MSAC Application 1708.1

Hepatitis Delta Virus (HDV) RNA PCR testing to determine eligibility and treatment for PBS-subsidised bulevirtide (HEPCLUDEX) for treatment of HDV

PICO Set

Population

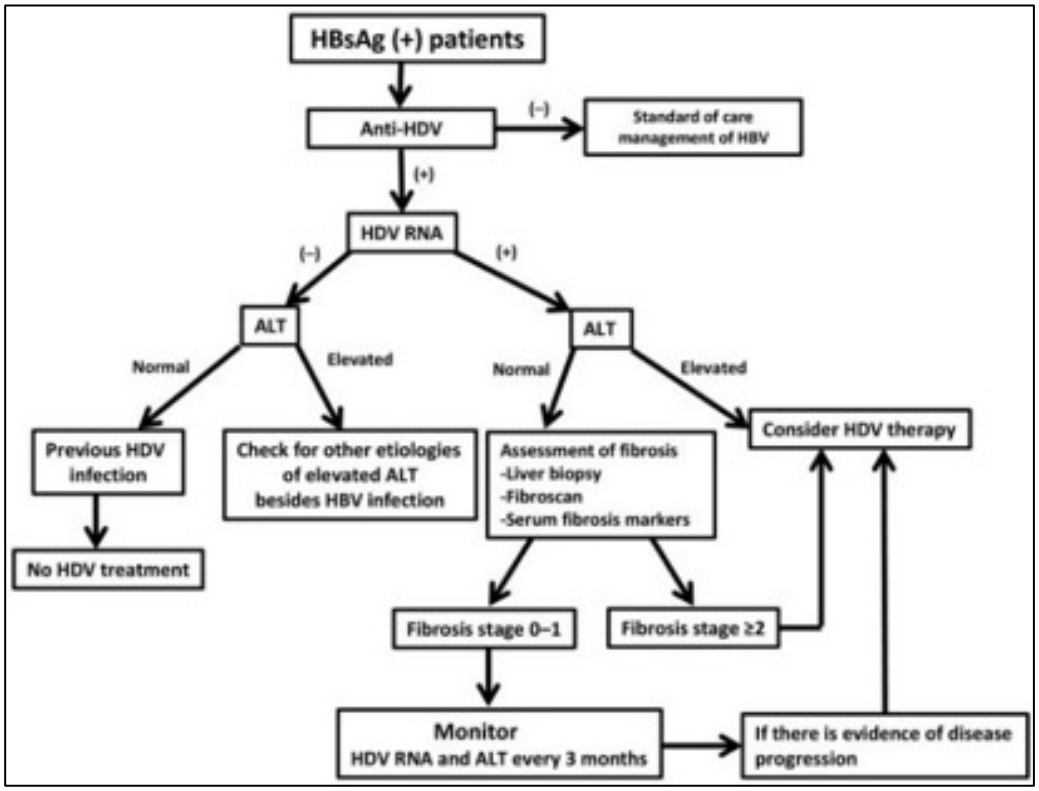
Describe the population in which the proposed health technology is intended to be used:
Hepatitis delta virus (HDV) is a rare and unique blood-borne virus that occurs in people infected with the hepatitis B virus (HBV) and is transmitted by exposure to contaminated blood or body fluids. HDV is reliant on HBV surface antigens (HBsAg) to infect human hepatocytes and to undergo viral assembly and transmission and therefore is only found either as a co-infection or as a super infection in patients with HBV infection. HDV infection causes hepatitis D, a form of viral hepatitis that is typically severe, rapidly progresses to cirrhosis, and is associated with increased risk of hepatocellular carcinoma (HCC) compared to HBV mono-infection. Liver cirrhosis and cancer occur on average earlier in HBV/HDV co-infection and the 5-year mortality of co-infected individuals is twice that of HBV mono-infection (Cornberg et al. 2020[1]). Chronic HDV infection has been described to cause cirrhosis and HCC with annual rates of 4% and 2.7%, respectively (Romeo et al. 2009[2]). There is currently no pharmacological standard of care for patients with HDV.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:
Proactive diagnosis and management of hepatitis D in people with hepatitis B is essential to mitigate or delay the elevated risk of cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC). Australian guidelines recommend that people with hepatitis D be referred to specialist care, due to the increased risk of poor outcomes and need for specialised treatment decisions compared to hepatitis B alone.

Per the Gastroenterological Society of Australia (GESA) 2009–10 chronic hepatitis B (CHB) guidelines, the principal goal of chronic hepatitis D (CHD) treatment is to prevent or delay development of the complications of cirrhosis and HCC by achieving undetectable HDV RNA per PCR, and normalisation of alanine aminotransferase (ALT; elevated ALT levels indicate liver injury).

[1] Cornberg M, et al. J Hepatol. 2020 Mar;72:539-57. doi: 10.1016/j.jhep.2019.11.003. Epub 2019 Nov 12.
[2] Romeo, R., et al., A 28-year study of the course of hepatitis delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology, 2009. 136(5): p. 1629-38.

Diagnosis and management flow for Hepatitis D



Source: Best international practice flow chart for diagnosis and treatment of hepatitis D. Sourced from Shah et al. 2019. ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; RNA, ribonucleic acid.

Provide a rationale for the specifics of the eligible population:
As above.

Are there any prerequisite tests?
Yes

Are the prerequisite tests MBS funded?
Yes

Provide details to fund the prerequisite tests:
anti-HDV antibody testing (MBS Items 69384, 69475, 69481). If positive, a HDV RNA PCR test (requested test) should be ordered.

Intervention

Name of the proposed health technology:
HDV RNA PCR Test

Describe the key components and clinical steps involved in delivering the proposed health technology:
Redacted

Identify how the proposed technology achieves the intended patient outcomes:
Used to diagnose chronic hepatitis delta (CHD) to determine eligibility to initiate treatment with HEPCLUDEX and assess clinical benefit with ongoing therapy.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
Provide a response if you answered 'Yes' to the question above

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes

Provide details and explain:
In Australia, only VIDRL is currently providing the proposed medical service, thus all samples collected nationally will need to be forwarded to VIDRL, Victoria for processing.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
Pathologists, in particular VIRDL.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
Not applicable and the proposed medical service could not be delegated or referred to another professional for delivery.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
If applicable, provide a description of any related health professionals here

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:
VIDRL perform annual quality assurance checks and have NATA accreditation for the HDV RNA PCR test.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☒ Laboratory
- ☐ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

Specify further details here

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:
Provide a response if you answered 'No' to the question above

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:
Test: No HDV RNA testing, i.e., no Medicare Benefits Schedule (MBS) item and no reference to HEPCLUDEX.

Drug: There is currently no pharmacological standard of care for patients with HDV.

List any existing MBS item numbers that are relevant for the nominated comparators:
Specify MBS item numbers here

Provide a rationale for why this is a comparator:
No HDV RNA testing, i.e., no Medicare Benefits Schedule (MBS) item and no reference to HEPCLUDEX

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?
☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☐ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☐ Health benefits
☐ Health harms
☐ Resources
☒ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Clinical Effectiveness Outcomes:

Combined response: Undetectable (<LoD) hepatitis Delta virus ribonucleic acid (HDV RNA) OR decrease by ≥ 2 log10 IU/ml from baseline AND with ALT normalization

Safety Outcomes:

Incidence of adverse events

Adverse events in non-cirrhotic and cirrhotic patients with compensated liver disease

Impact on patients of false positive and false negative test results

Test related

Diagnostic accuracy

Prognostic accuracy

Change in clinical management

Test turn-around time

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):
Self-funded by patients.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	
Category number	P3 – Microbiology
Category description	Pathology service
Proposed item descriptor	Quantitation of Hepatitis D viral RNA load in plasma or serum in: (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 antiviral 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.
Proposed MBS fee	$152.10 Benefit: 75% = $114.10 85% = $129.30
Indicate the overall cost per patient of providing the proposed health technology	The anticipated cost is $152.10 which is equivalent to Hepatitis B viral DNA testing (MBS item 69483).
Please specify any anticipated out of pocket expenses	Nil

Provide any further details and explain	Provide further details here

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
Current clinical management algorithm in **black**, plus red box for HDV RNA PCR test, reflects no funded HDV RNA PCR test of HEPCLUDEX for the treatment of CHD. Currently, patients pay out of pocket for HDV RNA PCR test following positive anti-HDV antibody test result. However, there is no treatment indicated to treat CHD in Australia (i.e., additional red boxes are not relevant for current management algorithm).

See diagram below.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
The proposed clinical management pathway (algorithm) would follow the same pathway. The difference is that the red boxes highlighting the HDV RNA test (and HEPCLUDEX) would be reimbursed through the MBS and PBS, respectively, rather than the HDV RNA PCR test not reimbursed and at a "private" cost to patients.

See diagram below.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
None

Explain what other healthcare resources are used in conjunction with the comparator health technology:
None

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
Nil

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
The proposed clinical management pathway (algorithm) would follow the same pathway. The difference is that the red boxes highlighting the HDV RNA test (and HEPCLUDEX) would be reimbursed through the MBS and PBS, respectively, rather than the HDV RNA PCR test not reimbursed and at a "private" cost to patients.

See diagram below.

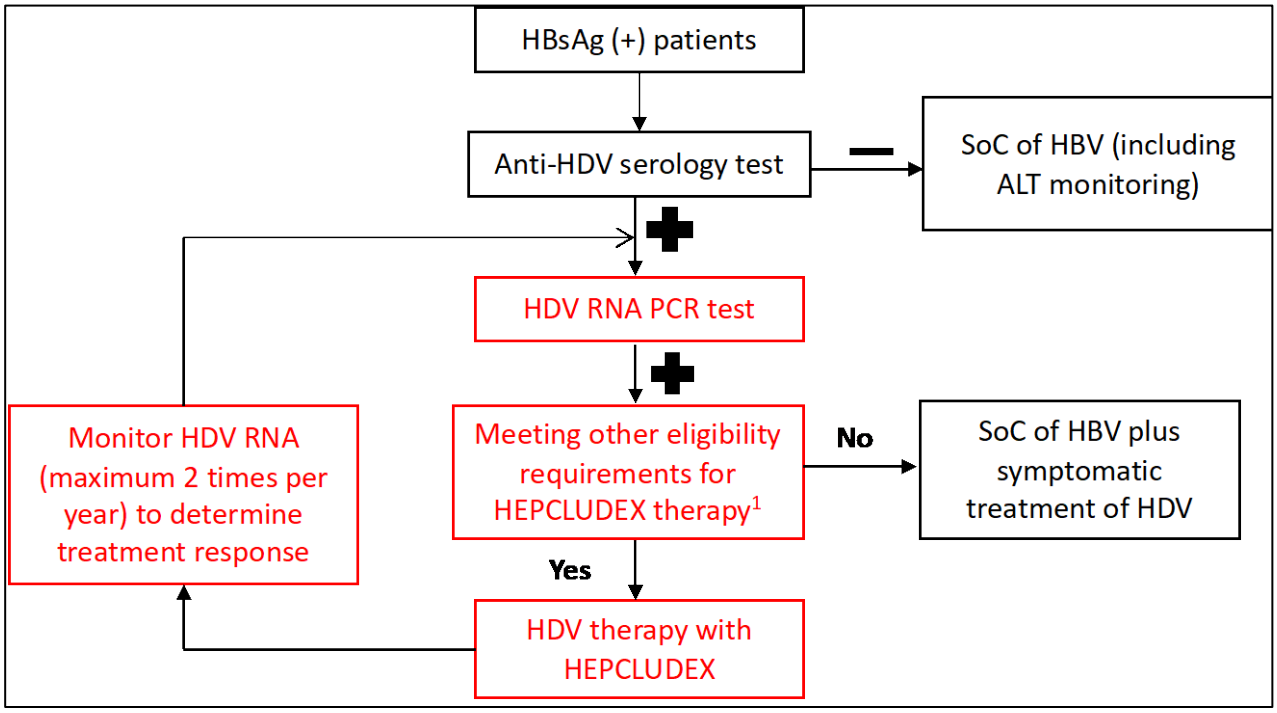
Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
The proposed clinical management pathway (algorithm) would follow the same pathway. The difference is that the red boxes highlighting the HDV RNA test (and HEPCLUDEX) would be reimbursed through the MBS and PBS, respectively, rather than the HDV RNA PCR test not reimbursed and at a "private" cost to patients.

See diagram below.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
Nil

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Proposed clinical management of Hepatitis D with HDV RNA PCR testing on the MBS and HEPCLUDEX on the PBS



Abbreviations: ALT, Alanine Aminotransferase; HBsAg, Hepatitis B Surface Antigen; HBV, Hepatitis V Virus; HDV, Hepatitis D virus; MBS, Medical Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; PCR, Polymerase Chain Reaction; RNA, Ribonucleic Acid; SoC, Standard of Care
Source: Application 1708 Ratified PICO and advice from local Hepatitis D experts.
Note: Management of HBV is not impacted by the presence of HDV and/or the treatment of chronic HDV with HEPCLUDEX (bulevirtide)
Note: If undetectable following first HDV RNA test, patients will continue SoC for HBV and may be retested if suspected of having CHD
Note: patients with detectable HDV RNA via PCR who do not meet other eligibility requirements for HEPCLUDEX may meet these criteria in the future and become eligible for treatment on the PBS

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?
☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
The overall clinical claim is one of superiority of HDV RNA PCR testing compares with no HDV RNA PCR testing.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
There is no comparator test.

Identify how the proposed technology achieves the intended patient outcomes:
Quantification of HDV RNA viral load to determine CHD diagnosis and, if treated with HEPCLUDEX, assessment of clinical benefit for ongoing therapy.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? No

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:
Quantification of HDV RNA viral load to determine CHD diagnosis and, if treated with HEPCLUDEX, assessment of clinical benefit for ongoing therapy.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?
☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
MBS listing HDV RNA PCR testing is an addition of a test which is not currently available on the MBS.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

Provide your response here

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Retrospective cohort study	A regular screening for hepatitis delta virus among chronic hepatitis B carriers improves the diagnostic of this infection and of subsequent cirrhosis development	Between January 2014 and October 2021, we annually tested all chronic HBs Ag-positive patients for HDV antibody (HDV Ab). Each HDV Ab positive patient underwent annually repeated elastometry. Patients with detectable HDV RNA levels (group 1) were compared to those with undetectable HDV RNA (group 2).	https://doi.org:10.1002/ueg2.12564	2024

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
2.	Observational study	Determinants of worse liver-related outcome according to HDV infection among HBsAg positive persons living with HIV: Data from the ICONA cohort.	People living with HIV (PLWH) from Italian Foundation cohort Naïve antiretrovirals (ICONA) with available HBsAg and HDV Ab were enrolled. HBsAg, HDV Ab, HDV-RNA and HDV genotypes were tested. Primary end-point: time from first HDV screening to Severe Liver Related Events (SLRE: decompensated cirrhosis, liver transplantation, HCC). Fine-grey regression models were used to evaluate the association of HDV Ab, HDV-RNA, HDV/HCV coinfection, CD4 nadir and outcome. Secondary end-points: time to SLRE or death; HDV Ab and HDV-RNA prevalence.	https://doi.org:10.1111/liv.15804	2024

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Retrospective Multicenter Registry	Characterizing Hepatitis Delta in Spain and the gaps in its management.	Retrospective data from anti-HDV positive patients with active follow-up between 2021 and 2023 were collected within a national registry within the Spanish Association for the Study of the Liver (AEEH) in a RedCap database. Patients with history of liver transplantation were excluded. All patients had at least 1 year of follow-up. Data on epidemiological characteristics (age, sex, country of origin, transmission risk factors, other viral coinfections) were collected. HBV status (HBsAg, HBeAg)	https://doi.org:10.1016/j.gastrohep.2024.502222	2024

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Randomised controlled trial	A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta (MYR301)	The planned 150 patients were randomised across 17 sites in Europe and USA. Patients were assessed for eligibility to enter the study during a 4-week screening period and eligible patients were randomised at Visit 1 in a 1:1:1 ratio, with stratification for the presence of liver cirrhosis (no/yes) to receive treatment as follows: •Arm A: Delayed HEPCLUDEX 10 mg/day for 96 weeks after an observational period of 48 weeks (i.e., no treatment for 48 weeks, followed by 48 weeks treatment with HEPCLUDEX 10mg/day), •Arm B: Immediate treatment with HEPCLUDEX 2 mg/day for 144 weeks, or •Arm C: Immediate treatment with HEPCLUDEX 10 mg/day for 144 weeks.	https://clinicaltrials.gov/study/NCT03852719	Week 144 datacut yet to be published.