

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1708 – Hepatitis Delta Virus (HDV) RNA PCR testing to determine eligibility for PBS-subsidised bulevirtide (HEPCLUDEX) for treatment of HDV

Applicant: Gilead Sciences Pty Limited

Date of MSAC consideration: 4-5 April 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of the application

The integrated codependent application requested:

- Medicare Benefits Schedule (MBS) listing of ribonucleic acid (RNA) polymerase chain reaction (PCR) testing to detect the presence of hepatitis D virus (HDV) ribonucleic acid (RNA) to determine eligibility for treatment with bulevirtide in patients with chronic HDV (CHD) with compensated liver disease;
- MBS listing of HDV RNA PCR testing to quantify the levels of HDV RNA for monitoring the efficacy of bulevirtide treatment; and
- Pharmaceutical Benefits Scheme (PBS) Section 100, Authority Required - Streamlined listing of bulevirtide for the treatment of CHD in patients with compensated liver disease and detectable HDV RNA.

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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Primary endpoint, composite endpoint at Week 48 of: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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 of 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. MSAC's advice to the Minister

After considering the strength of the evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding for Hepatitis Delta Virus (HDV) ribonucleic acid (RNA) polymerase chain reaction (PCR) testing to determine eligibility for PBS-subsidised bulevirtide (HEPCLUDEX) for treatment of HDV. The Pharmaceutical Benefits Advisory Committee (PBAC) had not supported public funding of the co-dependent treatment bulevirtide, from which the clinical utility of this testing was derived. The claim of co-dependency was not well established due to limited evidence that quantitative HDV RNA PCR testing would lead to a change in management. The evidence for comparative effectiveness of the test was at high risk of bias in all domains. There were numerous and important uncertainties associated with the economic model because it did not take into account false positive and false negative test results, and the pattern of use of testing and retesting. There were also uncertainties regarding the duration of treatment and therefore the duration and timing of associated testing. These uncertainties also affected the financial implications of the test.

Consumer summary

This was an application from Gilead Sciences requesting Medicare Benefits Schedule (MBS) listing of a test to detect the hepatitis D virus in patients. The test is also known as a HDV RNA PCR test, where HDV refers to the hepatitis D virus, RNA refers to ribonucleic acid which is a genetic material found in all living cells and PCR refers to polymerase chain reaction which is a testing method used to rapidly make copies of genetic material and amplify it to a large enough amount to study in detail. The test is a genetic test that can identify whether someone has a hepatitis D infection and can also measure the amount of virus present in the infected person. The test works by measuring how much genetic material (RNA) from the hepatitis virus there is in a sample from the patient using the PCR testing method.

The test results would be used to diagnose active hepatitis D infection and so provide access to a treatment called bulevirtide, and to monitor how well bulevirtide was helping the patient fight their hepatitis D. This was a codependent application, with MSAC considering the testing and the Pharmaceutical Benefits Advisory Committee (PBAC) considering the medicine.

Hepatitis D is an infection of the liver. It can result in cirrhosis (scarring) and liver cancer. Some people may develop end-stage liver disease and liver failure. There is currently no treatment available specifically for hepatitis D.

The hepatitis D virus only infects people who are already infected with the hepatitis B virus. Hepatitis B and D are relatively rare in Australia because there is an effective hepatitis B vaccine available. However, hepatitis B and D are more common in people born overseas, people from culturally and linguistically diverse communities, people who inject drugs, and in men who have sex with men.

Bulevirtide is a medication that works by preventing the hepatitis D virus from entering liver (hepatic) cells. This application proposed testing people who may have hepatitis D, and if they test positive, they can start bulevirtide treatment. Once on treatment, they would continue to have their levels of HDV RNA monitored to see how well the treatment is working.

The PBAC did not support funding bulevirtide on the Pharmaceutical Benefits Scheme (PBS). The PBAC considered that it was not clear if the strength of benefit for patients treated with bulevirtide in the long term could be reliably measured – that is, it was not clear how much the drug decreased the chances of progression to cirrhosis, liver cancer or death. The PBAC also did not consider the drug to be good value for money.

MSAC considered that since the PBAC did not support listing bulevirtide on the PBS (the medicine that would be initiated if hepatitis D were detected), there was not enough justification to fund the testing. In addition, MSAC was not certain how the results of testing would be used to manage treatment as there was little evidence to show that the levels of virus in patients (as detected by the test) would lead to changes in clinical management. There were also problems with the economic evaluation, meaning that MSAC was not certain that the test was good value for money. MSAC also considered that the cost to the MBS was overestimated, as there were errors in calculating the number of people who would need the tests.

MSAC recognised that some people suspected of having hepatitis D may want to know with more certainty whether they have it, even if there was no treatment available. MSAC noted there are existing MBS items available for hepatitis D testing. However, because the existing items are tests for viral antibodies, they are only able to identify whether someone has ever been exposed to the hepatitis D virus. It cannot confirm that a person has active disease, which is what the RNA test was proposed to do.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support listing HDV RNA testing on the MBS for diagnosis of active hepatitis D infection, for access to bulevirtide and to monitor treatment progress. MSAC considered that

there was insufficient clinical justification for the RNA test since the PBAC did not support listing of bulevirtide. In addition, MSAC did not consider the case for codependency had been well established, and it was unclear how HDV RNA levels would affect decisions about treatment.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Gilead Sciences was for Medicare Benefits Schedule (MBS) listing of ribonucleic acid (RNA) polymerase chain reaction (PCR) testing to detect hepatitis delta virus (HDV) RNA to determine eligibility for treatment with bulevirtide in patients with chronic HDV with compensated liver disease, and to quantify the levels of HDV RNA for monitoring the efficacy of bulevirtide treatment. This was a codependent application with the Pharmaceutical Benefits Advisory Committee (PBAC).

MSAC noted that HDV is a satellite RNA virus that requires hepatitis B virus (HBV) surface antigen (HBsAg) for entry into hepatocytes and for propagation. Oral nucleotide or nucleoside drugs used for HBV, and pegylated interferon (IFN), are not effective for HDV. Bulevirtide works by inhibiting the entry of HBV and HDV into hepatocytes by binding to and inactivating the sodium taurocholate cotransporting polypeptide (NTCP).

MSAC considered that the true incidence and prevalence of HDV in Australia were uncertain because there are no population-based data. MSAC noted the prevalence of HDV is likely to be low in Australia due to high rates of vaccination against HBV, but prevalence is likely to be much higher in the following populations: people born overseas, people from culturally and linguistically diverse backgrounds, people who inject drugs, and/or in men who have sex with men. HDV/HBV co-infection is associated with significantly higher risk of progression to cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and death than HBV infection alone. Persistent, severe HDV viremia is the most important risk factor for disease progression. There is currently no approved treatment in Australia for hepatitis D.

MSAC noted that the PBAC had not supported listing bulevirtide on the Pharmaceutical Benefits Scheme (PBS) due to uncertainties about the longer-term and patient-relevant benefits, the economic analysis and incremental cost-effectiveness ratio (ICER), and how bulevirtide was likely to be used in clinical practice. The PBAC considered that bulevirtide would not be cost-effective at the proposed price, and that a revised economic model and re-evaluation would be required.

MSAC noted that Hepatitis D serology testing should only be undertaken in people who are HBsAg-positive and that anti-HDV antibodies are the hallmark of exposure to HDV (present in all immunocompetent patients with the infection). MSAC noted that standard practice is if anti-HDV antibodies are detected, the patient should be tested for serum HDV RNA to determine whether an active infection is present – however there is currently no international standard for threshold levels of anti-HDV antibodies that are indicative of HDV exposure. There is also a lack of uniform international recommendations for screening for HDV infection in people with HBV.

MSAC noted that in most patients, serum HBV DNA is undetectable or at the borderline of detectability because of the repression of HBV viremia induced by HDV through interferon-dependent and interferon-independent mechanisms. However, HBsAg-positive persons with anti-HDV antibodies who do not have HDV RNA detectable in their serum may have had a previous HDV infection.

MSAC noted that the proposed test uses commercial or in-house reverse transcriptase (RT) polymerase chain reaction (PCR) assays. MSAC noted that HDV RNA levels are often very low and can be difficult to detect, although the sensitivity of available tests is improving. A 2016 international quality-control study showed a high variation in the detection and quantification of HDV RNA among assays, with consistent underestimations of the viral load. In addition, the optimal end point for therapy is loss of detectable HBsAg, but this is rare with treatments such as

IFN. In addition, long-term relapses are common due to high infectivity of residual, undetectable HDV in patients with persistent HBsAg.

MSAC considered that there is likely to be an unmet need for the detection and treatment of patients with CHD as the 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). MSAC noted that the 5-year mortality from HDV/HBV superinfection is twice that of HBV mono-infection. MSAC therefore considered this testing may potentially have prognostic value independent of its use for access to bulevirtide, although this had not been claimed.

MSAC considered that there may be merit in having two different items for testing: one for determining eligibility for treatment requestable by specialist or consultant physicians, and one for monitoring of response to treatment with no restriction on requestors. MSAC considered that this split would provide patients with the option of having follow up testing for monitoring of response to treatment undertaken by their GP under a shared care model, which is especially relevant for those living outside metropolitan areas. MSAC considered the proposed fee and the test not being pathologist-determinable appeared appropriate. MSAC also considered that the MBS descriptor would appropriately specify the exclusion of patients with decompensated liver disease (Child Pugh B or C), as eligibility for treatment with bulevirtide is not being sought for these patient groups. MSAC considered that there would be no need for a practice note to provide clinical guidance on determination of Hepatitis D chronicity as it is very unlikely in practice that cases of acute infection would be detected by an HDV RNA test. MSAC noted that ESC had recommended futureproofing the item descriptor by amending it to refer to PBS-listed chronic hepatitis D treatments in general rather than bulevirtide specifically. However, MSAC considered that because bulevirtide had not been approved by PBAC and there were presently no other equivalent medications under consideration, there was no current need to amend the descriptor to refer to PBS-listed chronic hepatitis D treatments in general.

MSAC noted that the European Association for the Study of the Liver (EASL) guidelines supported the use of quantitative testing but do not provide any guidance as to how the levels would change management and only recommend maintaining treatment until clinical benefit is observed (which is not dependent on the level of HDV RNA). MSAC therefore considered it may be reasonable to consider substituting qualitative testing for quantitative testing for eligibility as well as for monitoring (particularly in light of the limited evidence on the change in management due to the results of quantitative HDV RNA PCR testing as discussed below).

MSAC noted consumer feedback supported the application, and cited the value of knowing benefits of testing. MSAC considered that there are tests already available on the MBS that could be used to identify patients with HDV, but acknowledged that these are likely to be serology-based tests (testing if a person has ever been exposed to HDV), rather than RNA-based (indicative of active HDV infection).

In the key clinical trial used in the applicant-developed assessment report (ADAR), MYR301, a decrease of 2 log¹⁰ international units [IU]/mL in the HDV RNA level from the original viremic titre was used as a surrogate marker of potential benefit. However, evidence was required that a decrease in HDV RNA levels of at least this magnitude correlated with improvements in clinical end points such as progression to cirrhosis, HCC and death. MSAC considered this important, and this was not confirmed in the key trial. MSAC also noted that a threshold had not yet been defined for a serum HDV RNA level (other than undetectable HDV RNA) that corresponded to a clinical benefit.

MSAC noted that the test used in MYR301 was Robogene HDV RNA PCR, with a lower limit of detection (LLOD) of 6 IU/mL. Compared to patients in the control group, the treatment group patients had significantly higher rates of undetectable or at least a 2 log¹⁰ decrease in HDV RNA and normalisation of alanine transaminase (ALT). However, MSAC considered that longer-term data were needed to demonstrate clinical benefit.

MSAC noted the PICO and the proposed clinical management algorithm but considered that there were no continuation or discontinuation criteria for treatment outlined in the application or included in the algorithm. As a result, there was uncertainty in duration of treatment and the number of monitoring tests required per treated patient. MSAC disagreed with the pre-MSAC response, which stated that continuation and discontinuation criteria were unnecessary. MSAC noted the EASL guidelines suggest criteria for continuation or discontinuation of treatment (for example, consider discontinuation if undetectable HDV RNA and biochemical response beyond one year) and retesting recommendations (that is, at time of stopping, and at 1, 3, 6, 12 months and yearly thereafter to monitor for relapse). MSAC also noted the reference to detection and not quantification. MSAC noted the Product Information states “consideration to discontinue treatment should be given in case of sustained (six months) HBsAg seroconversion”. The guidelines also state that further studies with standardised assays are required to define the prognostic role of quantitative HDV RNA monitoring in untreated patients, noting that HDV RNA serum levels may fluctuate over time, becoming temporarily undetectable.

The proposed intervention in the application was an in-house assay (notably not the Robogene test as used in the MYR301 trial), which is the only assay currently available in Australia and is currently offered by one laboratory (the Victorian Infectious Diseases Reference Laboratory [VIDRL]), **redacted** MSAC noted the commentary raised the risk of false negative results due to suboptimal assays and/or a higher lower limit of detection (LLoD) with in-house assays compared to the LLoD of the Robogene assay used in the MYR301 trial. However, MSAC considered this may not be a clinically important difference in the future **redacted**.

MSAC noted that the linked evidence for clinical effectiveness (test accuracy and performance, prognostic evidence and change in patient management) was considered to be at high risk of bias in all domains and its generalisability was uncertain as no Australian studies were included. There was no evidence presented for clinical utility or treatment effect variation.

MSAC noted that the presence of HDV RNA as detected by PCR was inconsistently associated with poorer health outcomes (three out of five studies reported a statistically significant association). The prognostic evidence using the baseline presence or absence of HDV RNA was severely confounded by treatment variability. In addition, the presence of HDV RNA in patients with anti-HDV antibodies was not significantly associated with any liver-related outcomes, HCC or hepatic decompensation, but was reported in a single study to be significantly associated with risk of death or liver transplantation ($k = 1$, hazard ratio [HR] = 7.40, 95% CI 1.74, 31.47). However, MSAC noted that the response to treatments (other than bulevirtide) as determined by HDV RNA loss (undetectable HDV RNA or a $\geq 2 \log^{10}$ drop) was significantly associated with favourable clinical outcomes, and that the persistence of HDV RNA was associated with an increased hazard of any liver-related event. One study reported larger effect sizes by comparing health outcomes in patients who had maintained virologic response (no detectable HDV RNA for two years after completion of treatment) against those with detectable HDV RNA. This indicates that maintained response to treatment was more favourable in terms of health outcomes, than a single measurement of HDV RNA suggesting response to treatment.

MSAC agreed with ESC that codependency between testing and bulevirtide use had not been sufficiently established. As mentioned, the continuation and discontinuation criteria for bulevirtide were not included in the submission, and there were inconsistencies between the clinical criteria, the Product Information and the key trial MYR301. MSAC considered it was unknown whether the level of HDV RNA (other than the presence of HDV RNA) would be used to alter patient management in non-responders or partial responders. MSAC noted that the duration of the chronicity of detectable HDV RNA that would determine eligibility for bulevirtide had not been defined. MSAC considered that a duration of detectable HDV RNA of at least 6 months would be reasonable because only patients with chronic HDV infection required treatment, although detection of acute infection was unlikely. MSAC considered that this testing also has potential prognostic value from the detection of active infection.

MSAC noted that the ADAR did not explore alternative scenarios of test and treatment provision. The pre-MSAC response stated that alternative treatment pathways were out of scope, which MSAC did not agree with. MSAC considered that there may be benefits of testing independent of treatment, given the prognostic information that HDV RNA testing may provide. MSAC noted that public consultation supported this approach at the PICO confirmation stage, yet the ADAR had not subsequently addressed it.

MSAC noted that the economic evaluation was a cost-utility analysis comparing bulevirtide treatment to best supportive care (BSC) in patients with RNA-positive chronic HDV based on virologic response rates (defined as undetectable HDV RNA or a decrease in HDV RNA by $\geq 2 \log^{10}$ IU/mL from baseline) as reported in the MYR301 trial. MSAC noted that since patients entered the model at the point of treatment, the cost of testing to find one patient eligible for treatment was applied at model entry. MSAC considered that this was not its preferred approach as described in the MSAC Guidelines for submissions of codependent technologies, because it omits consideration of the impact of false results. MSAC considered that the impact of a false positive result could be significant because these patients may appear to (falsely) respond to bulevirtide treatment and depending on the continuation criteria for treatment, may receive ongoing treatment for no benefit. In addition, MSAC considered that false positive results may have differing and uncertain impacts depending on whether the test is used to determine eligibility for starting treatment or to monitor treatment.

MSAC noted that six-monthly monitoring with HDV RNA testing while on bulevirtide treatment was included in the economic modelling and was consistent with the proposed MBS item descriptor. However, the only change in management from the inclusion of HDV RNA monitoring that was modelled was to cease treatment in non-responders at week 96. As mentioned, MSAC noted that alternate scenarios of test and treatment provision were not explored in the submission. In addition, MSAC considered it likely that uptake and adherence to drug treatment had been overestimated by the ADAR, because drug administration is a daily injection for about 8 years. MSAC considered that the EASL guidelines' recommendations on retesting had additional implications for the projected utilisation of the test that had not been captured in the economic model (or the financial implications).

MSAC noted the base case incremental cost-effectiveness ratio (ICER) generated using a stepped approach was \$95,000 to < \$115,000 per quality-adjusted life year (QALY). MSAC considered this was high, and also highly uncertain for the reasons already discussed (it did not take false positive and false negative test results into account, and there was uncertainty around the pattern of testing and retesting and the average duration of treatment which further contributed to the uncertainty around number of tests used).

MSAC noted that the estimated base case budget impact was \$0 to < \$10 million in year 1, increasing to about \$0 to < \$10 million in years 2 and 3 and then decreasing to \$0 to < \$10 million in year 6, with the increase accounting for the testing of existing infections. However, MSAC noted errors with how the extent of use of HDV RNA testing was calculated, which it considered had resulted in an overestimation of the extent of use of HDV RNA testing:

- When HDV RNA testing was used to determine eligibility for bulevirtide treatment, the ADAR assumed that all patients who had serology testing for anti-HDV would also be eligible for HDV RNA testing. However, MSAC considered this assumption was incorrect and patients must have positive anti-HDV serology to be eligible for the HDV RNA test, therefore the use of HDV RNA testing had been overestimated.
- To estimate the number of HDV RNA tests performed for monitoring purposes, the ADAR erroneously multiplied the average proportion of patients who remain on treatment by the number of patients who receive HDV RNA testing to determine eligibility for bulevirtide treatment each year. However, a proportion of patients tested for HDV RNA will not be eligible for bulevirtide treatment and, therefore, will not need to be monitored.

MSAC noted the pre-MSAC response acknowledged these errors.

The commentary conducted sensitivity analyses, and MSAC noted that the budget impact was most sensitive to changes in the proportion of patients expected to be anti-HDV positive or HDV RNA positive, and the proportion of patients eligible and who uptake bulevirtide treatment and the expected uptake of HDV RNA testing.

MSAC noted the commentary's concerns regarding the proportion of patients considered eligible for bulevirtide treatment and therefore the uptake estimates applied for HDV RNA testing and bulevirtide treatment (given 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). MSAC noted the revised base case budget impacts were \$0 to < \$10 million in year 1 decreasing to \$0 to < \$10 million in year 6. However, there were also other considerations arising from the EASL guidelines, which resulted in MSAC considering the utilisation of the test may have been underestimated (after taking account of additional retesting requirements). Thus MSAC considered there was a considerable degree of uncertainty associated with the financial implications of the proposed test.

MSAC noted that an external quality assurance program (QAP) is required for in-house assays, particularly if they are adopted by laboratories other than VIDRL, because of technical aspects of the HDV RNA assay. However, as noted, only VIDRL is currently offering the assay in Australia. MSAC also noted that there is high genetic variability among genotypes, which can lead to underestimating the viral load. This can sometimes be by as much as $>2 \log^{10}$, which is a clinically important difference.

MSAC was not supportive of the application and identified the following deficiencies:

- The submission and the international guidelines were unclear as to how quantitative HDV RNA levels changes clinical decision making.
- The evidence submitted was at high risk of bias in all domains (particularly selection bias) and its generalisability was uncertain as no Australian studies were included.
- The economic model structure excluded consideration of false positive and false negative results for HDV RNA PCR testing for eligibility, as patients entered at treatment. The impact of a false positive result could be significant because these patients may appear to (falsely) respond to bulevirtide treatment and depending on the continuation criteria for treatment, may receive ongoing treatment for no benefit.
- The likely pattern of use of HDV RNA PCR testing and re-testing was uncertain and should have been more fully explored in the economic model. The uncertainty in the average duration of bulevirtide treatment also translated to uncertainty in the number of monitoring tests per treated patient. These considerations affected the certainty of both the economic and financial modelling.
- The proposed codependency was not well established and as the PBAC had not supported PBS listing of bulevirtide, MSAC considered that without the drug being publicly funded, there was insufficient clinical justification to fund the test.

MSAC considered that a resubmission would need to:

- Consider whether there was merit in proposing qualitative rather than quantitative testing, given lack of evidence that the levels of HDV RNA inform decision making.
- Identify continuation and discontinuation criteria, to provide more certainty around the likely duration of treatment and the number of tests required for monitoring treatment.
- Provide additional clarity around the likely pattern of testing and re-testing as per the EASL guidelines to better inform the economic evaluation.
- Identify and include any further new evidence given the high risk of bias in the submitted evidence.
- Provide updated economic evaluation and financial assessments that address MSAC's advice.

MSAC considered that there may also be a case for exploring the prognostic value of testing given the evidence of a worse outcome in those with HDV RNA viraemia, and considering testing independent of bulevirtide treatment.

4. Background

Applicant Developed Assessment Report (ADAR) 1708 was the first submission for HDV RNA PCR testing and treatment with bulevirtide.

5. Prerequisites to implementation of any funding advice

The Therapeutic Goods Administration (TGA) Priority Review of bulevirtide was lodged on 15 March 2023, and Australian Register of Therapeutic Goods (ARTG) registration is expected by February 2024 (Table 2).

Table 2 Anticipated timelines for TGA application for bulevirtide

| Regulatory milestone | Date scheduled/expected |
|---------------------------------|------------------------------|
| Lodgement of TGA dossier | 15 March 2023 |
| Completion of evaluation phase | Expected 30th September 2023 |
| Delegate request for ACM advice | Expected 31st October 2023 |
| ACM meeting | 15-17 November 2023 |
| Delegate's decision | Expected 29 November 2023 |
| ARTG registration | Expected by February 2024 |

Source: Table 1.3-1 p24 of the submission

ACM = Advisory Committee on Medicines, ARTG = Australian Register of Therapeutic Goods, TGA = Therapeutic Goods Administration

In Australia, the only HDV RNA PCR test currently available is an in-house assay developed by the Victorian Infectious Disease Reference Laboratory (VIDRL), which is accredited by the National Association of Testing Authorities (NATA). The test is a Class 3 in-house in vitro diagnostic (IVD) and therefore does not need to be included in the ARTG¹, although Class 3 IVDs do require NATA accreditation and need to meet the National Pathology Accreditation Advisory Council (NPAAC) standard².

6. Proposal for public funding

The proposed new MBS listing (as per the ratified PICO confirmation) is shown in Table 3. The test proposed is an in vitro diagnostic test which measures the amount of HDV RNA present in the blood. If HDV RNA is detected, then the patient is considered to have a current Hepatitis D infection and may be eligible for bulevirtide (if other clinical criteria are also met). The test is also

¹ Therapeutic Goods Administration (2018). Regulatory requirements for in-house IVDs. Version 2.2. Australian Department of Health

² National Pathology Accreditation Advisory Council (2018). Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices (IVDs). Canberra, Australia, Department of Health, Commonwealth of Australia.

proposed for monitoring the effectiveness of treatment, however *no separate treatment continuation criteria were provided.*

Table 3 Newly proposed MBS item for testing HDV RNA

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|--|
| Category 6 – PATHOLOGY SERVICES Group P3 - Microbiology |
| MBS item *XXXX |
| Quantitation of Hepatitis D viral RNA load in plasma or serum in: |
| <ul style="list-style-type: none"> a) The pre-treatment evaluation for access to therapy for chronic HDV in patients who are Hepatitis D viral antibody positive and suspected of having chronic hepatitis D; or b) A patient undertaking viral therapy for chronic hepatitis D with bulevirtide for the purpose of assessing treatment effectiveness. |
| To a maximum of 2 tests in a 12 month period |
| Fee: \$152.10 Benefit: 75% \$114.10 85% = \$129.30 |

ESC had recommended futureproofing the item descriptor by amending it to refer to PBS-listed chronic hepatitis D treatments in general rather than bulevirtide specifically. However, MSAC considered that because bulevirtide had not been approved by PBAC and there were presently no other equivalent medications under consideration, there was no current need to amend the descriptor to refer to PBS-listed chronic hepatitis D treatments in general.

7. Population

There are two populations proposed for HDV RNA PCR testing:

1. Patients who are hepatitis B surface antigen (HBsAg) positive and anti-HDV antibody positive (where testing is performed to confirm the diagnosis of CHD infection status and assist in determining eligibility for bulevirtide); and
2. Patients undertaking antiviral therapy for CHD with bulevirtide to measure the clinical benefit of treatment.

These proposed populations are consistent with the ratified PICO confirmation.

Hepatitis D virus (HDV) is a ‘satellite virus’ that requires the Hepatitis B virus (HBV) envelope protein for it to enter hepatocytes to replicate. Patients with HBV can contract HDV as a superinfection, most of the which progress to chronic HDV which may then exacerbate any pre-existing HBV-related liver damage. Alternatively, HBV and HDV may be contracted together as a coinfection. Coinfections usually resolve within 6 months (during the acute phase), with only 5-10% of coinfections becoming chronic.

HDV causes hepatitis D, which is frequently severe, leading to cirrhosis (scarring on the liver). Patients with chronic Hepatitis B (CHB) have a higher risk of decompensating cirrhosis events (variceal bleeding, encephalopathy and ascites), hepatocellular carcinoma, and death if they have concomitant HDV rather than a HBV mono-infection. Knowledge of HDV infection is prognostic and can also alter the management of the patient. Management of HDV infection is proposed with the antiviral bulevirtide.

To be eligible for HDV RNA testing, the patient must first be confirmed to have CHB by being positive for HBsAg, and then suspected of having CHD due to being positive for anti-HDV antibodies. *In the application form, anti-HDV antibodies were further defined as “IgM or IgG to HDV”.* If patients are positive for anti-HDV antibodies then they may be tested for HDV RNA, and if they have detectable HDV RNA and elevated alanine transaminase (ALT), then they may access

bulevirtide. Currently, bulevirtide is the only treatment specific to CHD, so in the absence of bulevirtide, symptom management is the standard practice in Australia.

Patients are proposed to be eligible for bulevirtide upon HDV RNA being detected. The Commentary noted that it is, however, possible that some patients tested may still be in the acute phase of infection, rather than having CHD (this differs from the key trial MYR301, which required patients to have the infection for at least 6 months prior to treatment initiation). The Commentary noted that PASC advised that a single positive HDV RNA PCR result would be sufficient to confirm chronic active HDV as it is very rare to identify acute HDV infection in clinical practice. Although this may be the case in current practice, the Commentary noted that if bulevirtide becomes available, it is possible that testing for anti-HDV-antibodies will be performed more regularly, which could increase the likelihood of identifying HDV RNA when the infection is in an acute rather than chronic phase. No evidence is available on the effectiveness of bulevirtide in acute HDV infection. The clinical implications of treating acute infections are therefore unclear.

Hepatitis D is a notifiable disease in Australia. Notifications can be made on the basis of a patient being positive for anti-HDV antibodies or following the detection of HDV on liver biopsy³. Data from the National Notifiable Disease Surveillance System (NNDSS) report that the incidence of HDV is low, with only 70 cases being reported in 2022. This corresponds to an incidence of 0.29 per 100,000 population. However, as the NNDSS only records positive serology, it is likely that some (up to half) of these cases may not have chronic infection and will be PCR negative. HDV may also be underdiagnosed as it is not routinely tested for. HDV disproportionately affects people born overseas, from cultural and linguistically diverse communities, and injecting drug users, all of whom may experience barriers to healthcare.

8. Comparator

The comparator to HDV RNA PCR testing is no HDV RNA PCR testing. The proposed test is expected to be used in addition to current tests, such as anti-HDV antibody tests and ALT testing, rather than as a replacement.

The comparator to treatment with bulevirtide is proposed to be current standard of care, which is symptom management. Treatment for the concomitant hepatitis B is not expected to alter with the addition of bulevirtide for hepatitis D.

This is consistent with the ratified PICO confirmation.

The Commentary noted that a weekly dose of pegylated interferon alpha (PEG- IFN- α) is currently recommended by some international guidelines, particularly European, to treat HDV⁴. In Australia, PEG-IFN- α is registered with the TGA for the treatment of CHB, so patients with CHD may be able to access it. It is possible that the use of bulevirtide may have some impact on the use of PEG-IFN- α , so it could be considered an additional comparator.

9. Summary of public consultation input

Consultation input was welcomed from three (3) professional organisations, three (3) consumer organisations and one (1) individual, who was a medical professional.

³ Communicable diseases network Australia (2004). [Hepatitis D - Australian national notifiable diseases case definition](#). Australian Department of Health. Accessed 12th December 2023.

⁴ Yardeni D, Heller T, Koh C. Chronic hepatitis D-What is changing? J Viral Hepat. 2022 Feb 4.

The five (5) organisations that submitted input were:

- Australian Pathology (AP)
- Gastroenterological Society of Australia (GESA)
- Hepatitis SA
- Hepatitis Queensland (HQ)
- Public Pathology Australia (PPA)
- Hepatitis NSW

The consultation feedback received was mostly supportive of public funding for Application 1708.

Benefits

- Current testing (serology) is inadequate as it only detects exposure to the virus, and does not distinguish between current and past infection.
- HDV infection is largely under-diagnosed due to the prohibitive cost of PCR testing and public funding of the testing would promote correct testing processes, standardisation of HDV testing and higher rates of diagnosis.
- RNA PCR testing has increased accuracy in diagnosing HDV, including quantification of virus levels, and determining active and past infections.
- Testing will allow regular monitoring of disease progression, improve access to appropriate treatment and prompt response to treatment failure and avoidance of unnecessary investigations or interventions.
- The rates of HDV transmission would reduce with increased rates of diagnosis and greater awareness.
- Current treatment for HBV/HDV chronic infection is only effective in a small portion of patients, with severe side-effects and minimal long-term benefits.
- Bulevirtide is a targeted therapy with a higher rate of efficacy and tolerability. The proposed treatment has shown specific response as an anti-HDV treatment with visible decline in HDV RNA and minimal side effects.
- Increased equity of access, as HDV priority populations experience multiple socio-economic barriers to healthcare.

Disadvantages

- Inconvenience of daily sub-cutaneous injections of the medication.

Additional comments (including feedback from late targeted consultation)

- Hepatitis-D Testing should not be restricted to Hepatitis-B-positive patients by the Descriptor due to the possibility of transmission via exposure to bodily fluids.
- The MBS items for the detection of the Hepatitis D surface antigen are too restrictive in the number of tests funded and these items should be revised to increase the limit to 6 tests, to allow pathologists to claim for more than 3 hepatitis antigen tests in a patient episode.
- The severity of disease caused by HDV co-infection warrants the screening of all HBV infected individuals for HDV antibodies and then anti-HD positive individuals for HDV RNA Liver function testing is essential before and during treatment to assess liver damage and response.
- Pre-test counselling and consent were identified as being needed to be delivered before the intervention.
- Consideration should be given to restricting this MBS item to infectious disease specialists as HDV treatment is usually managed by these specialists and there is limited benefit to performing the test outside of this setting.
- There may be a role for general practitioners (GPs) in requesting HDV RNA PCR testing for the purpose of monitoring response to the proposed treatment (bulevirtide).
- Access to specialist physicians in regional, rural and remote areas is challenging and problematic, even with advances in, and access to, telehealth services. Consequently,

there may also be a case for HDV RNA PCR testing for people living with hepatitis B and under the care of a GP rather than a specialist, or in a shared care arrangement.

10. Characteristics of the evidence base

The approach taken in the submission was to present evidence that the use of bulevirtide reduces the quantity of HDV RNA and ALT in those with detectable HDV RNA prior to treatment. These data were in turn linked to evidence indicating that those with undetectable HDV RNA have a better prognosis than those with detectable HDV RNA. A summary of the linked evidence approach is shown in Table 4.

Table 4 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. | <input checked="" type="checkbox"/> k=1 concordance study n=35 | High | No |
| Prognostic evidence (longitudinal accuracy) | Comparison of outcomes in patients receiving <i>usual care</i> , conditioned on the presence or absence of HDV RNA at baseline | <input checked="" type="checkbox"/> k=5 retrospective cohorts n=1896 | High | No |
| | Comparison of outcomes in patients receiving <i>usual care</i> , conditioned on the reduction of HDV RNA | <input checked="" type="checkbox"/> 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) | <input checked="" type="checkbox"/> k=2 uncontrolled before/after study n=129 | High | No |
| Health outcomes (clinical utility) | No evidence presented. | <input type="checkbox"/> k=0 n=0 | | |
| Predictive effect (treatment effect variation) | No evidence presented. | <input type="checkbox"/> 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. | <input checked="" type="checkbox"/> k=1 n=150 | Low | Yes |

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

11. Comparative safety

Adverse events from testing

The Commentary noted that the submission did not make any claims regarding the safety of testing. Testing is performed on serum or blood. When the proposed test is used for diagnosing HDV, reflex testing is proposed which means the test would be done on the same sample which was used for the antibody test, and no additional harms would occur. The Commentary noted that harms due to the test or obtaining a sample for the test are therefore highly unlikely when used for HDV diagnosis. However, when the test is used for monitoring, additional blood tests would be necessary which can lead to some side effects. Adverse events associated with diagnostic venepuncture include vasovagal reactions, pain and bruising, and nerve injuries.

The Commentary noted that the submission did not discuss the consequences of false positive or false negative test results. A small proportion of patients identified with HDV RNA may have an acute infection rather than a chronic infection and could be considered “false positives”. The adverse events related to the treatment of these patients with acute hepatitis D are likely to be consistent with the treatment of CHD.

The Commentary noted that **redacted**. There is a chance that patients may have very low levels of HDV RNA after treatment, which is undetected by the test used. These “false negatives” would be ineligible to continue treatment with bulevirtide. The safety implications of ceasing treatment are efficacy related (that is, there is a risk of relapse/rebounding if the HDV infection is still active and treatment is stopped).

Adverse events from changes in management

Table 5 below summarises the overall treatment-emergent adverse events (TEAEs) in the MYR301 trial. As patients in the delayed treatment arm received symptomatic management of CHD (or best supportive care (BSC)) for the first 48 weeks and were switched to bulevirtide 10 mg thereafter, safety data at Week 96 for this treatment arm do not inform the comparative safety of bulevirtide *versus* BSC and, therefore, are not presented in the table below.

Table 5 Summary of overall TEAEs in the MYR301 trial

| | Bulevirtide 2 mg (N=49) | Delayed treatment (N=51) | Comparison between bulevirtide 2 mg and delayed treatment (RR, 95%CI) | Bulevirtide 2 mg (N=49) |
|---|-------------------------|--------------------------|---|-------------------------|
| Data cut-off | Week 48 | Week 48 | Week 48 | Week 96 |
| TEAE | 41 (83.7%) | 39 (76.5%) | 1.03 (0.86, 1.24) | 47 (95.9%) |
| TEAE with Grade 3 or higher | 5 (10.2%) | 4 (7.8%) | 1.30 (0.37, 4.56) | 9 (18.4%) |
| TEAE related to study drug | 24 (49.0%) | 0 | 50.96 (3.19, 815.66) | 25 (51.0%) |
| TEAE related to study drug with Grade 3 or higher | 1 (2.0%) | 0 | 3.12 (0.13, 74.80) | 4 (8.2%) |
| TE serious AE | 2 (4.1%) | 1 (2.0%) | 2.08 (0.19, 22.23) | 2 (4.1%) |
| 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. Results in bold were statistically significant.

AE = adverse event; CI = confidence interval; RR = relative risk; SAS = Safety Analysis Set; TE = treatment-emergent; TEAE = treatment-emergent adverse event

The key trial (MYR301) reported an overall higher incidence of treatment-emergent adverse events (TEAEs) in bulevirtide 2 mg treated patients compared with patients receiving symptomatic management of CHD. However, the TEAEs were not severe enough to result in premature discontinuation of treatment. In the trial, no patient experienced serious TEAE related

to bulevirtide treatment, and no death was caused by the treatment. The Commentary noted that only the higher relative risk of TEAE in the bulevirtide arm related to the study drug was found to be statistically significant. By week 96, nearly all patients had experienced at least one TEAE, but only one additional patient was considered to have a TEAE related to the study drug (over and above those who had had a TEAE related to the study drug after 48 weeks).

Results of AEs of special interest (AESIs) in the MYR301 trial are presented in Table 6. All AESIs observed in the trial were Grade 1 or 2 in severity and none resulted in discontinuation of treatment.

Table 6 Summary of results of adverse events of special interest in 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

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. The Commentary noted that 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 the investigator was not reported as an AE as per the study protocol. Increases in bile salt is the most commonly reported bulevirtide-related adverse event in “real-world” bulevirtide studies (Section 2.12.2 of the submission). Since bile salts are renally excreted and the proposed PBS restriction does not restrict by patient’s renal function, bulevirtide treatment may have safety issues if used in patients with impaired renal function as safety data of bulevirtide in this group of patients is lacking.

12. Comparative effectiveness

The PICO Confirmation suggested a linked evidence approach to determine the effectiveness of PCR testing and bulevirtide. Table 7 shows which research questions (associated with different steps of the linked analysis) were informed by evidence in the submission.

Table 7 Research questions in linked analysis that were informed by evidence

| Research question outlined in PICO confirmation | Informed by evidence? Available data. |
|---|---|
| What is the concordance of the PCR test proposed for use in Australia, compared to the clinical utility standard? | Yes. Study by Bonanzinga et al. (2023). K=1, n=35 |
| What is the accuracy of HDV RNA PCR testing for predicting response to bulevirtide treatment in those diagnosed with hepatitis D? | Not informed by evidence. |
| Does the HDV RNA PCR test result lead to a change in clinical decisions? | Limited. Studies by Binter et al. (2021) and Dietz-Fricke et al. (2023). K=2; n=129 |
| How does bulevirtide treatment impact HDV RNA levels and ALT levels? | Yes. Study by Wedemeyer et al. (2023). K=1, n=150 |
| How does a decrease in HDV RNA levels and ALT levels lead to better health outcomes? | Yes. Prognostic evidence K=7, n=1687 |
| What is the safety of HDV RNA PCR testing? | Not informed by evidence. |
| What is the safety of bulevirtide treatment? | Yes. Study by Wedemeyer et al. (2023). K=1, n=150 |
| What is the safety, effectiveness and cost-effectiveness of HDV RNA PCR testing to determine eligibility for bulevirtide for the treatment of HDV compared to no HDV treatment in those diagnosed with HBV, and testing positive for serum anti-HDV antibodies? | Not informed by evidence. |
| How does bulevirtide treatment impact health outcomes? | Not informed by evidence. |
| How well does HDV RNA PCR distinguish response to treatment compared to background variation? | Not informed by evidence. |

ALT = Alanine Aminotransferase, HDV = Hepatitis D Virus, PCR = Polymerase Chain Reaction, RNA = Ribonucleic Acid

Not all parts of the analytic framework (as outlined in Table 8) were addressed.

Table 8 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

The Commentary noted that the populations, tests and treatment regimens were not always transferrable across the evidence linkages, as they varied considerably.

The Commentary noted that due to uncertainties with the timing of the testing and applicability of the patient samples, the evidence on test concordance was considered to be at high risk of bias (using QUADAS-2).

Effectiveness (based on linked evidence)

Comparative accuracy/test performance

The proposed test is an HDV PCR RNA test, as developed by VIDRL. The clinical utility standard was specified as the RoboGene RNA quantification kit (as conducted in the main bulevirtide trial), whereas the reference standards presented in the submission included the 1st WHO International Standard for Hepatitis D Virus RNA and the French National Reference Laboratory samples across multiple genotypes (used for calibration of PCR tests).

Agreement/concordance between the clinical utility standard and the test used in Australia by VIDRL was presented in the submission⁵ (one study). **redacted**

The Commentary noted that in addition to the evidence presented in the submission, one systematic review was identified during the evaluation that provided some additional relevant

⁵ Bonanzinga. HDV RoboGene Verification. 2023. Data on file.

information on the performance of HDV RNA tests (no specific assay) for diagnosing HDV⁶. Ten studies were included, of which four were also identified/included in the submission's literature search for diagnostic accuracy studies. The meta-analysis reported a sensitivity of 0.92 (95%CI 0.87, 0.95) and a specificity of 0.90 (95%CI 0.86, 0.93). The area under the curve (AUC) was 0.95 (95%CI 0.92, 0.96). It should be noted that in this systematic review both the index tests and the reference standards were different types of PCR assays, and therefore it technically does not meet the PICO criteria as stated in the PICO Confirmation. However, these results show that the different HDV RNA assays generally have similar test performance when diagnosing active HDV.

Prognostic evidence

Data on the association between the presence of HDV RNA and subsequent health outcomes (in patients receiving usual care or treatment other than bulevirtide) were provided in the submission in Section 2.3 and in Attachment 11. The Commentary noted that results were separated during the evaluation for presence/absence of HDV RNA at baseline (prior to treatment) and the presence/absence of detectable HDV RNA after treatment (monitoring treatment effectiveness). Studies were excluded if they: did not use HDV RNA as an independent variable (k=4); or included patients without anti-HDV antibodies (i.e. compared outcomes for patients with HBV against HBV/HDV) (k=7).

The Commentary noted that in those who had evidence of an HDV infection, presence of HDV RNA on PCR testing was inconsistently associated with poorer health outcomes (three out of five studies reported statistically significant associations). The prognostic evidence using the baseline presence or absence of HDV RNA was severely confounded (with treatment variability). Presence of HDV RNA in those with anti-HDV antibodies was not significantly associated with any liver related outcomes (k=3, HR=1.61, 95%CI 0.94, 2.76); HCC (k=2, HR=0.84, 95%CI 0.41, 1.72); or hepatic decompensation (k=2, HR=1.35, 95%CI 0.72, 2.53) but was reported in a single study to be significantly associated with risk of death or transplantation (k=1, HR=7.40, 95%CI 1.74, 31.47).

However, response to treatments (other than bulevirtide) as determined by HDV RNA loss (HDV RNA undetectable or $\geq 2 \log_{10}$ drop) was significantly associated with favourable clinical outcomes. Persistence of HDV RNA was associated with an increased hazard of any liver related event (k=4; HR=1.72, 95%CI 1.08, 2.76). A single study also reported significant associations between detectable HDV RNA at last follow-up and the likelihood of HCC (k=1, HR=2.46, 95%CI 1.35, 4.48), decompensated cirrhosis (k=1, HR=2.57, 95%CI 1.42, 4.63) and liver related mortality (k=1; HR=3.30, 95%CI 1.93, 5.66). Larger effect sizes were reported by one study that compared health outcomes in patients who had maintained virologic response (no detectable HDV RNA for two years after completion of treatment) against those with detectable HDV RNA. This suggests that maintained response to treatment was more favourable than a single measurement suggesting response to treatment.

Predictive evidence

The Commentary noted that no evidence was provided in the submission on the predictive validity of the test or was identified independently.

Change in management in practice

The Commentary noted that although no evidence was provided in the submission that testing of HDV RNA at diagnosis influences the management of patients, it can be assumed that HDV RNA testing would be key for treatment decision making in regard to the initiation of bulevirtide in

⁶Chen, S., et al. (2023). "Performance of Hepatitis Delta Virus (HDV) RNA Testing for the Diagnosis of Active HDV Infection: Systematic Review and Meta-analysis." *J Clin Transl Hepatol* 11(6): 1368-1376.

those who have detectable HDV RNA (given that evidence of HDV RNA is a proposed requirement for access to bulevirtide).

The Commentary noted that only very limited evidence was identified linking HDV RNA monitoring to changes in management. One uncontrolled before and after study of 15 patients from Austria reported that 2/15 patients had their bulevirtide treatment stopped due to a maintained virologic response (>6 months), and that one patient had their treatment regimen altered (by the addition of pegylated interferon) due to lack of virologic response to bulevirtide⁷. A case series of 114 patients treated with bulevirtide in Germany reported that one patient ceased treatment due to lack of response (likely determined by HDV RNA, although it was not explicitly described how this was defined)⁸. Only some of these changes in management are relevant to the Australian setting (ceasing treatment due to undetectable HDV RNA) given that pegylated interferon is currently not indicated for use by the Australian regulatory authorities to treat HDV. Although HDV RNA testing may be prognostic, a change in management (informed by HDV RNA testing during bulevirtide treatment) is required to demonstrate codependency between the ongoing monitoring and treatment.

The Commentary noted that if the proposed clinical criteria for bulevirtide (including detectable HDV RNA) must be met for ongoing eligibility for bulevirtide, then the link between HDV RNA testing (for a monitoring purpose) and treatment can be assumed if the test provides incremental information over the other clinical criteria (i.e. if some patients stop bulevirtide due to undetectable HDV RNA levels, who would not have otherwise stopped bulevirtide due to normalisation of the ALT values). It is unclear whether treatment would be ceased under these conditions in clinical practice.

Claim of codependence

The Commentary noted that the claim of codependence has not been properly addressed in the submission, for two reasons:

1. Duration of detectable HDV RNA for ≥ 6 months might help with decision making of who will receive bulevirtide treatment because only patients with chronic HDV infection need the treatment. However, the chronicity of detectable HDV RNA in eligible patients for bulevirtide has not been defined. Note that PASC advised that a single positive HDV RNA PCR result would be sufficient to confirm chronic active HDV, as it is very rare to identify acute HDV infection in clinical practice.
2. In the submission, it was not clear how the HDV RNA PCR testing for monitoring of response to bulevirtide, being claimed to be the codependent technology of bulevirtide treatment, would influence bulevirtide use. Although clinical criteria were provided suggesting that patients may only access bulevirtide if they have detectable HDV RNA and elevated ALT, it was unclear how frequently the presence/absence of detectable HDV RNA would impact on management, incremental to ALT levels.

13. Economic evaluation

Structure of the economic model

The submission presented a modelled economic evaluation which compared bulevirtide treatment to BSC in patients with HDV RNA positive chronic HDV based on virologic response

⁷ Binter T, Jachs M, Hartl L, Aberle S, Zoller H, Aigner E. Efficacy of long-term treatment of chronic hepatitis D patients with bulevirtide - results of a "real world" study. *Hepatology*. 2021;74:420A-1A.

⁸ Dietz-Fricke C, Tacke F, Zollner C, Demir M, Schmidt HH, Schramm C, et al. Treating hepatitis D with bulevirtide - Real-world experience from 114 patients. *JHEP Rep*. 2023 Apr;5(4):100686.

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.

Alternate scenarios of test/treatment provision were not explored in the submission. The Commentary noted that there may be some benefits of testing independent of treatment given the prognostic information about a patient's HDV that RNA testing may provide. This approach was supported by public consultation received on the PICO Confirmation.

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. The Commentary noted that entry at the point of treatment is not the approach preferred in the Guidelines for submissions of codependent technologies, 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 negative 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 as Australian sources were used to inform the yield of HDV RNA testing (which may therefore reflect performance of testing in practice), the impact of false negatives may have been captured in the yield data used. The impact of a false positive result may not be insignificant – these patients may appear 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.

The submission assumed that of patients who are anti-HDV positive and who are suspected of having chronic HDV, 56.2% would have detectable HDV RNA. The submission claimed that this was based on a weighted average from Coghill et al. (2018)⁹, Jackson et al. (2018)¹⁰ and Shadur et al. (2013)¹¹. The Commentary noted that while these sources appear reasonable and are likely applicable to the proposed setting, given that they were all reporting on Australian patients, the weighted average calculated from these sources was estimated during the evaluation to be 54.4%. The submission's estimate was derived by assuming that for Jackson et al. (2018)¹⁰ the proportion of positives in a randomly tested sample would be applied to the denominator for the sample where PCR testing had been requested, which may not be reasonable. Under the submission's assumption of the rate of HDV RNA positivity (56.2%) and 100% test performance, 1.78¹² patients require testing to identify one patient eligible for bulevirtide treatment (increasing to 1.83, assuming 54.4% test positive).

All patients identified with detectable RNA were assumed to be eligible and uptake bulevirtide treatment. The Commentary noted that limited information was provided on the patients tested in the studies used to estimate yield of HDV RNA testing. Patients found to be HDV RNA positive may not all be eligible for bulevirtide treatment, 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.

The submission used a Markov model structure that included eleven distinct health states: non-cirrhosis (separated into F0, F1, F2 and F3 states), compensated cirrhosis (CC) (i.e. F4),

⁹ 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.

¹⁰ 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.

¹¹ Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000-2009. *Intern Med J.* 2013 Oct;43(10):1081-7.

¹² $1 \div \text{yield [56.2\%]}$

decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplantation, post-liver transplantation, dead (liver-related) and dead (background). 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 (or regression of disease) and additional utility due to response.

As the MYR301 trial reported limited liver-related outcomes, transition probabilities were generally derived from external sources. Probabilities for chronic HDV disease progression were based on those in patients with HBV mono-infection, adjusted for an increased risk in patients with HBV/HDV concomitant infection. The Commentary noted that additional sources were identified during the evaluation that report outcomes directly in HBV/HDV patients. These may provide a more reasonable basis for deriving the transition probabilities for use 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). The Commentary noted that the submission did not justify the selection of this source, nor were alternate sources considered, which was not reasonable as alternate Australian data have been published.

Hazard ratios were applied to some of the transitions to model reduced disease progression in patients who achieved a response. The submission presented a systematic review and meta-analysis to estimate the relationship of HDV RNA reduction or undetectability or ALT normalisation on chronic HDV progression. The Commentary noted that the comparisons presented in several 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. 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.

Furthermore, the economic model used response rates from MYR301 defined as virologic response (undetectable RNA or decrease in HDV RNA levels by $\geq 2 \log_{10}$ IU/mL from baseline), which was noted to be broader than the definition of the surrogate measure (detectable versus undetectable RNA) used to estimate the effect of response on liver-related outcomes. While response rates from MYR301 defined as undetectable RNA may be more consistent with the studies included in the meta-analyses, heterogeneity was 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 submission assumed six-monthly HDV RNA testing while patients remained on treatment. The Commentary noted that 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. Patients who responded to treatment were assumed to remain on bulevirtide unless they experienced disease progression, HBsAg seroclearance, or discontinued due to other reasons.

A lifetime time horizon (i.e. until 100 years of age) was assumed, based on the claim that the treatment improved response delays, or potentially avoids, sequelae that result in substantial

excess mortality. Given an average age of 42 years on model entry, the time horizon was therefore 58 years. The Commentary noted that this was substantially longer than observed in the trial (96 weeks, 1.8 years) and what the PBAC had previously considered reasonable for models of chronic HBV infection (20 years, lamivudine, March 1999 PBAC meeting and Section 10, telbivudine PSD, March 2008 PBAC meeting).

Results of the economic analysis

The cost per test applied to determine initial eligibility to bulevirtide was \$152.10. Assuming that 1.78 tests are required to identify one patient that enters the model, the one-off cost applied on model entry was \$270.64. HDV RNA monitoring was assumed twice per year while on bulevirtide treatment. Therefore, the cost per year for monitoring was \$304.20. Given that the duration of bulevirtide treatment modelled is 8.8 years, cost of monitoring applied per treatment course was \$ **redacted** (undiscounted).

The results of the stepped economic evaluation are presented in Table 9. The Commentary noted that the stepped analyses presented in the submission combined several 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 9 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 | \$ redacted | \$0 | \$ redacted |
| Virologic response ^d at 48 weeks | 73.5% | 3.9% | 69.6% |
| Incremental cost/additional responder | | | \$ redacted 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 | \$ redacted | \$0 | \$ redacted |
| Virologic response ^d at 96 weeks | 75.5% | 4.2% | 71.3% |
| Incremental cost/additional responder | | | \$ redacted 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 patients with virologic response at 96 weeks. | | | |
| Costs | \$ redacted | \$0 | \$ redacted |
| QALY gained | 0.080 | 0.004 | 0.075 |
| Incremental cost/extra QALY gained | | | \$ redacted 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 | \$ redacted | \$8,688 | \$ redacted |
| LY gained | 1.688 | 1.674 | 0.015 |
| QALY gained | 1.396 | 1.323 | 0.074 |
| Incremental cost/extra QALY gained | | | \$ redacted 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 | \$ redacted | \$8,688 | \$ redacted |
| LY gained | 1.688 | 1.674 | 0.015 |
| QALY gained | 1.396 | 1.323 | 0.074 |
| Incremental cost/extra QALY gained | | | \$ redacted 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 | \$ redacted | \$68,278 | \$ redacted |
| LY gained | 10.851 | 8.462 | 2.389 |
| QALY gained | 8.548 | 6.327 | 2.221 |
| Incremental cost/extra QALY gained (base case) | | | \$ redacted ⁶ |

Source: Adapted from Table 3.8-1, p171 of the of the submission, and the attached 'Attachment 10 - Hepcludex HDV Section 3A Cost-Eff Model_vfinal.xlsm' and 'Attachment 13 - Hepcludex HDV Section 3A Stepped Evaluation.xlsx' files.

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.

^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.

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

The Commentary noted that sensitivity analyses were conducted during the evaluation to explore the sensitivity of the model to inputs related to testing. In general, the incremental cost-effectiveness ratio (ICER) was not sensitive to changes related to testing able to be explored with the provided model structure. Assumptions not able to be tested include the impact of false positive results from HDV RNA testing and the inclusion of acute patients in the population (both tested and treated). The ICER was however observed to be sensitive to the definition of response, source used to model chronic HDV disease progression, 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.

14. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the use and cost of HDV RNA testing and bulevirtide treatment. The Commentary considered that this was reasonable. Use of bulevirtide was estimated in three population groups: prevalent patients with known chronic HDV, prevalent patients with chronic HBV who have not previously been tested for HDV, and incident patients.

An increase in use and cost of HDV RNA testing was not assumed in prevalent patients with known chronic HDV who had previously received HDV RNA testing. The Commentary noted that in practice clinicians may repeat HDV testing in this patient population prior to initiating treatment with bulevirtide, to confirm presence of chronic HDV or to determine baseline levels of viral load. Therefore, the submission has only estimated the use and cost of HDV RNA testing to determine access to bulevirtide treatment in incident patients and prevalent patients, engaged in care, who had not previously been tested for HDV. The Commentary noted that 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. This may not be reasonable. With increased awareness of treatment options in chronic hepatitis following listing of bulevirtide, opportunistic testing may occur.

The submission's approach to estimate the use and cost of HDV RNA testing for determining access to bulevirtide is presented in Table 10. The Commentary noted that use of HDV RNA testing was erroneously based on the number of patients tested for anti-HDV (not those who were also anti-HDV positive) and so was overestimated. Use of HDV RNA testing in incident patients was estimated only in the additional patients who uptake anti-HDV testing (and so does not account for the increase in HDV RNA testing uptake following proposed listings in patients who would have otherwise received anti-HDV testing). Estimates calculated during the evaluation accounting for these issues are presented in Table 11.

While uptake of HDV RNA testing was assumed to increase from **redacted** prior to listing, to **redacted** following listing, the cost to the MBS was estimated only for those additional tests due to the listing of HDV RNA testing and bulevirtide treatment (i.e. proportion of tests above **redacted** %). The Commentary noted that this assumes that current payers for HDV RNA testing will continue to pay for testing that would have occurred in the absence of MBS listing. It is likely that with MBS listing, these costs will shift to the MBS and so costs estimated may underestimate those in practice. Furthermore, uptake of HDV RNA testing following listing may have been underestimated if the increase in anti-HDV testing was due to increased awareness and availability of HDV testing and bulevirtide treatment (i.e. it may be reasonable to assume those patients who additionally take up anti-HDV testing would also receive HDV RNA testing if eligible).

Table 9 Use and cost of HDV RNA testing for access to bulevirtide treatment, estimated in the submission

| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|---|-------------------------|-------------------------|-------------------------|-----------------------|-----------------------|------------------------|
| Prevalent population - unknown chronic HDV diagnosis | | | | | | | |
| A | No. prevalent chronic HBV patients (0.87% × Australian population projections 2023 age 0–100+) | redacted ¹ | | | | | |
| B | No. prevalent chronic HBV patients who are diagnosed prior to listing (A × 73.0%) | redacted ² | | | | | |
| C | No. prevalent chronic HBV patients who are engaged in care prior to listing (B × 30.9%) | redacted ³ | | | | | |
| D | Proportion of prevalent chronic HBV patients tested for anti-HDV following bulevirtide listing | redacted % ^a | redacted % ^b | redacted % ^c | | | |
| E | No. prevalent chronic HBV patients tested for anti-HDV following bulevirtide listing (C × D) | redacted ⁴ | redacted ⁵ | redacted ⁵ | | | |
| F | No. patients eligible for diagnostic HDV RNA testing (E × 100%) | redacted ⁴ | redacted ⁵ | redacted ⁵ | | | |
| G | Increase in patients receiving diagnostic HDV RNA tests following bulevirtide listing (above 44.4% assumed in absence of listing) | redacted % | redacted % | redacted % | | | |
| H | No. additional patients who receive diagnostic HDV RNA testing (F × G) | redacted ⁶ | redacted ⁶ | redacted ⁶ | | | |
| Incident patients | | | | | | | |
| I | No. incident chronic HBV patients diagnosed (0.02% × Australian population projections age 0–100+) | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ¹⁵ |
| J | No. incident chronic HBV patients engaged in care (I × 90.0%) | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ²⁵ |
| K | Increase in patients receiving anti-HDV testing following listing (above 35.0% assumed in absence of listing) | redacted % | redacted % | redacted % | redacted % | redacted % | redacted % |
| L | No. additional patients tested for anti-HDV (J × K) | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ |
| M | No. patients eligible for diagnostic HDV RNA testing (L × 100%) | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ |
| N | Increase in patients receiving diagnostic HDV RNA tests (above 44.4% assumed in absence of listing) | redacted | redacted % | redacted % | redacted % | redacted % | redacted % |
| O | No. additional patients who receive diagnostic HDV RNA testing (M × N) | redacted ⁷ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ |
| P | Total additional patients who receive diagnostic HDV RNA tests (H + O) | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ |
| | Additional HDV RNA tests (1 per patient) | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ |
| | Cost to the MBS (\$129.30 per test) | redacted ⁸ | redacted ⁸ | redacted ⁸ | redacted ⁸ | redacted ⁸ | redacted ⁸ |

Source: Table 4.5–4, pp199-200 and Table 4.5–5 and Table 4.5–6, p200 of the submission and the attached 'Attachment 14 - HEPCLUDEX HDV CoDep Section 4_final.xlsm' file.

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

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

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

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

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 to < 5,000
- 7 <500
- 8 \$0 to < \$10 million

Table 10 Use and cost of HDV RNA testing for access to bulevirtide treatment, revised during the evaluation

| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Prevalent patients (previously untested for HDV) | | | | | | | |
| Q | No. prevalent chronic HBV patients tested for anti-HDV following bulevirtide listing (Row E, Table 10) | redacted ¹ | redacted ² | redacted ² | | | |
| R | No. eligible for HDV RNA testing (i.e. chronic HBV patients with anti-HDV+) (Q × 4.06%) | redacted ³ | redacted ³ | redacted ³ | | | |
| S | Uptake of HDV RNA testing following listing | redacted % | redacted % | redacted % | | | |
| T | Patients tested with HDV RNA following listing (R × S) | redacted ³ | redacted ³ | redacted ³ | | | |
| Incident patients | | | | | | | |
| U | No. incident chronic HBV patients who are diagnosed and engaged in care (Row J, Table 10) | redacted ⁴ | redacted ⁴ | redacted ⁴ | redacted ⁴ | redacted ⁴ | redacted ⁴ |
| Use of anti-HDV and HDV RNA testing prior to listing | | | | | | | |
| V | No. chronic HBV patients tested for anti-HDV (U × 35.0%) | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ | redacted ⁵ |
| W | No. chronic HBV patients found with anti-HDV+ (V × 4.06%) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| X | No. patients with anti-HDV+ who received HDV RNA testing (W × 44.4%) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| Use of anti-HDV and HDV RNA testing after listing | | | | | | | |
| Y | Proportion incident chronic HBV patients tested for anti-HDV following bulevirtide listing | redacted % | redacted % | redacted % | redacted % | redacted % | redacted % |
| Z | No. incident chronic HBV patients tested for anti-HDV (U × Y) | redacted | redacted | redacted | redacted | redacted | redacted |
| AA | No. incident chronic HBV patients found with anti-HDV+ (Z × 4.06%) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| AB | Uptake of HDV RNA testing following bulevirtide listing | redacted % | redacted % | redacted % | redacted % | redacted % | redacted % |
| AC | No. incident chronic HBV patients with anti-HDV+ who received HDV RNA testing (AA × AB) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| AD | Increase in incident patients tested with HDV RNA (AC – X) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| AE | Total increase in patients tested with HDV RNA (T + AD) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| AF | Increase in HDV RNA testing (AE × 1) | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ | redacted ³ |
| | Cost to the MBS (AF × \$129.30) | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ | redacted ⁶ |

Source: Constructed during the evaluation from the 'Attachment 14 - HEPCLUDEX HDV CoDep Section 4_final.xlsm' file included with the submission.

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

- 1 10,000 to < 20,000
- 2 5,000 to < 10,000
- 3 < 500
- 4 5,000 to < 10,000
- 5 500 to < 5,000
- 6 \$0 to < \$10 million

The Commentary noted that the estimated number of incident patients found to be anti-HDV positive (<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 literature¹³, and an increase in notifications following listing may be reasonable. Though the extent estimated remains for MSAC consideration, given the number of assumptions used in the analysis.

To estimate the use and financial impact of HDV RNA testing for monitoring the effect of bulevirtide treatment, the submission converted the additional patients who received HDV RNA testing each year (calculated in Row P, Table 10) into patient-years on treatment and assumed two monitoring tests per patient-year on treatment (Table 12). The Commentary noted that this was incorrect. Firstly, the number of patients who additionally received HDV RNA testing does not represent the number of patients who initiate bulevirtide treatment. Secondly, it was not correct to apply this estimate to the average durations of treatment, which represent the time on treatment for patients initiating in the first year of listing. As the submission has estimated patient-years on treatment (Table 4.2–3, pp190-1 of the submission), this may be a more appropriate basis to derive the use and cost of HDV RNA testing for monitoring purposes (see revised estimates in Table 12).

Table 11 Estimated use of HDV RNA testing for treatment monitoring

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Submission | | | | | | |
| No. patients eligible for treatment monitoring (Row P, Table 10) | redacted ₁ | redacted ₁ | redacted ₁ | redacted ₁ | redacted ₁ | redacted ₁ |
| Average duration of treatment (by year) | redacted _% | redacted _% | redacted _% | redacted _% | redacted _% | redacted _% |
| No. monitoring tests (2 per year) | redacted ₁ | redacted ₂ | redacted ₂ | redacted ₁ | redacted ₁ | redacted ₁ |
| Cost to the MBS (\$129.30 per test) | redacted ₃ | redacted ₃ | redacted ₃ | redacted ₃ | redacted ₃ | redacted ₃ |
| Revised | | | | | | |
| No. patient years on treatment (Table 4.2–3 of the submission) | redacted ₄ | redacted ₄ | redacted ₄ | redacted ₄ | redacted ₄ | redacted ₄ |
| No. HDV RNA monitoring tests (2 per patient-year on treatment) | redacted ₄ | redacted ₁ | redacted ₁ | redacted ₁ | redacted ₁ | redacted ₁ |
| Cost to the MBS (\$129.30 per test) | redacted ₃ | redacted ₃ | redacted ₃ | redacted ₃ | redacted ₃ | redacted ₃ |

Source: Table 4.5–5 and Table 4.5–6, p200 of the submission and the attached 'Attachment 14 - HEPCLUDEX HDV CoDep Section 4_final.xlsm' file.

HDV = hepatitis D virus; RNA = ribonucleic acid.

1 500 to < 5,000

2 5,000 to < 10,000

3 \$0 to < \$10 million

4 < 500

Following the listing of HDV RNA testing and bulevirtide treatment, anti-HDV testing was assumed to increase given that anti-HDV testing is a pre-requisite to HDV RNA testing, and that use was expected to increase due to increased awareness of testing for HDV following the availability of the proposed codependent technologies on the MBS and PBS. The commentary considered this was reasonable. In incident patients, uptake of anti-HDV testing was assumed to increase from **redacted%** to **redacted%** following listing of bulevirtide. In prevalent patients who had not been HDV tested previously the submission assumed **redacted%** uptake over the first three years of listing in the **redacted%** of prevalent patients engaged in care who had not previously been tested for HDV. The Commentary noted that this was consistent with the epidemiological

¹³ Cosentino C, Clayton-Chubb D, Lubel JS. Management of hepatitis D in general practice. Aust J Gen Pract. 2023;52(8):536-9

approach used to estimate the number of patients eligible for treatment. The submission then applied **redacted** tests for each patient who received anti-HDV testing, based on the assumption that there may be some patients that would be initially diagnosed as anti-HDV negative but who would subsequently be re-tested at a later date. As Australian practice recommendations recommend screening for HDV at least once, the extent of repeated screening is unclear, though is unlikely to occur within the same year. The increase in cost of anti-HDV testing is presented in Table 13.

The net cost to the MBS for the increase in use and cost of HDV RNA and anti-HDV testing is presented in Table 13. The impact was estimated to be highest in the first three years of listing, due to testing in the prevalent population.

Table 12 Net financial implications to the MBS

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--|--|--|--|--|--|
| Cost to the MBS of HDV RNA testing ^a | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Revised ^b | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Cost to the MBS for changes in anti-HDV testing | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Net cost to the MBS Revised | redacted ¹ redacted ¹ | redacted ¹ redacted ¹ | redacted ¹ redacted ¹ | redacted ¹ redacted ¹ | redacted ¹ redacted ¹ | redacted ¹ redacted ¹ |

Source: Table 4.5–7, p201 of the submission and the attached 'Attachment 14 - HEPCLUDEX HDV CoDep Section 4_final.xlsm' file.

HDV = hepatitis D virus; RNA = ribonucleic acid.

^a Sum of HDV RNA costs for determining treatment initiation (Table 10) and monitoring (Table 12).

^b Sum of HDV RNA costs for determining treatment initiation (Table 11) and monitoring (Table 12).

¹ \$0 to < \$10 million

Key sensitivity analyses are presented in Table 14. The Commentary noted that the analyses 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 and who uptake bulevirtide treatment and the expected uptake of HDV RNA testing. 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).

Table 13 Key sensitivity analyses around the financial impact to the MBS

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Base case (revised) | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Proportion anti-HDV+, base case: redacted % | | | | | | |
| • redacted% | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Uptake of HDV RNA testing following listing, redacted % (base case: increasing from redacted % to redacted % by Year 3) | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Proportion tested who are HDV RNA+, base case: redacted % | | | | | | |
| • redacted % | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| • redacted % | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Proportion eligible for bulevirtide, 100% (base case: redacted %) | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| Uptake of bulevirtide, base case: increasing from redacted % to redacted % by Year 4 | | | | | | |
| • redacted % | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |
| • redacted % | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ | redacted ¹ |

Source: Constructed during the evaluation from the 'Attachment 14 - HEPCLUDEX HDV CoDep Section 4_final.xlsx' file included with the submission.

HDV = hepatitis D virus; RNA = ribonucleic acid.

¹ \$0 to < \$10 million

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The submission proposed a quantitative HDV RNA PCR test, however it did not clearly specify how quantitative RNA levels would change clinical decision making. The submission had defined a response to treatment as undetectable HDV RNA (HDV RNA < lower limit of detection) or a $\geq 2 \log_{10}$ drop in HDV RNA from baseline measured by quantitative testing. However, there was no evidence that a $2 \log_{10}$ drop in viraemia was associated with improvements in clinical outcomes. Therefore, there could be a role for qualitative HDV RNA testing in either triaging for or replacing quantitative HDV RNA testing, with an additional benefit from the fact that qualitative testing costs much less than quantitative testing.
- The evidence of an association between HDV RNA viral load and clinical outcomes was based on data from retrospective cohort studies and only looked at association between the presence/absence of HDV RNA in people at baseline and clinical outcomes. In addition, the evidence was at high risk of bias in all domains particularly selection bias, and its generalisability was uncertain as no Australian studies were included.
- There was limited evidence that the test results predicted clinical outcomes, although despite this lack of evidence, recent guidelines on decision-making included reference to testing HDV RNA PCR levels every 6 months to monitor response to treatment.
- The test used in the key trial evidence (Robogene® RNA quantification kit, the clinical utility standard) differed from the proposed test (developed by the Victorian Infectious Diseases Reference Laboratory (VIDRL)) **redacted**
- The ESCs considered the test should not be pathologist-determinable as this is not clinically required, the test is not likely to be subject to substantial loss to follow up, and making the test pathologist-determinable would likely result in over-testing.

Economic issues:

- The economic model structure excluded consideration of false positive and false negative results for HDV RNA PCR testing for eligibility, as patients entered at treatment.
- The ESCs considered the likely pattern of use of HDV RNA PCR testing and re-testing was uncertain and should have been more fully explored in the economic model.
- The ESCs noted there was uncertainty in the average duration of bulevirtide treatment, which translated to uncertainty in the number of monitoring tests per treated patient. There may therefore be merit in having separate MBS items to track utilisation of HDV RNA PCR testing for determining eligibility for treatment versus monitoring of treatment effectiveness.

Financial issues:

- The Commentary's revised financial estimates were significantly below the estimates provided in the submission, and the ESCs considered the revised estimates may be reasonable if MSAC agrees HDV RNA PCR testing should not be pathologist-determinable.

ESC discussion

The ESCs noted that the integrated codependent submission sought Medicare Benefits Schedule (MBS) listing of ribonucleic acid (RNA) polymerase chain reaction (PCR) testing to detect the

presence of hepatitis D virus (HDV) RNA to determine eligibility for treatment with bulevirtide in patients with chronic HDV (CHD) with compensated liver disease. A second MBS listing was requested for HDV RNA PCR testing to quantify levels of HDV RNA for monitoring efficacy of bulevirtide treatment.

The ESCs noted that HDV virions attach to the receptors on the surface of hepatocytes infected with the hepatitis B virus (HBV). They are then enveloped within a coating of HBV surface antigen before gaining entry into the hepatocyte. Bulevirtide binds to and inactivates the receptor that the HDV virions use to gain entry into the hepatocytes, thus blocking their entry into hepatocytes.

The ESCs noted that HDV cases in Australia were stable over time, and there were an estimated 70 reported cases of HDV in 2022¹⁴ based on positive HDV serology, representing an incidence of 0.29 cases per 100,000 population. The ESCs considered HDV is a rare disease in Australia, although it is more common in Europe, which made the applicability of international prevalence estimates to Australia uncertain. There is no current therapy available specifically for HDV. Pegylated interferon (peg-IFN) is used to treat HDV overseas, but is curative in only 30% of cases and is poorly tolerated. The ESCs noted that international guidelines¹⁵ recommend that patients should be eligible for bulevirtide only if they have failed a prior course of peg-IFN. This is similar to NICE eligibility requirements to access bulevirtide in the UK. The ESCs considered that a similar requirement would be difficult to implement in Australia due to patient and clinician preference for treatments other than peg-IFN. In addition, peg-IFN is not indicated for use for treatment of HDV in Australia, although it is known to be used off-label.

The ESCs noted that the PICO for this application was ratified three years ago, prior to the publication of the MYR 301 trial results in 2023 and this has led to differences in the proposed testing algorithm as it was not informed by the later trial results. Therefore, the ESCs considered that the proposed algorithm may require amendment and further investigation.

The ESCs noted that the proposed HDV RNA PCR test (a test developed by the only Australian laboratory that currently offers this testing, VIDRL) was different to the clinical utility standard (Robogene® RNA quantification kit) that was used in the key trial.

The ESCs noted two points raised by the National Pathology Accreditation Advisory Council (NPAAC) for MSAC consideration. Firstly, as testing is currently available in one laboratory in Australia, there was no general experience with the assay and no external quality assurance program (QAP) was currently available. Secondly, NPAAC Standards require that test performance is monitored by participation in an external QAP or, if this is not available, an equivalent documented internal program such as sample exchange with another laboratory. The ESCs recalled NPAAC had also advised there was no QAP in place when this application went to PASC 3 years ago. The ESCs considered it would be informative for the applicant to confirm whether unpublished validation information from VIDRL meets regulatory/accreditation requirements currently, **redacted**.

The ESCs considered that the proposed clinical management algorithms were overly simplistic, and that additional consideration may be needed of the potential role for qualitative testing in this algorithm. This is discussed further below.

¹⁴ Australian Department of Health and Aged Care, 'National Communicable Disease Surveillance Dashboard', in *National Notifiable Disease Surveillance System*. February 2024, viewed on 16 February 2024, <https://nindss.health.gov.au/pbi-dashboard/>

¹⁵ European Association for the Study of the Liver (EASL) (2023). "EASL Clinical practice guidelines on hepatitis delta virus." *J Hepatol* 79(2):433-460. doi: 10.1016/j.jhep.2023.05.001

The ESCs suggested revisions to the proposed MBS item descriptor are below (Table 13).

Table 13 ESC's suggested revisions to the proposed MBS item descriptor

| Category xx – Pathology service – P3 – Microbiology |
|---|
| <p>AAAA Quantitation of Hepatitis D viral RNA load in plasma or serum in:</p> <ul style="list-style-type: none"> (a) the pre-treatment evaluation for access to therapy a treatment listed on the Pharmaceutical Benefits Scheme (PBS) for chronic HDV hepatitis D in patients who are Hepatitis D viral antibody positive and suspected of having chronic Hepatitis D; or (b) a patient undertaking antiviral therapy for chronic hepatitis D virus with bulevirtide a treatment listed on the PBS for the purpose of assessing treatment effectiveness. <p>To a maximum of 2 tests in a 12 month period.</p> <p>Fee: \$152.10 Benefit: 75% = \$114.10 85% = \$129.30</p> <p>Practice note Patients with decompensated liver disease (Child Pugh B or C) are not eligible for testing</p> |

ESC's changes are shown in green text (deletions shown in strikethrough).
Source: ESC

The ESCs considered that the proposed item descriptor broadly captured the pivotal elements of the test, including the population (which broadly matched the population from the evidence) and the proposed use of the test in clinical practice. In the pre-ESC response the applicant agreed that patients classified as Child Pugh B and C should be excluded from testing. The ESCs considered that a practice note should be added to exclude patients classified as Child Pugh B or C, as these patients are not eligible for treatment.

The ESCs considered this test could potentially also be used to determine eligibility for future PBS-listed treatments for this patient group, and proposed futureproofing the item descriptor by amending it to refer to PBS-listed chronic hepatitis D treatments in general rather than bulevirtide specifically.

The ESCs noted that the Commentary raised the issue of ensuring the item descriptor limited the test to patients with chronic Hepatitis D, i.e. excluding patients with acute Hepatitis D. The ESCs considered that while theoretically this could be implemented by requiring evidence of chronic viraemia (for example by requiring two tests a minimum number of months apart for confirmation that viraemia is chronic), in practice it was very unlikely that cases of acute infection would be detected by a HDV RNA test. Overall, the ESCs considered that detecting patients with acute Hepatitis D was unlikely, but if MSAC had concerns about this risk then it could be better addressed by including clinical guidance on eligibility in the Practice Note than by adding the requirement for prior testing to conclusively determine chronicity to the item descriptor.

The ESCs considered that while the proposed MBS item fee of \$152.10 was reasonable as it matched the fee for item 69482 (quantitation of Hepatitis B viral DNA), this fee was higher than the ~~redacted~~ currently charged privately by VIDRL ~~redacted~~. The ESCs noted that the IVD test kit used in the pivotal clinical trials, Robogene®, was listed for sale in the US at US\$3,026 (approximately AUD \$4,600).

The ESCs noted that the likely pattern of use of HDV RNA PCR testing and re-testing was uncertain and this was partly due to the uncertainty in number of monitoring tests per patient which in turn was caused by uncertainty in the average duration of treatment for bulevirtide. Therefore the ESCs queried whether there may be merit in having separate MBS items (one for

determining eligibility for treatment and one for monitoring of response to treatment) to track utilisation of HDV RNA PCR testing for each purpose.

The ESCs considered the item descriptor requiring that anti-HDV positivity is established prior to HDV RNA PCR testing was appropriate, and noted that the MBS fees for testing HDV serology were lower than the proposed fees for HDV RNA testing. The ESCs noted as a side issue that Australian Pathology is requesting access to up to 6 hepatitis antigen/antibody tests per patient episode covering all hepatitis serology testing including Hepatitis B and C but if this is approved then the value of using the lower cost antigen/antibody test (items 69475, 69478, 69481) as a triage test before HDV RNA testing would be diminished. The current listed MBS items for HDV antigen/antibody tests (e.g, 69475, 69478, 69481) allowed for up to 3 tests per patient episode.

The ESC noted PASC's and the applicant's proposal that HDV RNA PCR testing could be pathologist determinable and still subject to this requirement for anti-HDV positivity insofar as HDV RNA PCR testing could be triggered by a positive HDV antigen/antibody test (e.g, 69475, 69478, 69481). However, the ESCs questioned whether there was a clear clinical indication to justify this **redacted**. The ESCs noted the submission's argument that reflex testing is recommended to ensure that a diagnosis of chronic Hepatitis D is not overlooked by healthcare providers inexperienced in the management of chronic Hepatitis D and also reduces the need for an additional specimen to be taken from the patient. However, the ESCs noted that:

- These patients are typically already managed by specialists who are experienced in hepatitis management.
- Any potential loss to follow up testing was likely to be low and no different from that in other serological testing in practice and could be managed as the need arises.
- Reflex testing was not standard of care in the management of other patients with hepatitis e.g. Hepatitis C.

The ESCs also considered it was unclear whether making HDV RNA PCR testing pathologist-determinable would be implementable given the very high rates of false positivity for HDV antigen/antibody testing (only 54.4% of anti-HDV positive cases have detectable HDV RNA). In addition, pathologists were unlikely to be aware of a patient's other clinical history and features to help them determine whether the patient is suspected of having chronic hepatitis D as per part (a) of the proposed item descriptor (e.g., elevated ALT levels, liver stiffness).

The ESCs noted Hepatitis Queensland proposed requestors should be restricted to specialists only as this patient population are managed by them, and agreed that requestors would generally be consultant physicians practising as specialist gastroenterologists. However, the ESCs queried whether there may also be a role for general practitioners (GPs) in requesting HDV RNA PCR testing for the purpose of monitoring treatment response, given that some rural and regional patients may face barriers to accessing specialists. In particular, the ESCs considered that for such patients it may be faster to respond to a testing requirement via the patient's GP than their specialist, even if the patient has access to a specialist. The ESCs considered further input from consumers would allow MSAC to get a better understanding of whether and how such access issues (including requestor types) affect timely testing, including where there are intersecting barriers to access.

The ESCs considered that while the proposed item allows for HDV RNA PCR testing up to two times in 12 months and this appears reasonable for monitoring treatment response, this may not be appropriate for determining eligibility for treatment, because patients who test negative at different points in the proposed testing pathway could be considered for re-testing at a future point in time.

The ESCs noted the pre-ESC response's argument that the proposed use for monitoring of treatment effectiveness (i.e. objective (b)) was not intended as the basis of a formal continuation/stopping rule for bulevirtide, but to provide prognostic information to support ongoing clinical care. The ESCs considered this reasonable as bulevirtide is not curative as its main mechanism of action is through viral suppression, and noted the applicant's advice about late response: the onset of response can take months or years (for hepatocytes previously infected with HDV to be cleared by the immune system) of no apparent treatment response before the patient starts responding. The ESCs also considered it reasonable that there should not be a requirement for ongoing detectable HDV RNA to continue therapy, and that this should be explicitly accounted for in the economic modelling.

The ESC considered the possibility of having a qualitative HDV RNA PCR testing item similar to MBS item 69499 as a triage test prior to the proposed HDV RNA quantitation. Under this approach, testing would be initially with a qualitative HDV RNA PCR test (after the patient is found to be positive for HDV antibodies) and a quantitative HDV RNA PCR test is then undertaken if patient is a candidate for treatment. The ESCs considered that exploration of this alternative triage approach would require additional modelling to include the lower cost of qualitative testing, and quantitative testing of only the relevant population of patients in the F2 (significant fibrosis) to F4 (cirrhosis) liver fibrosis states.

The ESCs also considered whether quantitative HDV RNA PCR testing was necessary to inform treatment with bulevirtide or whether qualitative testing would suffice, particularly given that there was no evidence to support a correlation between a 2 log₁₀ drop in HDV viraemia and clinical outcomes, and because qualitative testing is simpler and costs less than quantitative testing.

The ESCs considered that there may be a role for qualitative rather than quantitative HDV RNA PCR testing, for multiple reasons:

- As noted above, there was a significant lack of data for correlation of viral load with clinical outcomes thus some clinicians may use qualitative testing instead of quantitative testing during monitoring.
- If treatment is indefinite, use of an ongoing qualitative test may suffice.
- Following treatment cessation, the patient may continue to be tested, and a qualitative test would be reasonable and cheaper than a quantitative test.
- There is good clinician experience with the roles of both qualitative and quantitative testing in viral hepatitis due to experience with Hepatitis C.
- A qualitative PCR test would be valuable to inform patient prognosis, even if these patients are not eligible for treatment.

The ESCs noted that a linked evidence approach was used by the submission and that evidence was provided for the following steps:

- The concordance of the proposed HDV RNA PCR test compared to the clinical utility standard, from one study with 35 participants.
- Prognostic evidence that a decrease in HDV RNA levels and ALT levels leads to better health outcomes, comprising 7 studies with a total of 1687 participants (although only 5 of these studies were used in the economic modelling).
- Evidence that a HDV RNA PCR test result leads to a change in clinical decisions, comprising 2 studies with a total of 129 participants.

However, the ESCs noted the following areas of testing safety and efficacy that were not informed by evidence:

- The accuracy of HDV RNA PCR testing for predicting response to bulevirtide treatment in those diagnosed with hepatitis D
- The safety of HDV RNA PCR testing
- How well HDV RNA PCR distinguishes response to treatment compared to background variation.

The ESCs noted that the submission did not raise any comparative safety concerns. However, the ESCs considered that the risks associated with false positive and false negative results were not addressed by the submission. Specifically, the Commentary raised the potential for false negative results given that **redacted**. It is unknown whether this would lead to a clinically important difference and missed treatment for patients with a false negative result. **redacted**. The ESCs considered there would be the need for an external quality assurance program for the proposed test given the characteristics of HDV RNA assays such as multiple manual steps in extraction, and high genetic variability among genotypes which may lead to an underestimation of viral load.

The ESCs noted that concordance of the proposed HDV RNA PCR test (developed by VIDRL) compared to the clinical utility standard (Robogene® RNA quantification kit) was informed by one study, which found that **redacted**. The ESCs noted that a separate systematic review and meta-analysis of diagnostic studies¹⁶ showed an AUC (Area Under the Curve) of 0.95 indicating that different assays have similar test performance.

The prognostic value of a baseline positive HDV RNA PCR test was supported by seven studies, however all studies were low quality with retrospective cohort design, were subject to a high risk of bias (particularly selection bias and multiple confounders) and only examined the relationship between baseline HDV RNA levels and clinical outcomes. No studies provided evidence to support the prognostic value of a reduction in HDV viraemia by 2 log₁₀. The generalisability of the evidence was also uncertain as no Australian studies were included.

While two studies were identified as relevant to evidence for changes in clinical decision making only one of these studies was directly relevant to providing evidence that HDV RNA PCR test results lead to changes in clinical decision making and this study¹⁷ had 15 patients. The other study¹⁸ noted that 1 out of 114 patients treated with bulevirtide stopped therapy but did not state if this related to the results of HDV RNA PCR testing. However, despite this lack of evidence the pre-ESC response noted that regular monitoring of viral load levels on treatment is consistent with the recent European Association for the Study of the Liver (EASL) (2023) international treatment Hepatitis D virus guidelines.

The ESCs noted two concerns from the Commentary that suggested that the claim of codependency between the HDV RNA test and bulevirtide treatment was not properly established. The first concern was that the submission had not addressed how it would establish the chronicity of detectable HDV RNA to determine eligibility for bulevirtide. However, as noted previously, the ESCs agreed with PASC that there would be no need to establish whether a patient had chronic HDV infection as nearly all identified cases would be chronic and the likelihood of detecting an acute HDV infection would be low – therefore the ESCs considered that this was not a reason for concluding that codependency had not been established. The second concern, which the ESCs considered more compelling, was that the submission did not clearly detail how HDV RNA PCR testing would be used to monitor the response to bulevirtide and how

¹⁶ Chen, S., et al. (2023). "Performance of Hepatitis Delta Virus (HDV) RNA Testing for the Diagnosis of Active HDV Infection: Systematic Review and Meta-analysis." *J Clin Transl Hepatol* 11(6): 1368-1376.

¹⁷ Binter T, et al. (2021). "Efficacy of long-term treatment of chronic hepatitis D patients with bulevirtide - results of a "real world" study." *Hepatology* (Baltimore, Md);74:420A-1A.

¹⁸ Dietz-Fricke C, et al (2023). " Treating hepatitis D with bulevirtide - Real-world experience from 114 patients." *JHEP Rep.* Apr;5(4):100686.

this would affect decision-making about ongoing bulevirtide use. Specifically, the ESCs noted that it was unclear from the clinical criteria how frequently the presence or absence of detectable HDV RNA would impact on management as undetectable HDV RNA was not considered a reason to stop therapy (particularly considering the risk of rebound viraemia). The ESCs considered that alternatively, quantitative HDV RNA PCR testing may be useful in determining which patients are not responding to treatment (due to insufficient reduction in levels of HDV RNA detected), which may influence decisions on whether bulevirtide should be discontinued. The ESCs noted that MSAC may wish to consider whether codependency could be better justified with qualitative testing, if it is concluded that undetectable viral load is of relevance to eligibility for treatment in the first place.

The ESC noted that patients entered the economic model at the point of treatment. The ESCs noted that this meant that the model lacked a decision tree prior to treatment to capture all test results (true positives, false positives, true negatives, false negatives), and considered it introduced an element of structural uncertainty into the model results.

The ESCs considered that the omission of a decision tree may be reasonable given that it is unlikely that there would be sufficient direct evidence available to populate the missing branches of the decision tree (for false positive and false negative results), but this did not mean accepting the contention of the pre-ESC response that **redacted**. The ESCs considered that accepting this omission as reasonable (given the lack of direct evidence) meant the per patient cost applied for eligibility testing at model entry (of **redacted** RNA tests) needs further scrutiny, and may need to be increased to better reflect testing (and re-testing) pathways in clinical practice.

The ESCs noted that the Commentary had applied sensitivity testing to the corrected base case assumption of 54.4% positivity rate for HDV RNA (by applying a lower bound of 46% and an upper bound of 65.9%) and found that this made almost no change to the ICER.

The ESCs noted the limited evidence linking monitoring tests with clinical utility, but considered that this link was assumed in the economic modelling because the only modelled change in management due to inclusion of HDV RNA monitoring was cessation of treatment in non-responders at week 96, despite six monthly monitoring being included as a cost in the model. However, the ESCs considered that this had been satisfactorily addressed by the pre-ESC response's argument that the proposed monitoring of treatment effectiveness had value more in terms of prognostic value rather than change in management.

The ESCs considered that there may be benefits of testing independent of treatment given the prognostic information about a patient's HDV that RNA testing may provide, and that these could be explored in alternate scenarios of test and treatment provision. The ESCs considered prognostic value of this testing could be, for example, because patients with chronic Hepatitis B (CHB) have a higher risk of adverse liver related outcomes if they have concomitant HDV rather than HBV mono-infection. The ESCs noted that the pre-ESC response maintained that MSAC consideration should be limited to the use of HDV RNA PCR testing for the purpose of determining eligibility and responsiveness to bulevirtide, and any additional 'public health' considerations regarding uses of HDV RNA testing were "out of scope". The ESCs did not accept this contention as reasonable, because it contradicted the applicant's own position that HDV RNA PCR testing could provide useful prognostic information regardless of treatment status.

On the utilisation estimates and financial modelling, the ESCs noted that this relied on an epidemiological approach for estimating the number of HDV RNA PCR tests, which it considered was reasonable. The ESCs noted that the submission had estimated a net cost to the MBS of \$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6 while the Commentary's revised estimates were a net cost to the MBS of \$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6. The ESCs noted the Commentary's conclusion that there were errors in calculations that may have substantially over-estimated the use of HDV RNA PCR testing in the submission, and

that the pre-ESC response had accepted the Commentary's revisions. On the other hand, if HDV RNA testing were to be made pathologist determinable, the ESCs considered the Commentary revisions would then likely have under-estimated the use of HDV RNA PCR testing. The ESCs considered that if it was decided that HDV RNA PCR testing should not be made pathologist determinable, then the Commentary revisions are likely to be more reasonable although neither the submission nor the Commentary estimates had accounted for the possibility of repeat testing in patients with previous negative test results. In addition, the ESCs considered another area of uncertainty around the financial estimates was the duration of treatment, which would have implications for the total number of monitoring tests per patient.

The ESCs noted that the financial estimates had only considered the number of chronic Hepatitis B patients currently engaged in care and did not account for a potential increase in Hepatitis B patients seeking care due to the availability of Hepatitis D treatment if bulevirtide were PBS-listed. The ESCs noted that the pre-ESC response argued that an increase was unlikely because, despite the availability of highly effective treatment for chronic Hepatitis B on the PBS for 10-15 years, the proportion of Hepatitis B patients engaged in care has not increased substantially over time. The ESCs considered this was reasonable.

17. Applicant comments on MSAC's Public Summary Document

Gilead Sciences thanks the organisations who provided input through the consultation process and will continue to work with the MSAC to provide MBS access to the HDV RNA PCR test in Australia.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)