing to █ % from Year 3 (assumption)	As for the prevalent, population these estimates are uncertain.
Proportion chronic HBV patients who are anti-HDV+	4.06% (Coghill 2018 ^c , Jackson 2018 ^d and Shadur 2013 ^e)	The evaluation considered this was reasonable. The DUSC noted that the weighted value was 4.21%. The DUSC considered this may be an overestimate, and that sensitivity analyses down to 3 times the numbers reported in the National Notifiable Disease Surveillance System (NNDSS) may be informative. The Pre-PBAC Response reiterated this figure was based on a weighted average of three high quality Australian studies and should be considered reliable.
Uptake of RNA testing in anti-HDV+ prior to bulevirtide listed	44.4% (Coghill 2018 ^c , Jackson 2018 ^d and Shadur 2013 ^e)	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.
Uptake of RNA testing in anti-HDV+ after bulevirtide listed	█ % in Year 1 increasing to █ % from Year 3 (assumption, supported by clinician discussions)	Uptake of HDV RNA testing may be higher than assumed in initial years as the increase in anti-HDV testing is due to increased awareness and availability of HDV RNA testing and bulevirtide treatment.

Public Summary Document – March 2024 PBAC Meeting

Parameter	Value applied and source	Comment
Proportion HDV RNA positive	56.2% (Coghill 2018 ^c , Jackson 2018 ^d and Shadur 2013 ^e)	Jackson (2018) ^d reported the proportion of RNA positives in anti-HDV+ with PCR requests (29/63, 46%) and patients who were randomly tested (i.e. without a PCR request) and found to be anti-HDV+ (10/20, 50%). The estimate applied from this study was 50% of 63, which may not be reasonable.
Proportion HDV RNA positive patients eligible for bulevirtide	82.0% (MYR301)	Reasons for patients who failed screening in MYR301 were not clear. The evaluation considered the trial exclusion criteria may be stricter than the proposed PBS restriction (e.g. Child-Pugh score >7 were excluded, where restriction only excludes patients with decompensated cirrhosis). 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 and cost		
Uptake of bulevirtide treatment in HDV RNA positive patients	█% in Year 1, increasing to █% from Year 4 (assumption)	The evaluation considered it may be reasonable to assume that all patients who take up testing and are HDV RNA positive would receive bulevirtide. The pre-PBAC response argued that not all patients who are eligible will choose to commence treatment with bulevirtide, so the uptake estimate will be a subset of those who are positive for HDV RNA.
Proportion of patients remaining on treatment per year	Year 1: 93.8% Year 2: 83.0% Year 3: 60.3% Year 4: 54.9% Year 5: 50.0% Year 6: 45.7% (Section 3 economic model)	The treatment continuation and stopping rules applied in the model were not consistent with the proposed PBS listing or use as observed in the trial. The effect of these differences on the financial impact was not clear.
Scripts dispensed per patient-year	5.48 (no. scripts per year [365.25/60], assuming 90% compliance)	While reduced compliance may be expected in practice relative to the MYR301 trial, the ESCs considered it was not appropriate to apply this adjustment to bulevirtide costs in the economic model without adjustment to outcomes. DUSC considered 90% may be an overestimate of compliance for PBS utilisation - a real world retrospective cohort study (2019-2021) by De Ledinghen V et al suggested 91% at 6 months, 88% at 12 months and 78% at 24 months.
Cost per script of bulevirtide	\$█ (proposed Section 100 HSD Private/Community Access DPMQ)	This was not consistent with the cost applied in the economic analysis, which assumed 20% of scripts would be dispensed in a public hospital.
HDV RNA PCR testing	\$129.30 (proposed MBS item fee ^f)	This was reasonable.
Anti-HDV antibody testing	\$13.35 (MBS item 69475 ^f)	This was reasonable.

Source: Table 4.1–2, pp185–7 of the submission.

HBV = hepatitis B virus, HDV = hepatitis D virus.

^a McCulloch K, Romero N, MacLachlan JH, Cowie BC. National Surveillance for Hepatitis B Indicators: Measuring the progress towards the targets of the National Hepatitis B Strategy – Annual Report 2020. Melbourne: WHO Collaborating Centre for Viral Hepatitis, The Doherty Institute 2021.

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

^c Coghill S, McNamara J, Woods M, Hajkovic K. Epidemiology and clinical outcomes of hepatitis delta (D) virus infection in Queensland, Australia. *Int J Infect Dis*. 2018 Sep;74:123-7.

^d Jackson K, MacLachlan J, Cowie B, Locarnini S, Bowden S, Higgins N, et al. Epidemiology and phylogenetic analysis of hepatitis D virus infection in Australia. *Intern Med J*. 2018 Nov;48(11):1308-17.

^e Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000-2009. *Intern Med J*. 2013 Oct;43(10):1081-7.

^f Assuming 85% benefit.

^g MacLachlan JH, Romero N, Purcell I, Cowie BC. Viral Hepatitis Mapping Project: Hepatitis B. National Report 2021. Darlinghurst, NSW: Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine (ASHM), 2023. ashm.org.au/vh-mapping-project/

6.84 The submission's estimates for the number of patients eligible for bulevirtide over the first six years of listing are presented in Table 17. These were generated across three population groups: prevalent chronic HBV patients with known chronic HDV, prevalent chronic HBV patients untested for HDV, and incident patients. This approach may not be comprehensive. Repeat testing in prevalent patients who were previously anti-HDV negative or those who were anti-HDV positive and had not received HDV RNA testing was not considered. Further, the submission assumed use only in prevalent patients who were currently engaged in care, with no increase in the proportion of prevalent patients engaged following the listing of bulevirtide. This may not be reasonable. With increased awareness of treatment options in chronic hepatitis following listing of bulevirtide, opportunistic testing may occur.

6.85 The estimated number of incident patients found to be anti-HDV positive (< 500 - < 500 per year) was noted to be higher than current HDV notifications (70–80 per year, which would also capture diagnoses in prevalent patients). This was due to an increase in anti-HDV testing following listing of HDV RNA testing and bulevirtide treatment. Underdiagnosis of HDV in Australia has been acknowledged in the literature,²¹ and an increase in notifications following listing may be reasonable.

Table 17: Number of patients eligible for treatment

		2024	2025	2026	2027	2028	2029
Use in the prevalent population							
A	No. prevalent chronic HBV patients (0.87% × Australian population projections 2023 age 0–100+)	■ ¹					
B	No. prevalent chronic HBV patients who are diagnosed prior to listing (A × 73.0%)	■ ²					
C	No. prevalent chronic HBV patients who are diagnosed and engaged in care prior to listing (B × 30.9%)	■ ³					
Prevalent population – with prior known chronic HDV diagnosis							
D	No. chronic HBV patients previously tested for anti-HDV (C × 35.0%)	■ ⁴					
E	No. chronic HBV patients found with anti-HDV+ (D × 4.06%)	■ ⁵					

²¹ Cosentino C, Clayton-Chubb D, Lubel JS. Management of hepatitis D in general practice. *Aust J Gen Pract*. 2023;52(8):536-9.

Public Summary Document – March 2024 PBAC Meeting

F	No. patients with HDV+ antibodies who received HDV RNA testing (E × 44.4%)	6					
G	No. previously found with detectable HDV RNA (F × 56.2%)	6					
H	No. eligible for bulevirtide treatment (G × 82.0%)	6					
Prevalent population - unknown chronic HDV diagnosis							
I	Proportion of prevalent chronic HBV patients tested for anti-HDV following bulevirtide listing	% ^a	% ^b	% ^c			
J	No. prevalent chronic HBV patients tested for anti-HDV following bulevirtide listing (C × I)	4	5	5			
K	No. chronic HBV patients with anti-HDV+ (J × 4.06%)	6	6	6			
L	Uptake of HDV RNA testing following listing	%	%	%			
M	No. prevalent chronic HBV patients with anti-HDV+ who received HDV RNA testing (K × L)	6	6	6			
N	No. with detectable HDV RNA (M × 56.2%)	6	6	6			
O	No. eligible for bulevirtide treatment (N × 82.0%)	6	6	6			
Use in the incident population							
P	No. incident chronic HBV patients diagnosed (0.02% × Australian population projections age 0–100+)	5	5	5	5	5	5
Q	No. incident chronic HBV patients engaged in care (P × 90.0%)	5	5	5	5	5	5
R	Proportion incident chronic HBV patients tested for anti-HDV following bulevirtide listing	%	%	%	%	%	%
S	No. incident chronic HBV patients tested for anti-HDV following bulevirtide listing (Q × R)	7	7	7	7	7	7
T	No. incident chronic HBV patients found with anti-HDV+ (S × 4.06%)	6	6	6	6	6	6
U	Uptake of HDV RNA testing following listing	%	%	%	%	%	%
V	No. incident chronic HBV patients with anti-HDV+ who received HDV RNA testing (T × U)	6	6	6	6	6	6
W	No. with detectable HDV RNA (V × 56.2%)	6	6	6	6	6	6
X	No. eligible for bulevirtide treatment (W × 82.0%)	6	6	6	6	6	6
Y	Total eligible for bulevirtide treatment (H + O + X)	6	6	6	6	6	6

Source: Table 4.2–1, pp188–9, Table 4.2–2, pp189–190 of the submission.

HBV = hepatitis B virus, HDV = hepatitis D virus.

^a Prevalent patients who haven't previously been tested for HDV (65.0%) × the proportion of prevalent patients expected to uptake testing in Year 1 (65.0%)

^b Prevalent patients who haven't previously been tested for HDV (65.0%) × the proportion of prevalent patients expected to uptake testing in Year 2 (65.0%)

^c Prevalent patients who haven't previously been tested for HDV (65.0%) × the proportion of prevalent patients expected to uptake testing in Year 3 (65.0%)

The redacted values correspond to the following ranges:

¹ 200,000 to < 300,000

² 100,000 to < 200,000

³ 50,000 to < 60,000

⁴ 10,000 to < 20,000

⁵ 5,000 to < 10,000

⁶ < 500

⁷ 500 to < 5,000

- 6.86 The total cost to the PBS/RPBS of listing bulevirtide was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$80 million to < \$90 million in the first 6 years of listing (Table 18).

Table 18: Estimated net cost of bulevirtide to the PBS

	2024	2025	2026	2027	2028	2029
No. eligible for bulevirtide (Row Y, Table 17)	1	1	1	1	1	1
Uptake of bulevirtide	%	%	%	%	%	%
No. patients initiating bulevirtide	1	1	1	1	1	1
Patient-years on treatment, by year of treatment:						
First year (93.8%)	1	1	1	1	1	1
Second year (83.0%)		1	1	1	1	1
Third year (60.3%)			1	1	1	1
Fourth year (54.9%)				1	1	1
Fifth year (50.0%)					1	1
Sixth year (45.7%)						1
Total patient-years on treatment	1	1	1	1	1	1
No. scripts (5.48 per patient-year on treatment)	2	2	2	2	2	2
Cost to the PBS (\$ per script)	3	4	4	4	4	4
Patient copayments (\$22.96 per script)	3	3	3	3	3	3
Cost to the PBS, less patient copayments	3	4	4	4	4	4

Source: Table 4.2–3, pp190–1, Table 4.2–4, p191 and Table 4.2–8, p195 of the submission.

HBV = hepatitis B virus, HDV = hepatitis D virus.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

- 6.87 The cost to the PBS may be an underestimate given concerns noted regarding the size of the population eligible for treatment. Further, the submission estimated an increase in uptake of anti-HDV testing following listing of HDV RNA testing and bulevirtide treatment. While the evaluation considered this was reasonable, estimates of uptake to HDV RNA testing and then bulevirtide were subsequently applied which may underestimate use if the increase in anti-HDV testing was for the purpose of HDV RNA testing and then access to bulevirtide treatment.
- 6.88 The effect of differences between treatment continuation assumptions and stopping criteria on the financial impact is uncertain. While some responders may cease treatment after experiencing undetectable RNA or normal ALT levels, there is evidence to suggest that this effect may not be sustained after treatment cessation (and so they may become subsequently eligible). In those patients who do not respond, it is unclear when in practice clinicians would cease treatment.

- 6.89 While the submission has proposed a grandfathering listing, grandfathered patients have not been included in the financial estimates. The submission considered that these patients (currently $n = 3$) would be assumed as part of the epidemiological estimates. This was reasonable.
- 6.90 The financial estimates were most sensitive to changes in the proportion of patients expected to be anti-HDV positive or HDV RNA positive, the proportion of patients eligible for bulevirtide treatment and the expected uptake of HDV RNA testing and bulevirtide. Concerns were noted regarding the proportion of patients considered eligible for bulevirtide treatment and uptake estimates applied for HDV RNA testing and bulevirtide treatment (given that an increase in anti-HDV testing was also assumed, and drivers for the increase in uptake may be for access to HDV RNA testing and bulevirtide treatment).
- 6.91 The DUSC considered the utilisation of bulevirtide was likely overestimated. In addition to the views raised in Table 16, the DUSC considered it was likely the availability of an effective treatment for CHD would increase testing rates in practice, but that not all patients who had testing for anti-HDV antibodies would be eligible for HDV RNA testing. The DUSC also considered the limited number of testing centres may further limit the use of HDV RNA quantification testing. In addition to issues with testing, the DUSC considered some of the inputs were uncertain or inappropriate (Table 16), the uptake of bulevirtide in the requested population was also highly uncertain due to its administration requirements. The DUSC considered that additional sensitivity analyses may be informative. DUSC considered the issues with the utilisation and financial estimates model were complex.

Quality use of medicines

- 6.92 The submission presented “EU Risk Management Plan for Hepcludex® (Bulevirtide)”, which will form the basis for the Australian Risk Management Plan (RMP). The EU RMP includes:
- Pharmacovigilance plan. Adverse reaction information is collected continuously and regularly analysed including PSUR assessment. One registry study (GS-US-589-6206) and two clinical studies (MYR301 and MYR204) for bulevirtide are included to provide AE information.
 - Risk minimisation measures. The routine risk minimisation measure for bulevirtide comprise of the Summary of Product Characteristics (SmPC), the package leaflet, and the legal status of the product.
- 6.93 The DUSC considered the treatment modality of bulevirtide presents a number of barriers for people living with CHD, including the requirement for daily injection, and specific reconstitution and refrigeration requirements. The DUSC also considered the demographics of CHD in Australia likely includes a significant number of people from disadvantaged backgrounds with poorer access to health care in health education,

increasing the risks of compliance issues and missed or unviable dosing which could lead to hepatic flares.

Financial management – risk sharing arrangements

- 6.94 The submission stated that a risk sharing arrangement was not proposed due to the small number of patients expected to be commencing treatment with bulevirtide (<500 annually) and all eligible patients will be confirmed by HDV RNA PCR test. It was noted that a large proportion of people living with diagnosed chronic HBV are currently not engaged in care (and so are not assumed to receive testing for HDV). The impact to the MBS and PBS may be higher than expected if there is substantial use (due to opportunistic testing) in these patients.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of bulevirtide for the treatment of chronic hepatitis D (CHD) infection. The PBAC considered the available evidence indicates that bulevirtide, for some patients, is effective in terms of reducing or achieving an undetectable viral load and/or normalising some liver enzyme parameters (such as alanine transaminase (ALT)). However, the PBAC considered the magnitude of long-term benefits in terms of clinical and patient-relevant benefits could not be reliably quantified, which led to major uncertainties with the economic evaluation. The PBAC also considered that the economic model presented likely did not reflect how bulevirtide is used in Australian clinical practice as testing, treatment persistence, and clinical decisions around treatment discontinuation were uncertain. The PBAC considered that the ICER was likely underestimated and bulevirtide was not considered cost effective at the requested price. The PBAC considered the utilisation and financial estimates to be uncertain.
- 7.2 The PBAC advised the key reason for not recommending the listing was the economic evaluation.
- 7.3 The PBAC noted bulevirtide was designated by the TGA for priority review, however that at time of consideration, the TGA Delegate's Overview was not available.
- 7.4 The PBAC noted the input from health care professionals and consumer organisations supported the listing of bulevirtide and highlighted the long-term impacts of CHD infection. Consumers noted that patients with CHD had limited treatment options and the PBAC acknowledged there was 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.
- 7.5 The PBAC considered 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. The Committee noted the PSCR clarified that the requested listing was to be limited to patients with no or well-compensated liver disease (i.e.

Child Pugh Class A) which was consistent with the population included in the clinical trial. The PBAC also considered that it would be appropriate for the listing to be silent on age, rather than specifying patients must be over 18 years. The PBAC agreed with the ESC 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.

- 7.6 The PBAC noted that no separate continuation criteria or explicit stopping rule was proposed for the listing. The PBAC considered the decision to continue or cease treatment, based on response, was a matter of clinical judgement, and considered an explicit stopping rule was not appropriate because of the risk of viral breakthrough should treatment be ceased. The PBAC noted the advice from the Secretariat and input from the Sponsor through the PSCR and pre-PBAC response, and considered the proposed restriction should be revised to ensure patients who achieve an undetectable viral load and/or ALT normalisation were not inappropriately excluded from accessing ongoing treatment. The Committee noted the issue raised in terms of continuing treatment also applied to the current restrictions for CHB and requested the Department review the relevant restrictions to ensure the intended continuing use is clear (paragraph 3.5).
- 7.7 The PBAC agreed with the ESCs that the way bulevirtide would be used in practice was somewhat uncertain. The Committee noted PEG-IFN- α was not widely used in practice in Australia for CHD, however considered it was unclear whether, in the presence of an additional viral suppressive agent such as bulevirtide, combined use of these agents may occur in practice with an objective to attempt viral clearance of HDV. The PBAC agreed with the ESCs that it would not be appropriate to require use of PEG-INF prior to bulevirtide given PEG-INF is not commonly used in Australian practice.
- 7.8 The PBAC considered the nominated comparator of symptomatic management of CHD (also referred to as BSC) was reasonable.
- 7.9 The PBAC noted the PBS component of the submission was supported a single Phase 3, open label trial (MYR301) comparing the effectiveness and safety of two dose regimens of bulevirtide (2 mg daily and 10 mg daily) and a delayed treatment group (BSC for 48 weeks followed by bulevirtide treatment) over 144. The PBAC noted the submission requested PBS listing of the 2 mg dose only as TGA registration is being sought for this dose only and both dose options showed comparable effectiveness. The PBAC considered 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. However, the Committee agreed with the ESCs that there were substantial uncertainties with the approach used to translate these surrogate measures to target clinical outcomes (as discussed in paragraphs 6.34-6.38), and that given viral suppression requires ongoing treatment with bulevirtide, assumptions around duration of treatment would impact on long-term outcomes.

- 7.10 The PBAC noted the results of the MYR301 trial found that at the primary endpoint of 48 weeks, 22/49 of patients (44.9%) had achieved a combined response (virologic response and ALT normalisation) in the bulevirtide arm versus 1/51 (2.0%) in the delayed treatment arm, with the proportion of responders in the bulevirtide arm increasing to 27/41 (55.1%) at the exploratory timepoint of 96 weeks. The PBAC also noted that statistically significant differences were demonstrated at 48 weeks with virologic response observed in 36 patients (73.5%) in the bulevirtide arm and 2 (3.9%) in the delayed treatment arm and ALT normalisation in 25 patients (51.0%) in the bulevirtide arm and 6 (11.8%) in the delayed treatment arm. In addition, in the bulevirtide arm, 6 patients at week 48 had achieved undetectable HDV RNA levels (increasing to 10 patients at week 96). The PBAC considered 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 as noted above, the translation of these surrogate outcomes to clinical and patient-relevant benefits, especially over the longer term, is highly uncertain and presents significant uncertainty for assessing the cost effectiveness of bulevirtide in the economic model presented.
- 7.11 The PBAC noted the submission described bulevirtide as having a manageable safety profile compared to BSC. The Committee considered that whilst there was limited data on the safety of bulevirtide arising from the small size of the trial and limited follow-up period (especially given bulevirtide may be used for long periods), the available data did not suggest major differences in rates of treatment-emergent adverse events (TEAEs) between bulevirtide and BSC/delayed treatment out to week 48 and therefore, the claim may be adequately supported, with the caveat that longer-term safety data would be informative to further support this claim.
- 7.12 The PBAC agreed with the ESC that the economic model was unreliable for decision-making. The PBAC noted that the benefits of viral suppression in the economic evaluation were modelled based on extrapolation of sustained viral immune clearance (either spontaneous or associated with interferon treatment). The PBAC 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 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 6.35). 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. 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 (i.e. patients with little or no hepatic impairment at baseline), the time horizon (58 years), and the source used to model the natural history of chronic HDV. Further, the likely role of testing 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.

- 7.13 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 noted more conservative inputs such as a definition of response that was more consistent with the surrogate to final transformation, removal of utility gains in responders, a shorter time horizon, alternative sources for transition probabilities had a substantial cumulative impact on the ICER, resulting in an ICER that was very high. Therefore, the PBAC considered the listing of bulevirtide was not cost effective at the requested price.
- 7.14 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. The PBAC also considered a reduction in the price of bulevirtide would be required, given that more conservative model inputs would substantially increase the ICER. 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.
- 7.15 The PBAC considered that there are relatively reliable sources for estimating the prevalence of CHB, HDV and CHD and considered that the most recent Australian sources should be used for these inputs. The PBAC noted that as CHD is relatively rare there are likely to be less than 100 incident patients per year eligible for treatment with bulevirtide. However, the PBAC considered the likely uptake of both testing and treatment, and utilisation and duration of therapy with bulevirtide, to be highly uncertain in practice. The PBAC noted that in the proposed PBS population for bulevirtide (patients with no or well-compensated cirrhosis), most patients would likely have no or limited symptoms of hepatic disease. Therefore the Committee considered, given the onerous administration requirements of daily and ongoing injections, treatment uptake and persistence is uncertain. Furthermore, the Committee noted and agreed with the DUSC that the use of HDV RNA quantification testing to determine eligibility may have been overestimated, and that some inputs such as the proportion of CHB patients engaged in care, anti-HDV antibody testing rates and proportion eligible for bulevirtide were uncertain. The PBAC noted the

pre-PBAC response disagreed with the DUSC regarding numerous inputs to the utilisation estimates; however considered that overall there were substantial uncertainties with the way HDV is tested for and managed in practice that may also change with the availability of a treatment option where few or no options exist.

7.16 The PBAC noted the submission claimed that the 'Rule of Rescue' would apply to bulevirtide. The PBAC considered that the "Rule of Rescue" criteria were not met for bulevirtide for the following reasons:

1. No nonpharmacological or pharmacological interventions for these patients: The PBAC considered that while there is no TGA registered medicine or identified alternative approved therapy for the treatment of CHD in Australia, PEG-IFN- α is used to a limited extent.
2. The medical condition is severe, progressive, and expected to lead to premature death: The PBAC acknowledged CHD is progressive and is associated with substantially increased mortality compared with CHB infection alone; however, the Committee also noted the requested patient population was in early stage of disease, and the estimated 5-year survival probability in Child-Pugh Class A patients was 90% for anti-HDV positive/HbeAg negative patients.
3. The medical condition applies to only a very small number of patients: The PBAC noted bulevirtide has been granted orphan drug status by the TGA and that the incidence of HDV infection in Australia is relatively low; however the Committee also considered there is a prevalent pool of patients that is likely not insignificant, and the availability of a treatment option for CHD may increase testing and identify additional patients.
4. The medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition: The PBAC acknowledged the trial data for bulevirtide showed relevant and important improvements in surrogate outcomes in the target population; however, the PBAC considered the magnitude of benefit in terms of patient-relevant and clinically important outcomes, especially over the longer term, was uncertain.

7.17 The PBAC considered a resubmission for bulevirtide should address the following issues:

- 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.
- A revised economic model with inputs that are more conservative (see scenarios in Table 14) and better aligned with the approach used to model the surrogate to final clinical outcomes. The PBAC also considered, given the implausible gain in survival for bulevirtide in the model, that adjustments should ensure that the model results in more plausible effects on liver-related outcomes and survival gains.

- 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 as noted in Table 16. In addition, the PBAC considered additional sensitivity analyses to allow a more thorough investigation of the impact of different scenarios in terms of testing and treatment uptake would be informative.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

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

The sponsor had no comment.