

Reimbursement Recommendation

Bulevirtide (Hepcludex)

Indication: For the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease

Sponsor: Gilead Sciences Canada, Inc.

Final recommendation: Reimburse with conditions

Correction note: This report was initially published in January 2026 and subsequently revised in June 2026 to correct albumin levels for patients eligible for coverage.

Summary

What Is the Reimbursement Recommendation for Hepcludex?

Canada's Drug Agency (CDA-AMC) recommends that Hepcludex should be reimbursed by public drug plans for the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease if certain conditions are met.

Which Patients Are Eligible for Coverage?

Hepcludex should only be covered to treat adult patients with compensated liver disease and confirmed chronic HDV infection, evidenced by a positive serum anti-HDV antibody result and detectable HDV ribonucleic acid (RNA) by polymerase chain reaction (PCR) within the past 6 months. These patients must also have elevated liver enzymes (alanine aminotransferase [ALT] levels between 1 and 10 times the upper limit of normal) and a blood albumin level greater than 28 g/L. Patients who do not meet the eligibility criteria include those with decompensated liver disease or a total bilirubin level of 34.2 µmol/L or higher.

What Are the Conditions for Reimbursement?

Hepcludex should only be reimbursed if the patient is under the care of a hepatologist or infectious disease specialist with experience in the treatment of viral hepatitis and if the cost of Hepcludex is reduced. To continue receiving Hepcludex, a patient's HDV infection must respond to treatment within the first 48 weeks. This means the HDV RNA level is no longer detectable in the blood or has dropped by at least 100 times compared to the start of treatment. After this, the need for ongoing treatment should be checked every 48 weeks. The patient's liver enzyme levels should continue to be monitored by a specialist. Hepcludex should not be reimbursed for patients when used concurrently with pegylated interferon (PEG-IFN) therapy for chronic HDV infection.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that 48 weeks of treatment with Hepcludex likely results in an improvement in the surrogate outcomes of combined response (virologic response [undetectable HDV RNA or a reduction of at least 100 times from baseline] and ALT normalization), virologic response, and liver stiffness.
- Hepcludex meets some patient needs because it is the first approved treatment that is likely effective in suppressing the virus and has no major safety concerns.

Summary

- Based on the CDA-AMC assessment of the health economic evidence, Hepcludex does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Hepcludex is estimated to cost the public drug plans approximately \$45 million over the next 3 years.

Additional Information

What Is HDV Infection?

Hepatitis D is a rare and serious liver infection caused by the hepatitis D virus. The virus can only infect liver cells and multiply if the hepatitis B virus (HBV) is also present. Common symptoms of HDV infection include fever, tiredness, loss of appetite, nausea or vomiting, stomach pain, dark urine, pale stools, joint pain, and yellowing of the skin or eyes. If left untreated, chronic HDV infection could lead to complications such as scarring of the liver or liver cancer.

Unmet Needs in HDV Infection

Hepcludex is currently the only approved treatment for adults with chronic HDV infection who have compensated liver disease. There is a need for therapies that reduce the virus level, improve liver function, and lower the risk of serious liver complications.

How Much Does Hepcludex Cost?

Treatment with Hepcludex is expected to cost approximately \$159,641 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that bulevirtide be reimbursed for the treatment of chronic HDV infection in adults with compensated liver disease only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

HDV infection is rare, serious, progresses rapidly, and associated with significant morbidity and mortality. There are currently no available treatments in Canada for chronic HDV infection in adults with compensated liver disease. Patients typically receive best supportive care, consisting of nucleos(t)ide analogue therapy, which is effective against HBV coinfection but ineffective against HDV infection. Considering this, CDEC acknowledged that there is a significant unmet need among patients with HDV infection for therapies that mitigate disease progression.

One ongoing phase III, randomized, open-label, parallel-group, multicentre study (MYR301; N = 150) demonstrated with moderate certainty that, compared with delayed treatment with bulevirtide 10 mg following a 48-week observational period, treatment with bulevirtide 2 mg likely results in an improvement in the surrogate outcomes of combined response (virologic response and ALT normalization) (between-group difference = 42.9%; 96% confidence interval [CI], 27.0% to 58.5%) and virologic response (undetectable HDV RNA or a reduction of at least 2 log₁₀ from baseline) (between-group difference = 69.5%; 96% CI, 54.1% to 81.9%) at week 48. CDEC acknowledged input from clinical experts that the magnitude of improvement is clinically meaningful; however, the committee noted some uncertainty regarding whether these end points could reliably predict longer-term clinical outcomes important to patients and clinicians. Comparative evidence versus delayed treatment from the MYR301 study demonstrated with moderate certainty that treatment with bulevirtide 2 mg likely results in an improvement in the liver stiffness surrogate outcome at week 48 (between-group difference in least squares [LS] means of change = -3.93 kPa; 95% CI, -6.23 kPa to -1.63 kPa). Although the results from the MYR301 study suggested no clinically important difference in the change from baseline in health-related quality of life (HRQoL) at week 48 compared to delayed treatment, CDEC was unable to draw definitive conclusions on the effect of bulevirtide 2 mg on patients' HRQoL due to limitations in the available evidence.

Patients identified a need for accessible and effective treatment options for chronic HDV infection that have few side effects, reduce the frequency of clinic visits for injections and monitoring, improve HRQoL by reducing disease symptoms and slowing disease progression, and ultimately reduce the need for a liver transplant. CDEC noted that although there is no evidence that bulevirtide would slow disease progression and reduce the need for a liver transplant, bulevirtide may potentially address some unmet needs identified by patients because it is the only currently available treatment for chronic HDV infection in Canada, has shown efficacy in improving surrogate end points, and appears to have no major safety concerns. Furthermore, bulevirtide may be administered in an outpatient setting; this may be more convenient for some patients, although specialist oversight of disease management remains essential.

Using the sponsor-submitted price for bulevirtide and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for bulevirtide is \$383,943 per quality-adjusted life-year (QALY) compared with best supportive care. At this ICER, bulevirtide is not cost-effective at a willingness-to-pay (WTP) threshold of \$50,000 per QALY for the treatment of chronic HDV infection in adults with compensated liver disease. A price reduction is required for bulevirtide to be considered cost-effective at a WTP threshold of \$50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with bulevirtide should be reimbursed when initiated in adult patients with chronic HDV infection who have all the following: 1.1. a positive serum anti-HDV antibody result 1.2. a positive PCR result for serum or plasma HDV RNA within the past 6 months 1.3. ALT level ≥ 1 ULN but < 10 ULN 1.4. serum albumin > 28 g/L.	The evidence from the MYR301 trial supported the efficacy and safety of treatment with bulevirtide for patients with the outlined characteristics.	The MYR301 trial did not include patients older than 65 years or those with advanced liver disease but normal ALT levels. CDEC considered clinical expert input and noted that it is appropriate to leave the determination of eligibility for bulevirtide in these patients to the clinical judgment of the treating physician. Patients and treating physicians should be aware of a potential risk of disease exacerbation upon treatment discontinuation.
2. Treatment with bulevirtide should not be reimbursed when initiated in patients who had: 2.1. decompensated liver disease 2.2. total bilirubin ≥ 34.2 $\mu\text{mol/L}$.	There is a lack of evidence that bulevirtide would benefit patients with the outlined characteristics.	In the MYR301 trial, decompensated liver disease was defined as a Child-Pugh score > 7 .
Renewal		
3. The maximum duration of initial authorization is 48 weeks. For renewal after initial authorization, a patient must have either an undetectable HDV RNA level or a decrease of $\geq 2 \log_{10}$ IU/mL in HDV RNA from baseline. Subsequent renewal should be assessed every 48 weeks. ALT levels should be monitored by a specialist as part of the assessment for ongoing clinical benefit.	The MYR301 trial assessed the primary end point of combined response and the key secondary end point at week 48. There appeared to be an increase in the proportion of patients who had ALT normalization with bulevirtide treatment beyond week 48 (51.0% at week 48 and 63.3% at week 96). Although combined response was a composite end point that included ALT normalization, the clinical experts consulted by CDA-AMC as well as the clinician groups indicated that ALT normalization may not be achievable in some patients for reasons unrelated to HDV infection. CDEC noted that ongoing monitoring of ALT levels should be	The clinical experts consulted by CDA-AMC noted that regular monitoring of other clinical parameters, such as an annual fibrosis assessment (e.g., FibroScan) and ultrasound every 6 months for hepatocellular carcinoma screening, is important in assessing response to treatment.

Reimbursement condition	Reason	Implementation guidance
	considered in evaluating treatment response and that clinical judgment should guide decision-making.	
Discontinuation		
4. Treatment with bulevirtide should be discontinued if any of the following occurs: 4.1. liver transplant 4.2. hepatocellular carcinoma.	There is no evidence to support a beneficial effect with continued use of bulevirtide treatment following liver transplant or hepatocellular carcinoma. The clinical experts noted to CDEC that occurrence of these clinical events would lead to discontinuation of bulevirtide treatment in clinical practice.	The optimal duration of bulevirtide treatment is unclear. The clinical experts suggested that treatment discontinuation could be considered in patients who have undetectable HDV RNA levels for 96 weeks. The experts also noted that if there is a relapse, treatment may be reinitiated. In the absence of evidence supporting this treatment approach, CDEC considered it reasonable to leave the decision to the clinical judgment of the treating physician.
Prescribing		
5. The patient must be under the care of a hepatologist or infectious disease specialist with experience in the treatment of viral hepatitis.	Accurate diagnosis and management of patients with chronic HDV infection are important to ensure that bulevirtide is prescribed to the appropriate patients.	—
6. Treatment with bulevirtide should not be reimbursed in combination with pegylated interferon therapy for chronic HDV infection.	There is no evidence to demonstrate a beneficial effect of bulevirtide treatment when used in combination with pegylated interferon for the treatment of chronic HDV infection.	—
Pricing		
7. A reduction in price.	The ICER for bulevirtide is \$383,943 per QALY gained when compared with best supportive care. The cost-effectiveness is uncertain given the lack of evidence to support model assumptions regarding duration of benefit and uncertainties to the optimal treatment duration. Price reductions of approximately 80% would be required for bulevirtide to achieve an ICER of \$50,000 per QALY compared to best supportive care although higher price reductions may be required due to the uncertainties. Price reductions for different thresholds are available in Appendix 4 in the Pharmacoeconomic Review report.	—

ALT = alanine aminotransferase; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; HDV = hepatitis D virus; ICER = incremental cost-effectiveness ratio; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; RNA = ribonucleic acid; ULN = upper limit of normal.

Discussion Points

- **Reconsideration request:** The sponsor and the drug plans requested a minor reconsideration of the initial draft recommendation to reimburse bulevirtide with conditions for the treatment of chronic HDV infection in adults with compensated liver disease. During the minor reconsideration discussion, a CDEC subpanel discussed the issues raised by the sponsor and the drug plans in their request for reconsideration. The sponsor proposed changes to the initiation and renewal criteria. The drug plans sought clarification on the initiation and discontinuation criteria. CDEC also discussed feedback from clinician groups and the clinical experts consulted by CDA-AMC on the initial draft recommendation.
- **Significant unmet need:** CDEC deliberated on bulevirtide considering the criteria for significant unmet need that are described in the Procedures for CDA-AMC Reimbursement Reviews. CDEC acknowledged that HDV infection is a rare and rapidly progressing disease, which occurs as a coinfection with HBV and is associated with a significantly higher risk of cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC). CDEC noted there are currently no established consensus guidelines for the management and treatment of HDV infection in Canada. There are currently no effective treatments available in Canada. PEG-IFN is an off-label therapy that is no longer routinely used in clinical practice due to its significant adverse effects, a global shortage, and a lack of availability in Canada. Best supportive care consists of nucleos(t)ide analogues that are effective against HBV infection but have no efficacy against HDV infection. Considering the rarity and severity of the condition and the absence of effective treatments, CDEC concluded that the available evidence reasonably suggests that bulevirtide likely improves biochemical and virologic responses which, based on clinical expert input, could potentially be predictive of a delay in disease progression.
- **Certainty of evidence:** CDEC noted that the review focused on between-group comparisons up to week 48, specifically for bulevirtide 2 mg, which is in line with the proposed Health Canada indication. The use of bulevirtide 10 mg as a comparator beyond 48 weeks was considered irrelevant because it is not an approved dosage by Health Canada and does not align with clinical practice. CDEC noted that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the evidence from the pivotal MYR301 trial demonstrated with moderate certainty that, compared with delayed treatment, bulevirtide 2 mg likely results in a clinically meaningful increase in the proportion of patients with combined response and virologic response at week 48, and likely results in improvement in liver stiffness at week 48. The certainty of evidence was considered moderate due to imprecision, including potential for treatment overestimation due to the small sample size. No definitive conclusion can be drawn regarding the effects of bulevirtide treatment on HRQoL and serious adverse events (AEs) due to the potential bias from assessor knowledge of treatment assignment and imprecision in the data, making the direction of effects unclear.
- **Indirect evidence:** The results of the sponsor-submitted indirect treatment comparison (ITC) suggested that, compared with PEG-IFN and best supportive care (nucleos[t]ide analogues), bulevirtide may offer potential benefit in achieving combined response at week 48. However, the interpretation of the ITC is limited by several factors, including methodological limitations, between-

trial heterogeneity, a sparse network, and small sample sizes, which preclude definitive conclusions on the comparative efficacy and harms of bulevirtide.

- **Studies addressing gaps:** Two additional studies evaluated bulevirtide. One compared bulevirtide 2 mg to PEG-IFN in patients with HDV infection (MYR203) and one evaluated bulevirtide treatment (up to 96 weeks) in patients with HDV-related cirrhosis (SAVE-D). However, the limited sample size and exploratory design of the MYR203 study and the single-arm design of the SAVE-D study limited the ability to assess comparative effectiveness and causality. Key limitations of both studies include a risk of bias due to missing outcome data that contributes to uncertainty in the effect estimates, limited generalizability to patients in Canada, and the lack of reporting of HRQoL outcomes, which patients identified as important.
- **Biochemical response and virologic response as surrogate end points for long-term clinical outcomes:** There is no comparative evidence beyond week 48 for bulevirtide versus relevant comparators. CDEC noted that, in the MYR301 trial, clinically meaningful outcomes for patients, such as progression to cirrhosis, decompensated liver disease, and the need for a liver transplant, were not adequately evaluated or the results were not available at the time of this review. Biochemical response and virologic response were used as surrogate markers in clinical trials to predict the benefit of treatment in the absence of data on these long-term hard clinical outcomes. Evidence supporting the surrogacy of these end points in the treatment of HDV infection was not submitted. The clinical experts consulted by CDA-AMC noted that these are standard measures in clinical trials and may serve as meaningful indicators of disease activity and progression. CDEC noted that longer-term data are necessary to assess the efficacy of bulevirtide on clinical outcomes.
- **Initiation of treatment:** During the reconsideration meeting, the CDEC subpanel discussed whether it is appropriate to require a platelet count of at least 60,000 cells/mm³ and a positive PCR result for HDV RNA within the past 6 months for initial reimbursement of bulevirtide. These issues were raised by the sponsor. The subpanel discussed that the MYR301 trial did not include patients with a platelet count of less than 60,000 cells/mm³ and no evidence for bulevirtide treatment in this population was reviewed by CDA-AMC. The generalizability of trial findings to these patients is unclear; the clinical experts consulted by CDA-AMC suggested that the effects of bulevirtide may be different in these patients compared to the trial population. The clinical experts also indicated that although a low platelet count may signal liver dysfunction, it may not reliably reflect the level of dysfunction or decompensation. They noted that clinicians should rely on other signs of decompensation when assessing treatment eligibility, such as ascites, encephalopathy, or variceal bleeding. Based on the clinical expert input, the subpanel agreed that removing the platelet count criterion was reasonable. Regarding HDV RNA confirmation, the subpanel noted that requiring PCR positivity within the past 6 months aligns with the MYR301 trial inclusion criteria. The subpanel also noted that this requirement helps avoid treating patients with acute HDV infection, who may recover spontaneously, thereby preventing unnecessary harm. This requirement also reflects the clinical expert input, which supported the need to document HDV RNA positivity within 6 months before starting therapy.

- Continuation of treatment:** During the reconsideration meeting, the CDEC subpanel discussed whether it is appropriate to require ALT normalization for the renewal of bulevirtide reimbursement, an issue raised by the sponsor and drug programs. The subpanel discussed that patients were allowed to continue treatment after biochemical and virologic responses in the MYR301 trial. The primary end point was combined response, defined as ALT normalization, plus either an undetectable HDV RNA level or a decrease of at least $2 \log_{10}$ IU/mL in HDV RNA from baseline at week 48. This aligned with the renewal criteria in the draft recommendation. The subpanel re-examined the submitted evidence and noted that the proportion of patients who had ALT normalization appeared to have increased with continued bulevirtide treatment over time. In clinical practice, ALT levels are monitored to assess liver function but may fluctuate due to factors other than disease progression from HDV infection. The subpanel discussed that some patients may still derive benefit from achieving virologic response despite having an elevated ALT level at 48 weeks and that continuing treatment could allow patients to maintain this benefit. Therefore, the subpanel considered it appropriate to allow the prescribing specialist to determine whether ongoing clinical benefit from bulevirtide treatment exists based on ALT levels.
- Discontinuation of treatment:** During the reconsideration meeting, the CDEC subpanel discussed the drug programs' request to clarify whether bulevirtide reimbursement should be discontinued in patients who require a liver transplant for reasons other than decompensated liver disease. There is limited evidence from the submission to guide treatment discontinuation. After considering clarifications from the clinical experts, the subpanel felt it was reasonable to discontinue bulevirtide reimbursement following liver transplant, regardless of the indication for transplantation. The subpanel discussed that there is a theoretical risk of HDV reinfection post-transplant, which may be mitigated by continued HBV prophylaxis. The subpanel noted that there is no evidence for reinitiating bulevirtide treatment if HDV infection recurs; however, allowing this approach at the discretion of the treating specialist may be appropriate.
- Challenges in diagnosing HDV infection:** Patients identified a need for enhanced early HDV infection diagnosis to facilitate timely treatment and prevent progression to severe liver disease. CDEC acknowledged that HDV testing is not systematically conducted among individuals with HBV infection. CDEC also acknowledged patient and clinician group input that it is important to increase health care provider education and reflex testing in provincial or local laboratories for individuals who test positive for hepatitis B surface antigen. CDEC acknowledged clinical expert input that HDV testing is primarily limited to hepatology specialists and performed opportunistically rather than as part of routine screening.
- Challenges in bulevirtide treatment:** CDEC discussed the challenges associated with bulevirtide treatment, which include the need for drug reconstitution, supply requirements, and associated costs, particularly given the chronic nature of the disease and the requirement for daily administration. CDEC noted that initiation and monitoring of bulevirtide treatment should be managed by clinicians experienced in treating viral hepatitis, recognizing that access to these specialists may be difficult,

particularly in rural areas, because of geographic limitations and the complexities of treatment, including daily injections and the need for patient counselling.

- **Economic considerations:** The committee discussed the economic evidence for bulevirtide and noted that bulevirtide was associated with incremental costs of \$1,297,909, 3.38 incremental QALYs and 4.01 incremental life-years compared with best supportive care. The incremental cost is driven by drug acquisition costs, which account for 89% of the total costs associated with bulevirtide treatment. The committee noted that the results of the analysis are highly uncertain because of the lack of evidence to support model assumptions regarding duration of benefits beyond 144 weeks and the optimal duration of treatment. The committee further expressed concern about the use of biochemical response and virologic response from the clinical trials to predict the impact on long-term hard clinical outcomes within the economic model. A higher price reduction may be required due to these uncertainties.

Background

Hepatitis D is a rare, severe, and progressive liver disease caused by HDV, an incomplete RNA virus that requires the HBV envelope to enter cells and replicate. HDV is considered the fastest progressing and most severe form of all viral hepatitis infections. HDV is a “satellite virus,” meaning it can only infect individuals with a concomitant HBV infection. Chronic HDV infection is defined as an infection lasting 6 months or longer. The likelihood of progression to chronic hepatitis depends on whether the HDV infection occurs as a coinfection with HBV or as a superinfection in a patient with pre-existing chronic HBV. Less than 5% of patients progress to a chronic HDV infection after coinfection; however, HDV infection does become chronic in more than 80% of individuals with HBV and HDV superinfection. A 2024 study from the Polaris Observatory found that the adjusted prevalence of HDV infection among the population with HBV infection in Canada is approximately 3.0%. Because the prevalence of chronic HBV infection in Canada is estimated at 0.66% and the HBV infection diagnosis rate is 70%, the calculated estimate of HDV infection prevalence in Canada is 0.020% to 0.032%, corresponding to 2.0 to 3.2 individuals per 10,000 population (including both chronic and acute HDV infection).

Key signs and symptoms of chronic HDV infection can range from nonspecific symptoms to rapidly progressing hepatitis. Symptoms may include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, clay-coloured bowel movements, joint pain, and jaundice. Chronic HDV infection usually exacerbates any pre-existing liver disease associated with HBV infection. Recovery is unlikely once infected, with the likelihood of recovery decreasing as the disease progresses. Only 35% of patients with acute HDV infection, and even fewer patients (9.96%) with chronic HDV infection, experience recovery. Without recovery at early stages of the disease, HDV infection is associated with an accelerated progression to fibrosis, early liver decompensation with cirrhosis, and increased risk of HCC, leading to greater liver-related mortality compared to HBV or hepatitis C virus (HCV) infections.

The indication under review for bulevirtide is for the treatment of chronic HDV infection in adults with compensated liver disease; the sponsor's submitted reimbursement request aligns with this indication. Bulevirtide is a synthesized lipopeptide derived from the HBV-L protein, consisting of 47-amino acids and N-terminally myristoylated. It acts as a potent, highly selective entry inhibitor of HDV. Bulevirtide is available as a powder for solution for injection, with the recommended dosage of 2 mg to be administered once daily by subcutaneous injection. The optimal treatment duration is unknown. Treatment should be continued as long as it is associated with clinical benefit.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, randomized, open-label, multicentre study in adults with chronic HDV infection and compensated liver disease; 1 ITC; and 2 additional studies addressing gaps in the evidence
- patients' perspectives gathered by 2 patient groups, Liver Canada and the BC Hepatitis Network
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with chronic HDV infection
- input from 1 clinician group, the Canadian Hepatitis B Network
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's and the public drug plans' request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received 1 joint patient input submission from 2 organizations: Liver Canada and the BC Hepatitis Network. Patient perspectives were gathered by conducting an online survey between February 21 and March 8, 2025, via social media. Survey respondents were 6 people with HDV infection and/or caring for someone with HDV infection living in British Columbia, Alberta, or Ontario. They ranged in age from 30s to 60s. The patient groups described how having a diagnosis of HDV infection significantly impacts patients' HRQoL and is associated with disease-specific symptoms, which include general physical and psychological symptoms. PEG-IFN is used off-label in Canada for the treatment of HDV infection. Patients who indicated they have experience with PEG-IFN highlighted that it is associated with intolerable side effects; frequent clinic visits for injections, including the need to travel to receive their injections; and frequent blood tests for monitoring purposes. The patient respondents indicated a preference for treatments that require fewer injections and blood tests. They described an important outcome as stabilization of their liver disease. This refers to slowing the progression to liver fibrosis, cirrhosis, or liver cancer; improving decompensation

events; and reducing the need for a liver transplant. According to the patient input received for this review, chronic HDV infection is most common among people who have recently immigrated to Canada, who face multiple barriers to timely diagnosis. Further, according to patient input, these individuals are less likely to be screened for viral hepatitis, face limited access to routine care, and are more likely to have fears and stigma surrounding hepatitis. These barriers combined place individuals at higher risk for late diagnosis and advanced viral hepatitis-related liver disease. Patient respondents identified reflex testing for HDV for individuals with HBV infection as an important unmet need.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted by CDA-AMC for this review identified significant unmet needs in the management of chronic HDV infection in Canada and emphasized the absence of approved or reimbursed therapies. The clinical experts indicated that although PEG-IFN was previously used off-label for the treatment of HDV infection, it is no longer used in clinical practice due to its poor tolerability, limited accessibility, and lack of feasibility for routine use. The clinical experts consulted emphasized that currently available therapies for HBV infection, including nucleos(t)ide analogues, are ineffective against HDV infection, which remains the primary driver of liver damage in individuals with coinfection. As a result, patients with HDV infection face progressive liver disease without access to an effective treatment option. The clinical experts highlighted the need for a targeted therapy to reduce HDV viral load, normalize ALT levels, potentially stabilize or improve liver fibrosis, and mitigate the risk of HCC and liver decompensation. This need is particularly urgent due to the aggressive nature of HDV infection and its associated risk of rapid progression to cirrhosis and HCC. The clinical experts noted that early initiation of bulevirtide is recommended to help mitigate the risk of progression to advanced liver disease. The clinical experts consulted stated that bulevirtide would be used in combination with nucleos(t)ide analogues, such as tenofovir or entecavir, which are used to manage the HBV coinfection but are ineffective against HDV. The clinical experts consulted by CDA-AMC identified individuals with compensated cirrhosis as the most in need of bulevirtide treatment but emphasized that all patients with chronic HDV infection require treatment due to the potential for rapid disease progression.

The clinical experts noted that the key outcomes used to determine response to treatment with bulevirtide include virologic response (i.e., undetectable HDV RNA or reduction in HDV RNA levels), biochemical response (i.e., normalization of ALT), and stabilization or improvement in liver fibrosis. According to the clinical experts consulted, long-term outcomes, such as improvements in portal hypertension, reduced progression to cirrhosis, and lower rates of HCC, would also be clinically impactful but were not captured in trials. The clinical experts consulted indicated that bulevirtide treatment should generally be discontinued in cases of progression to decompensated liver disease requiring transplant or the development of HCC requiring alternative therapy. However, they emphasized that treatment decisions for patients with decompensated liver disease and those with HCC should be made on a case-by-case basis because discontinuing HDV infection therapy in these individuals could potentially worsen their condition. The clinical experts noted that discontinuation can be considered in the event of severe adverse reactions, such

as allergy or significant injection site reactions, or if the patient is unable to adhere to the daily injectable regimen. The clinical experts indicated that the diagnosis, prescribing, and monitoring of bulevirtide be managed by clinicians with specialized expertise in hepatology or infectious diseases due to the complexity of HDV infection and the need for accurate interpretation of HDV RNA and ALT levels. The clinical experts also noted that the optimal duration of bulevirtide therapy remains uncertain for patients who show a slower response to treatment. According to the clinical experts consulted, underdiagnosis of HDV infection is a significant issue in practice, largely due to the limited availability of HDV RNA testing and lack of routine screening, which pose a barrier to timely treatment initiation. The clinical experts noted that systematic screening is lacking, particularly in individuals with HBV infection managed in primary care.

Clinician Group Input

Ten clinicians from the Canadian Hepatitis B Network provided input. The Canadian Hepatitis B Network is a collaborative organization of health care professionals and researchers from across Canada with an interest in advancing excellence in hepatitis B patient care, research, and education. The clinician group stated that there is an unmet medical need for improved therapies for HDV and HBV coinfection. Currently there are no treatments approved by Health Canada indicated for HDV infection. HDV causes the most severe form of viral hepatitis in humans. HDV requires the HBV surface (or envelope) protein in order to infect the liver. Thus, HDV can only infect people who also have HBV infection. Individuals can acquire HBV and HDV at the same time or HDV can superinfect a patient with underlying chronic HBV infection because of a shared route of transmission. The drug under review, bulevirtide, is a novel antiviral drug that specifically targets the binding of HDV (and HBV) to the liver-specific cell surface bile acid receptor. Based on input received from the clinician group, patients with HBV and HDV coinfection who have positive HDV RNA are most likely to respond to the drug under review.

Patients who have an HDV coinfection are at significant risk of liver disease and cirrhosis within 5 years, regardless of any disease characteristics. Patients best suited for treatment with the drug under review would be identified based on the clinical judgment of expert specialists in hepatology or infectious disease as well as HDV RNA testing. The clinician group highlighted that outcomes used in clinical practice are aligned with the outcomes typically used in clinical trials. A clinically meaningful response to treatment would be HDV RNA suppression, biochemical normalization, improvement in noninvasive fibrosis tests, and/or improvement in symptoms of liver disease decompensation (ascites, variceal bleeding). Based on input received from the clinician group, criteria for discontinuing treatment include failure to respond to therapy (HDV RNA decline and ALT normalization), disease progression, and limited lifespan. The clinician group expressed that the drug under review can be appropriately prescribed by a hepatology or infectious disease specialist in a specialty clinic setting.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The sponsor performed a systematic review with comparators noted to be PEG-IFN-alpha and best supportive care (nucleos[t]ide analogues). Three open-label RCTs were identified (MYR202, MYR203, MYR301). The MYR202 study used TDF (tenofovir) 245 mg as a comparator for a 48-week group, the MYR203 used PEG-IFN-alpha 180 mcg as a comparator. In MYR301 bulevirtide 2 mg was compared with delayed treatment with bulevirtide 10 mg after an observational period of 48 weeks. What is the most relevant comparator(s) in clinical practice?	According to the clinical experts consulted by CDA-AMC, there is currently no approved treatment for HDV infection in Canada. The clinical experts indicated that PEG-IFN and best supportive care alone (i.e., nucleos[t]ide analogues) may be considered as relatively appropriate comparators for bulevirtide. However, the clinical experts noted that although PEG-IFN can be used off-label to treat HDV infection, its use in clinical practice has become uncommon due to significant adverse effects, a global shortage, and limited availability in Canada. The clinical experts also noted that although nucleos(t)ide analogues are used to manage HBV infection, they have no direct antiviral activity against HDV infection. CDEC acknowledged the clinical experts' input.
There are no treatment options approved by Health Canada for treatment of CHD (chronic hepatitis D). Off-label PEG-IFN-alpha is not publicly funded across all jurisdictions. Those that do have criteria for coverage of hepatitis B, do not specifically refer to hepatitis D.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
HDV is known as a "satellite virus" requiring an envelope provided by HBV to enter host cells — this requiring concomitant HBV infection. It is assumed HDV enters hepatocytes through the same mechanism as HBV. In all patients, HBV infection should be managed simultaneously, as clinically appropriate. Diagnosis requires blood tests that include standard tests (i.e., LFTs) as well as tests that are available via the NML in Winnipeg. The sponsor is advising that access to the required lab tests is widely available across Canada. Is there a specific stage of fibrosis which would determine eligibility for treatment? This would be a helpful parameter for CDEC to identify and highlight. It is unclear if there would be excessive wait times for testing depending on location.	The clinical experts indicated that treatment initiation criteria based on stage 2 fibrosis, commonly used in HBV or HCV infection management, may not be appropriate for HDV infection. Given the more aggressive and rapidly progressive nature of HDV infection, the clinical experts emphasized the importance of earlier intervention to stop viral replication and prevent disease progression. CDEC acknowledged the clinical experts' input and noted that patients with decompensated liver disease would not be eligible for treatment as per the trial design of the MYR301 study.
As per the indication, patients must have chronic HDV (CHD) which, by definition, is a HDV infection lasting 6 months or longer. Would there be any circumstances where you would choose to treat HDV infection prior to the 6-month mark? The 3 trials included patients with detectable anti-HCV antibodies, while HCV RNA remained negative. The trials also excluded patients with HIV infection. In the case of patients having concomitant HDV and HCV (HCV RNA positive), how would the treatment approach	According to the clinical experts consulted by CDA-AMC, treatment for HDV infection may be initiated before the 6-month mark in patients with confirmed HDV RNA and elevated ALT. The infection is typically chronic by the time patients are evaluated, having often been present but undiagnosed. Considering that HDV infection is a rapidly progressive condition and that patients are managed by specialists with experience in treating viral hepatitis, CDEC noted that it would be appropriate to require only one HDV RNA positive result within the past 6 months for treatment initiation to enable timely access. According to the clinical experts, in patients who have HDV

Implementation issues	Response
differ? Would treatments targeting each virus be administered concurrently? How would the treatment approach differ in patients with both HDV and HIV? Study participants were restricted between the ages of 18 and 65 years. Would you offer treatment to patients outside of this age range?	and HCV coinfection, the recommended approach is to first treat HCV using direct-acting antivirals, followed by initiation of HDV-directed treatment. The clinical experts indicated that, in patients with HBV coinfection with HDV and HIV, HDV treatment would be introduced once HBV therapy is established, as this is typically already included in standard HIV treatment regimens. CDEC noted that HCV and HIV infection status would not preclude eligibility for bulevirtide treatment. The clinical experts noted that although patients older than 65 years were excluded from the clinical trials, age alone should not preclude treatment with bulevirtide in clinical practice. The clinical experts emphasized that treatment decisions for older adults should be made on an individual basis, considering comorbidities, functional status, and patient preferences. The clinical experts indicated that a strict upper age limit should not be imposed; however, they acknowledged that treatment may not be appropriate in patients older than 80 years of age, particularly if the treatment burden may outweigh the potential benefits. CDEC considered the clinical experts' input and noted that it would be reasonable to allow reimbursement of bulevirtide treatment in patients aged 18 years and older. Patients older than 65 years may be eligible for treatment at the discretion of the treating physician.
Given that there are no currently approved medications for the treatment of HDV, are there any off-label medications that would be required prior to eligibility?	CDEC agreed with the clinical experts that there are no off-label medications that would be required before initiating treatment with bulevirtide. The clinical experts noted that although patients are often already receiving treatment for HBV infection, this is not considered a prerequisite for bulevirtide therapy.
In cases where discontinuation has occurred and further monitoring shows relapse, would the patient be eligible for re-treatment? If yes, what would the expected treatment duration be?	According to the clinical experts, there is currently no evidence to guide decisions regarding re-treatment with bulevirtide following discontinuation and subsequent reversal of response. CDEC agreed with the clinical experts that, in cases in which a patient initially responded to treatment but experienced a relapse after stopping it, re-treatment may be reasonable. However, they emphasized the need for additional data to guide such decisions. CDEC noted that it would be appropriate to leave the decisions to the clinical judgment of the treating physician.
The sponsor's systematic review highlighted a special subgroup of interest, being patients who are ineligible for PEG-IFN-alpha due to failure, intolerance, or contraindication. In the potential scenario where PEG-IFN-alpha is a required prior therapy, would these patients be eligible for treatment with bulevirtide? Two of the trials excluded patients with a CrCl < 60 mL/min, and the drug product monograph also notes that the safety and efficacy of bulevirtide has not been evaluated in this population. Would you avoid treatment with bulevirtide in patients who have moderate to severe renal impairment (CrCl < 60 mL/min)?	CDEC agreed with the clinical experts that patients with moderate renal impairment (e.g., CrCl approximately 60 mL/min) may still be considered for treatment with bulevirtide, provided they are closely monitored and managed with caution. CDEC agreed with the clinical experts who noted that in cases of more severe renal impairment (e.g., CrCl approximately 40 mL/min), greater caution would be necessary and consultation with a nephrologist may be appropriate. CDEC agreed with the clinical experts that no off-label medications, including PEG-IFN, are required before initiating treatment with bulevirtide. The clinical experts noted that PEG-IFN is neither available nor used in Canada.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
Given the recommendation is to continue to treat as long as there is associated clinical benefit, what are the appropriate monitoring parameters for defining adequate response? The “combined treatment response” is defined as undetectable HDV RNA (HDV RNA < LLoD, where LLoD = 6 IU/mL) or decrease in HDV RNA by $\geq 2 \log_{10}$ IU/mL from baseline and ALT normalization (defined as an ALT value within the normal range). The sponsor considered efficacy outcomes of proportion of patients with undetectable HDV RNA, ALT normalization or change in ALT, negative PCR results, and HRQoL. The trials used time points in 24-week intervals for response assessments. • It would be helpful to drug plans to have defined parameters. • At what time intervals should reassessments occur? • If the combined treatment response is an eligibility requirement for ongoing treatment, would a patient with partial response be eligible to continue treatment (i.e., HDV reduction is met but ALT normalization is not met)?	According to the clinical experts, continued benefit from bulevirtide should be assessed using surrogate markers, such as undetectable HDV RNA, at least $2 \log_{10}$ IU/mL reduction in HDV RNA, and ALT normalization, along with longer-term indicators such as fibrosis improvement. The clinical experts indicated that although reductions in liver cancer and hepatic decompensation are important, these are not expected within 1 year. The clinical experts indicated that monitoring of HDV infection should occur regularly, with liver enzyme and function tests every 1 to 3 months, HDV RNA testing every 3 months, and noninvasive fibrosis assessments (e.g., FibroScan) every 6 to 12 months. According to the clinical experts consulted, patients with HDV infection who are not receiving treatment are typically seen in clinic every 6 to 12 months, depending on disease severity. Those patients receiving treatment are generally monitored every 3 months to assess treatment response, check for adverse events, and ensure compliance. Routine bloodwork is conducted every 3 to 6 months, and ultrasounds are performed every 6 months for hepatocellular carcinoma screening. The clinical experts noted that patients with partial or slow response should continue treatment given the progressive nature of HDV infection and the limited available treatment options. CDEC acknowledged the clinical experts’ input and noted that, based on the submitted evidence, it would be appropriate to allow renewal of bulevirtide treatment in patients with virologic response assessed every 48 weeks. CDEC noted that there is a lack of evidence regarding the clinical benefits of partial response to inform the continued use of bulevirtide in patients with a partial response.
Considerations for discontinuation of therapy	
What would define loss of response or absence of clinical benefit?	According to the clinical experts consulted, loss of response is defined as an initial virologic response — such as an undetectable HDV RNA level or at least $2 \log_{10}$ reduction in HDV RNA — followed by viral rebound. This may be associated with issues related to treatment adherence, although the potential for antiviral resistance remains unclear. Discontinuation of therapy is not necessarily recommended in such cases because it may trigger an HDV infection flare and lead to clinical deterioration. The clinical experts indicated that absence of clinical benefit is defined as a less than $1 \log_{10}$ reduction in HDV RNA at week 48 of treatment. CDEC acknowledged the clinical experts’ input.
Question for clinical experts: If treatment is interrupted for any reason unrelated to ongoing HDV infection, can treatment be resumed?	According to the clinical experts consulted, if treatment is interrupted for reasons unrelated to HDV infection, it should be resumed when appropriate with reassessment of HDV RNA, liver enzymes, and bilirubin levels, while routine monitoring should

Implementation issues	Response
	continue every 3 months as per typical protocol. CDEC agreed with the clinical experts.
Considerations for prescribing of therapy	
Question for clinical experts: Given there were other doses studied beyond 2 mg (i.e., 5 mg, 10 mg), would an increase in dose be considered to achieve clinical benefit in patients who are not meeting the primary outcomes?	According to the clinical experts, increasing the bulevirtide dose greater than 2 mg is not supported by current evidence. The clinical experts indicated that phase III trial data did not demonstrate added benefit with higher doses of bulevirtide, and they emphasized that treatment duration, rather than dose escalation, is likely more important for achieving clinical benefit. CDEC noted that the 5 mg and 10 mg doses are not approved by Health Canada and are not of interest to this reimbursement review.
Bulevirtide is administered by subcutaneous injection.	This is a comment from the drug programs to inform CDEC deliberations.
It is recommended that bulevirtide be initiated and monitored by a clinician experienced in the management of viral hepatitis. Access to these clinicians may be challenging in some areas.	This is a comment from the drug programs to inform CDEC deliberations.
Are there circumstances where clinicians would prescribe bulevirtide in combination with PEG-IFN-alpha or nucleos(t)ide analogues or both?	The clinical experts consulted stated that bulevirtide would typically be used in combination with nucleos(t)ide analogues, such as tenofovir or entecavir, which are used to manage the HBV infection and have no effect on HDV infection. CDEC noted that there is no evidence to inform the concurrent use of bulevirtide and PEG-IFN in the population under review.
Generalizability	
Since the mechanism of HDV entry into hepatocytes is the same as HBV, the mechanism of action of the treatment is also the same for both viruses. Would this medication be used to treat HBV in the absence of HDV? Would this medication be used as prophylaxis for HBV and/or HDV infection?	According to the clinical experts consulted, there are currently no data to support the use of bulevirtide for the treatment of HBV infection in the absence of HDV infection, or for the prophylaxis of HBV and/or HDV infection. CDEC acknowledged the clinical experts' input.
Care provision issues	
Administration would require training, as it is given by subcutaneous injection, but it is not a prefilled syringe. It requires reconstitution.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Training in reconstitution and administration would be required. Who would cover the costs involved in this? Who would cover the cost of supplies (e.g., needles)?	The CDA-AMC review team noted that it is unclear who would cover these costs in practice. In the sponsor's economic model, it was assumed that training costs would be covered by the public drug plans, and no assumptions were made regarding the cost of supplies.

ALT = alanine aminotransferase; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CHD = chronic hepatitis D; CrCl = creatinine clearance; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HRQoL = health-related quality of life; LFT = liver function test; LLoD = lower limit of detection; NML = National Microbiology Laboratory; PCR = polymerase chain reaction; PEG-IFN = pegylated interferon; RCT = randomized controlled trial; RNA = ribonucleic acid.

Clinical Evidence

Systematic Review

Description of the Study

The sponsor-conducted systematic literature review identified 1 pivotal ongoing, phase III, randomized, open-label, parallel-group, multicentre trial (MYR301; N = 150). The primary objective of the MYR301 trial was to evaluate the efficacy and safety of bulevirtide at a dose of 2 mg compared to delayed treatment with bulevirtide 10 mg after an observational period of 48 weeks in adult patients with HDV infection and compensated liver disease. The secondary objectives of the trial included assessing the safety of bulevirtide and determining the optimal treatment duration. Patients were enrolled from 16 sites across 4 countries: Germany, Italy, Russia, and Sweden. The study included a 4-week screening period, a 144-week treatment period, and a 96-week follow-up period. Following screening, patients were randomized using an electronic randomization system in a 1:1:1 ratio to receive delayed treatment with bulevirtide 10 mg after an observational period of 48 weeks (n = 51), immediate treatment with bulevirtide 2 mg (n = 49), or immediate treatment with bulevirtide 10 mg (n = 50). This report primarily focuses on between-group comparisons of study end points up to week 48, specifically for bulevirtide at a dose of 2 mg, which is in line with the proposed Health Canada indication. Data for the study group receiving immediate treatment with bulevirtide at a dose of 10 mg are not presented in this report because this dose is neither approved nor used in Canada. Efficacy end points of interest to this review included combined response, undetectable HDV RNA or HDV RNA decrease of at least $2 \log_{10}$ IU/mL from baseline, change in liver stiffness from baseline, ALT normalization, undetectable HDV RNA, liver-related clinical events, HRQoL, and safety outcomes. The primary and secondary end points of the MYR301 trial were analyzed using data up to the cut-off date of September 30, 2022, with the database locked on June 8, 2023.

The mean age was higher in the bulevirtide 2 mg group (mean = 44 years; standard deviation [SD] = 9.0 years) compared to the delayed treatment group (mean = 41 years; SD = 7.5 years). A larger proportion of patients in the bulevirtide 2 mg group were male (61.2%) compared to the delayed treatment group (51.0%). Overall, nearly half the patients (47.3%) had cirrhosis at the time of randomization, which were all classified as Child-Pugh Class A. At baseline, all patients in both the bulevirtide 2 mg and delayed treatment groups had HDV genotype 1. In the bulevirtide 2 mg group, a larger proportion of patients had a Child-Pugh score of 6 (30.4% versus 20.8% in the delayed treatment group), HBV genotype D (95.9% versus 86.3% in the delayed treatment group), and HBV RNA greater or equal to the lower limit of quantification (67.3% versus 52.9% in the delayed treatment group). A total of 32 patients (65.3%) in the bulevirtide 2 mg group and 32 patients (62.7%) in the delayed treatment group received oral anti-HBV treatment during the MYR301 trial, with 54.7% of these patients having initiated treatment before baseline. Additionally, 53.1% of patients in the bulevirtide 2 mg group and 62.7% of patients in the delayed treatment group had previously been treated with interferon. In the delayed treatment group, for most disease characteristics, the summary statistics remained similar between randomization and week 48, with a few notable exceptions. Specifically, mean serum ALT level was higher at randomization (102 U/L; SD = 61.9 U/L) compared to week 48 (82 U/L;

SD = 51.1 U/L). Mean liver stiffness was 15.3 kPa (SD = 8.95 kPa) at randomization and 16.1 kPa (SD = 11.84 kPa) at week 48.

Efficacy Results

Combined Response

Combined response at week 48 was a primary end point in the MYR301 trial. A combined response was defined as the simultaneous fulfillment of 2 conditions: undetectable HDV RNA (less than the lower limit of detection) or a decrease of at least 2 log₁₀ IU/mL from baseline and ALT normalization. At week 48, the proportion of patients in the bulevirtide 2 mg group who had a combined response was 44.9% (95% CI, 30.7% to 59.8%) compared to 2.0% (95% CI, 0.0% to 10.4%) in the delayed treatment group. The between-group difference in response rates was 42.9% (96% CI, 27.0% to 58.5%; P value < 0.0001) in favour of the bulevirtide 2 mg group compared to the delayed treatment group. The sensitivity analysis results, using the missing-equals-failure approach, were consistent with the primary analysis. Subgroup analyses of the primary end point — combined response at week 48 — were conducted based on cirrhosis status. The proportion of patients without cirrhosis who had a combined response in the bulevirtide 2 mg group was 53.8% (95% CI, 16.4% to 57.3%) compared to 34.8% (95% CI, 33.4% to 73.4%) among patients with cirrhosis. In the delayed treatment group, the proportion of patients with cirrhosis who had a combined response was 4.2% (95% CI, 0.1% to 21.1%) compared to 0.0% (95% CI, 0.0% to 12.8%) in those without cirrhosis.

Undetectable HDV RNA at Weeks 24 and 48 After Scheduled End of Treatment

An undetectable HDV RNA at weeks 24 and 48 after scheduled end of treatment (sustained virologic response) was a secondary end point in the MYR301 trial; however, the results for this end point were not reported due to an insufficient follow-up period because the study is still ongoing.

Undetectable HDV RNA or a Decrease by at Least 2 Log₁₀ IU/mL at Week 48

A decrease in HDV RNA of at least 2 log₁₀ IU/mL or undetectable HDV RNA (virologic response) at week 48 was an additional secondary end point in the MYR301 trial. At week 48, 73.5% (95% CI, 58.9% to 85.1%) of patients in the bulevirtide 2 mg group had a virologic response, compared to 3.9% (95% CI, 0.5% to 13.5%) in the delayed treatment group. The between-group difference in response rates was 69.5% (96% CI, 54.1% to 81.9%; P value < 0.0001) in favour of the bulevirtide 2 mg group compared to the delayed treatment group. Subgroup analyses of virologic response were conducted based on cirrhosis status and concomitant HBV medication (ad hoc analysis). At week 48, the proportion of patients with cirrhosis who had a virologic response was 82.6% (95% CI, 61.2% to 95.0%) in the bulevirtide 2 mg group 8.3% (1.0% to 27.0%) in the delayed treatment group. Among patients without cirrhosis, the corresponding proportions were 65.4% (95% CI, 44.3% to 82.8%) and 0.0% (95% CI, 0.0% to 12.8%), respectively. At week 48, 78.1% (95% CI, 60.0% to 90.7%) of patients receiving concomitant HBV medication in the bulevirtide 2 mg group had a virologic response, compared to 6.3% (95% CI, 0.8% to 20.8%) in the delayed treatment group. Among those who did not receive HBV medication, the corresponding proportions were 64.7% (95% CI, 38.3% to 85.0%) and 0.0% (95% CI, 0.0% to 17.6%), respectively.

Change From Baseline in Liver Stiffness at Week 48

The change from baseline in liver stiffness as assessed by FibroScan was a prespecified secondary end point for week 48 analysis. At week 48, the LS mean of change from baseline in liver stiffness was -3.06 kPa (95% CI, -4.67 kPa to -1.45 kPa) in the bulevirtide 2 mg group and 0.87 kPa (95% CI, -0.79 kPa to 2.53 kPa) in the delayed treatment group. Compared to the delayed treatment group, the between-group difference in LS mean of change in liver stiffness was -3.93 kPa (95% CI, -6.23 kPa to -1.63 kPa; P value = 0.0009), favouring the bulevirtide 2 mg group. Subgroup analyses of the change in liver stiffness were conducted based on cirrhosis status. At week 48, in the bulevirtide 2 mg group, the mean change from baseline in liver stiffness was -5.70 kPa (SD = 6.94 kPa) among patients with cirrhosis, compared to -0.35 kPa (SD = 2.08 kPa) among patients without cirrhosis. In the delayed treatment group, the mean change from baseline in liver stiffness was -0.20 kPa (SD = 4.00 kPa) among patients without cirrhosis, compared to 1.78 kPa (SD = 10.1 kPa) among patients with cirrhosis.

Liver-Related Clinical Events

Health-Related Quality of Life

The Hepatitis Quality of Life Questionnaire (HQLQ) was used to assess the quality of life of patients in the MYR301 trial. The HQLQ includes both the Short Form (36) Health Survey (SF-36) items and 4 hepatitis-specific health domain scores. These are hepatitis-specific domains including health distress, positive well-being, hepatitis-specific limitations, and hepatitis-specific health distress. Each domain is scored on a scale from 0 to 100, with higher scores indicating better HRQoL.

At week 24, compared to the delayed treatment group, the LS mean differences in the bulevirtide 2 mg group were [REDACTED] for the HQLQ Physical Component Summary score, [REDACTED] for the HQLQ Mental Component Summary score, [REDACTED] for the HQLQ Health Distress Scale score, [REDACTED] for the HQLQ Positive Well-Being Scale score, [REDACTED] for the HQLQ Hepatitis-Specific Limitations Scale score, and [REDACTED] for the HQLQ Hepatitis-Specific Health Distress Scale score.

At week 48, compared to the delayed treatment group, the LS mean differences in the bulevirtide 2 mg group were 1.5 (95% CI, -0.5 to 3.6) for the HQLQ Physical Component Summary score, 2.8 (95% CI, -0.3 to 5.9) for the HQLQ Mental Component Summary score, 6.5 (95% CI, -1.5 to 14.5) for the HQLQ Health Distress Scale score, 1.8 (95% CI, -5.5 to 9.0) for the HQLQ Positive Well-Being Scale score, 7.5 (95% CI, 0.3 to 14.8) for the HQLQ Hepatitis-Specific Limitations Scale score, and 9.5 (95% CI, 1.1 to 17.8) for the HQLQ Hepatitis-Specific Health Distress Scale score.

Undetectable HDV RNA

Undetectable HDV RNA (less than the lower limit of quantification, target not detected) at week 48 was a key secondary end point in the MYR301 trial. At week 48, 12.2% (95% CI, 4.6% to 24.8%) of patients in the bulevirtide 2 mg group had undetectable HDV RNA, compared to 0.0% (95% CI, 0.0% to 7.0%) in the delayed treatment group. The between-group difference in response rates was calculated for the bulevirtide 10 mg group, with the bulevirtide 2 mg group as the reference; however, this comparison is not of interest for this review. Subgroup analyses of the key secondary end point were conducted based on cirrhosis status and concomitant nucleos(t)ide (ad hoc analysis). In the bulevirtide 2 mg group, 21.7% (95% CI, 7.5% to 43.7%) of patients with cirrhosis had undetectable HDV RNA at week 48 compared to 3.8% (95% CI, 0.1% to 19.6%) of those without cirrhosis. In the delayed treatment group, 0.0% (95% CI, 0.0% to 14.2%) of patients with cirrhosis achieved an undetectable HDV RNA at week 48 compared to 0.0% (95% CI, 0.0% to 12.8%) of those without cirrhosis. Similarly, 15.6% (95% CI, 5.3% to 32.8%) of patients in the bulevirtide 2 mg group who were receiving concomitant HBV medication achieved undetectable HDV RNA at week 48 compared to 5.9% (95% CI, 0.1% to 28.7%) of those who were not receiving HBV medication. In the delayed treatment group, 0.0% of patients achieved undetectable HDV RNA at week 48 regardless of whether they were receiving concomitant HBV medication.

ALT Normalization

ALT normalization at week 48 was a secondary end point in the MYR301 trial. At week 48, 51.0% (95% CI, 36.3% to 65.6%) of patients in the bulevirtide 2 mg group had ALT normalization compared to 11.8% (95% CI, 4.4% to 23.9%) in the delayed treatment group. The between-group difference in response rates was 39.3% (96% CI, 20.0% to 55.8%; P value < 0.0001) in favour of the bulevirtide 2 mg group compared to the delayed treatment group. Subgroup analyses of ALT normalization were conducted based on cirrhosis status and concomitant HDV medication. At week 48, 61.5% (95% CI, 40.6% to 79.8%) of patients without cirrhosis achieved ALT normalization in the bulevirtide 2 mg group compared to 39.1% (95% CI, 19.7% to 61.5%) of patients with cirrhosis. In the delayed treatment group, 7.4% (95% CI, 0.9% to 24.3%) of patients without cirrhosis achieved ALT normalization at week 48 in the bulevirtide 2 mg group compared to 16.7% (95% CI, 4.7% to 37.4%) of patients with cirrhosis. In addition, 52.9% (95% CI, 27.8% to 77.0%) of patients in the bulevirtide 2 mg group who did not receive concomitant HBV medication achieved ALT normalization at week 48 compared to 50.0% (95% CI, 31.9% to 68.1%) of those who received HBV medication. In the delayed treatment group, 15.8% (95% CI, 3.4% to 39.6%) of patients who did not receive concomitant HBV medication achieved ALT normalization at week 48 compared to 9.4% (95% CI, 2.0% to 25.0%) of those who received HBV medication.

Combined Response Over Time

The combined response at each study visit, an exploratory end point in the MYR301 trial, was analyzed exclusively using a missing-equals-failure approach. In contrast, the primary end point analysis incorporated a last observation carried forward (LOCF) approach to account for missing data due to COVID-19 at weeks 24 and 48. The combined response rates in the bulevirtide 2 mg group demonstrated consistent improvement over time: 34.7% (95% CI, 21.7% to 49.6%) at week 24, 44.9% (95% CI, 30.7% to 59.8%)

at week 48 [REDACTED], 55.1% (95% CI, 40.2% to 69.3%) at week 96, and 57.1% (95% CI, 42.2% to 71.2%) at week 144.

Virologic Response Over Time

The virologic response at each study visit, an exploratory end point in the MYR301 trial, was analyzed exclusively using a missing-equals-failure approach. The virologic response rates in the bulevirtide 2 mg group demonstrated improvement over time: 55.1% (95% CI, 40.2% to 69.3%) at week 24, 73.5% (95% CI, 58.9% to 85.1%) at week 48, [REDACTED] (95% CI, [REDACTED] to [REDACTED]) at week [REDACTED], 75.5% (95% CI, 61.1% to 86.7%) at week 96, and 73.5% (95% CI, 58.9% to 85.1%) at week 144.

Harms Results

Adverse Events

At week 48 in the MYR301 trial, the proportion of patients who experienced at least 1 AE was 83.7% in the bulevirtide 2 mg group and 80.4% in the delayed treatment group. The most common AEs in the bulevirtide 2 mg group were headache (14.3% versus 25.5% in the delayed treatment group), followed by vitamin D deficiency (14.3% versus 25.5% in the delayed treatment group), leukopenia (14.3% versus 19.6% in the delayed treatment group), thrombocytopenia (10.2% versus 15.7% in the delayed treatment group), and pruritus (12.2% versus 0.0% in the delayed treatment group). The proportion of patients with AEs of grade 3 or higher was 10.2% in the bulevirtide 2 mg group and 7.8% in the delayed treatment group. The AEs of grade 3 or higher in the bulevirtide 2 mg group included depression (2.0% versus 0.0% in the delayed treatment group), foot fracture (2.0% versus 0.0% in the delayed treatment group), decreased neutrophil count (2.0% versus 0.0% in the delayed treatment group), osteopenia (2.0% versus 0.0% in the delayed treatment group), and thrombocytopenia (2.0% versus 5.9% in the delayed treatment group).

At week 144 in the MYR301 trial, the proportion of patients who experienced at least 1 AE in the bulevirtide 2 mg group was 98.0%, including 24.5% of patients with AEs of grade 3 or higher. The most common AEs in the bulevirtide 2 mg group were vitamin D deficiency (44.9%), headache (20.4%), leukopenia (20.4%), thrombocytopenia (20.4%), lymphopenia (16.3%), and neutropenia (16.3%).

Serious Adverse Events

At week 48 in the MYR301 trial, the proportion of patients who experienced at least 1 serious AE was 4.1% in the bulevirtide 2 mg group and 2.0% in the delayed treatment group. The most serious AEs were reported in 1 patient in both treatment groups. The serious AEs in the bulevirtide 2 mg group included foot fracture (2.0% versus 0.0% in the delayed treatment group), headache (2.0% versus 0.0% in the delayed treatment group), hemiparesis (2.0% versus 0.0% in the delayed treatment group), and depression (2.0% versus 0.0% in the delayed treatment group). The serious AEs that occurred in the delayed treatment group included cholelithiasis (2.0% versus 0.0% in the bulevirtide 2 mg group) and COVID-19 (2.0% versus 0.0% in the bulevirtide 2 mg group).

At week 144 in the MYR301 trial, the proportion of patients who experienced at least 1 serious AE in the bulevirtide 2 mg group was 6.1%, including varices esophageal (2.0%), foot fracture (2.0%), headache (2.0%), hemiparesis (2.0%), and depression (2.0%). Between weeks 48 and 144 (representing 96 weeks of

treatment with bulevirtide at a dose of 10 mg), the proportion of patients who experienced at least 1 serious AE in the delayed treatment to bulevirtide 10 mg group was 6.0%, including COVID-19 (2.0%), urinary tract infection (2.0%), and plasma cell myeloma (2.0%).

Withdrawals Due to Adverse Events

By week 144, no AEs led to discontinuation of the study drug in the MYR301 trial.

Mortality

By week 144, no deaths were reported in either the bulevirtide 2 mg group or the delayed treatment group.

Notable Harms

At week 48 in the MYR301 trial, the proportion of patients who experienced at least 1 hepatic AE was 14.3% in the bulevirtide 2 mg group and 9.8% in the delayed treatment group. The hepatic AEs in the bulevirtide 2 mg group included increased ALT (4.1% versus 7.8% in the delayed treatment group), hyperbilirubinemia (4.1% versus 0.0% in the delayed treatment group), increased blood bilirubin (4.1% versus 0.0% in the delayed treatment group), increased aspartate aminotransferase (2.0% versus 5.9% in the delayed treatment group), and hepatic pain (2.0% versus 0.0% in the delayed treatment group). At week 144, the proportion of patients in the bulevirtide 2 mg group who experienced at least 1 hepatic AE was 28.6%.

At week 48 in the MYR301 trial, the proportion of patients who experienced at least 1 renal AE was 8.2% in the bulevirtide 2 mg group and 5.9% in the delayed treatment group. The hepatic AEs in the bulevirtide 2 mg group included proteinuria (6.1% versus 3.9% in the delayed treatment group) and urinary retention (2.0% versus 0.0% in the delayed treatment group). At week 144, the proportion of patients in the bulevirtide 2 mg group who experienced at least 1 renal AE was 10.2%. At week 48, the proportion of patients who experienced eosinophilia was 10.2% in the bulevirtide 2 mg group versus 0.0% in the delayed treatment group. At week 144, the proportion of patients in the bulevirtide 2 mg group experiencing eosinophilia was 10.2%. At week 48, the proportion of patients who experienced an injection site reaction was 6.1% in the bulevirtide 2 mg group versus 0.0% in the delayed treatment group. At week 144, the proportion of patients in the bulevirtide 2 mg group who experienced an injection site reaction was 20.4%.

Critical Appraisal

Randomization in the MYR301 trial was performed using an appropriate methodology, and stratification was prespecified. All efficacy and safety analyses were conducted using the full and safety analysis sets, respectively, which included all randomized patients who received at least 1 dose of bulevirtide after randomization. There were some imbalances observed in baseline characteristics of patients in the MYR301 trial, likely due to small sample sizes, which may have hindered the achievement of true prognostic balance. Because of the rarity of HDV infection and challenges in patient recruitment, achieving large sample sizes in clinical trials is often not feasible. The open-label design of the MYR301 trial introduces a potential bias in the assessment of study outcomes; however, this bias was mitigated by using central laboratories for hematology and biochemistry that were blinded to actual treatment allocation. Knowledge of the assigned treatment could have led to bias in the reporting and measurement of subjective outcomes, including patient-reported outcomes (e.g., HRQoL) and subjective AEs. However, the extent and direction of bias due

to treatment knowledge is uncertain. Although there are always some concerns about risk of bias due to deviations from the intended interventions in open-label trials, there were relatively few protocol deviations; these were balanced across the groups and unlikely to have influenced the study results. Adherence to the interventions and study completion rates were high overall in the intervention groups of interest in this review, which reduces concerns regarding deviations from the intended interventions that could have arisen due to the trial context.

According to FDA guidance, because there are no drugs currently approved for the treatment of HDV infection, a placebo-controlled trial is the preferred design for a phase III clinical trial. However, an alternative trial design could be a randomized controlled trial in which patients are randomized to receive either the investigational drug (immediate treatment group) or placebo for a prespecified duration followed by open-label treatment with the investigational drug (deferred treatment group). According to FDA guidance, a surrogate end point providing evidence of both a decline in virologic replication and an improvement in associated liver inflammation, as evident by biochemical response, could reasonably predict clinical benefit. However, FDA guidance suggests that subsequent confirmation using clinical end points is required, and these should be collected as part of the long-term follow-up data. Based on the enrolled sample size, the study was powered to test its primary and key secondary end points. The statistical analysis methods appear to be acceptable. Both interim analyses at weeks 24 and 48 were planned a priori. In the MYR301 trial, the risk of bias due to missing outcome data is considered low. The lack of adjustment for multiple comparisons for all but the primary and key secondary end points increases the risk of type I error, in which false positives may be incorrectly identified as significant. Bulevirtide was favoured in the analysis, but there was uncertainty due to the small sample size, which increased the risk that prognostic balance was not achieved. The unadjusted comparisons and the decision not to stratify the analysis by cirrhosis due to the small sample size may introduce bias and reduce the accuracy of the estimated treatment effects. Subgroup analyses by cirrhosis status and prior use of nucleos(t)ide analogues were prespecified; however, they were descriptive and were limited by small sample sizes. No strong conclusions about HRQoL could be drawn about the effect of bulevirtide compared with delayed treatment due to the risk of bias from assessors being aware of treatment assignments as well as serious imprecision, with wide CIs that included both potential benefit and harm.

According to the clinical experts consulted by CDA-AMC, the inclusion and exclusion criteria of the MYR301 trial appropriately reflect the patient population with HDV infection who are eligible for bulevirtide therapy in clinical practice. Although patients older than 65 years were not included in the trial, the clinical experts emphasized that age alone should not preclude treatment with bulevirtide in clinical practice. The clinical experts noted that, in clinical practice, physicians are unlikely to delay treatment initiation for patients with HBV and HDV coinfection who present with advanced fibrosis, suggesting that earlier intervention may be clinically appropriate in such cases. In the MYR301 trial, patients with HCV or uncontrolled HIV coinfection were not included. However, the clinical experts noted that, in clinical practice, these coinfections can be sequentially managed, with the HIV or HCV treated first, followed by HBV and HDV infection therapy. The clinical experts noted that although patients with creatinine clearance less than 60 mL/min were not

included in the trial, those with moderate renal impairment may be considered for treatment with appropriate monitoring.

The clinical experts consulted by CDA-AMC agreed that it is reasonable to expect that a significant proportion of patients treated for HDV infection in clinical practice will have cirrhosis because many are diagnosed at more advanced stages of the disease. Furthermore, the clinical experts noted that, in clinical practice, patients with early-stage fibrosis (stages F1 or F2) may be more likely to seek treatment to prevent disease progression. As a result, treatment in real-world settings may be initiated across a broader range of disease severity than is typically represented in clinical trials. Approximately 65% of patients in the MYR301 trial received concomitant oral anti-HBV therapy at baseline and this was balanced across groups. However, the clinical experts consulted indicated that this proportion is lower than expected in clinical practice; nearly all patients with HDV infection are typically treated with nucleos(t)ide analogues. The clinical experts noted that although HBV therapy may slow the progression of fibrosis, this is unlikely to affect the generalizability of the study because improvements in both virologic and fibrosis outcomes were observed in patients who had previously received HBV therapy (54.7%) and had progressed to advanced disease. According to the clinical experts consulted, the surrogate outcomes used in the MYR301 trial — such as HDV RNA reduction or undetectability, ALT normalization, and changes in liver fibrosis — were appropriate for assessing treatment benefit. The clinical experts indicated that 48 weeks is a reasonable duration to assess efficacy in the MYR301 trial using surrogate outcomes; however, longer-term follow-up would be required to assess hard clinical outcomes, such as liver cancer, hepatic decompensation, or death, which are not expected to manifest within 1 year. In the MYR301 trial, the study population was drawn from several sites across 4 European countries, with no Canadian sites included. Overall, the clinical experts consulted indicated that there are no major concerns with generalizing the findings from the trial to the Canadian clinical setting.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: combined response, virologic response, change from baseline in liver stiffness, HRQoL, and serious AEs.

[Table 3](#) presents the GRADE summary of findings for bulevirtide 2 mg versus delayed treatment.

Table 3: Summary of Findings for Bulevirtide 2 mg vs. Delayed Treatment for Patients With HDV Infection — MYR301 Trial

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Combined response^a				
Proportion of patients with combined response at week 48	99 ^b (1 RCT)	• Bulevirtide 2 mg: 449 patients per 1,000 • Delayed treatment:^c 20 patients per 1,000 • Difference: 429 more patients per 1,000 (96% CI, 270 to 585 more patients per 1,000)	Moderate ^d	Bulevirtide 2 mg likely results in a clinically important increase in the proportion of patients with combined response at week 48 when compared with delayed treatment.
Virologic response^{e,f}				
Proportion of patients with virologic response at week 48	99 ^b (1 RCT)	• Bulevirtide 2 mg: 735 patients per 1,000 • Delayed treatment:^c 39 patients per 1,000 • Difference: 695 more patients per 1,000 (96% CI, 541 to 819 more patients per 1,000)	Moderate ^g	Bulevirtide 2 mg likely results in a clinically important increase in the proportion of patients with virologic response at week 48 when compared with delayed treatment.
Change from baseline in liver stiffness^{f,h}				
Change from baseline in liver stiffness at week 48	99 ^b (1 RCT)	• Bulevirtide 2 mg: LS mean = −3.06 (SE = 0.81) • Delayed treatment:^c LS mean = 0.87 (SE = 0.84) • LS mean difference: −3.93 (95% CI, −6.23 to −1.63)	Moderate ⁱ	Bulevirtide 2 mg likely results in an improvement in liver stiffness at week 48 when compared with delayed treatment. The clinical importance of the improvement is uncertain.
HRQoL^f				
Change from baseline in HQLQ at week 24	99 ^b (1 RCT)	Change from baseline in Health Distress Score LS mean (SE) • Bulevirtide 2 mg: █████ • Delayed treatment:^c █████ • LS mean difference (95% CI): █████ to █████) Change from baseline in Positive Well-Being Score LS mean (SE) • Bulevirtide 2 mg: █████ • Delayed treatment:^c █████ • LS mean difference (95% CI): █████ to █████) Change from baseline in Hepatitis-Specific Health Distress Score LS mean (SE)	Very low ^j	The evidence is very uncertain about the effect of bulevirtide 2 mg on HRQoL at week 24 when compared with delayed treatment.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Bulevirtide 2 mg: [REDACTED] • Delayed treatment:^c [REDACTED] • LS mean difference (95% CI): [REDACTED] to [REDACTED]		
Change from baseline in HQLQ at week 48	99 ^b (1 RCT)	Change from baseline in Health Distress • Bulevirtide 2 mg: LS mean = 16.6 (SE = 2.87) • Delayed treatment:^c LS mean = 10.1 (SE = 2.84) • LS mean difference: 6.5 (95% CI, -1.5 to 14.5) Change from baseline in Positive Well-Being Score • Bulevirtide 2 mg: LS mean = 6.5 (SE = 2.31) • Delayed treatment:^c LS mean = 1.4 (SE = 2.28) • LS mean difference: 5.1 (95% CI, -1.3 to 11.5) Change from baseline in Hepatitis-Specific Health Distress Score • Bulevirtide 2 mg: LS mean = 18.3 (SE = 2.90) • Delayed treatment:^c LS mean = 11.4 (SE = 2.93) • LS mean difference: 6.9 (95% CI, -1.2 to 15.1)	Very low ⁱ	The evidence is very uncertain about the effect of bulevirtide 2 mg on HRQoL at week 48 when compared with delayed treatment.
Harms				
Proportion of patients with serious adverse events at week 48	99 ^b (1 RCT)	• Bulevirtide 2 mg: 42 patients per 1,000 • Delayed treatment:^c 20 patients per 1,000 • Difference: 22 more patients per 1,000 (95% CI, NR)	Very low ^k	The evidence is uncertain about the effect of bulevirtide 2 mg on serious adverse events at week 48 when compared with delayed treatment.

CDA-AMC = Canada's Drug Agency; CI = confidence interval; HDV = hepatitis delta virus; HQLQ = Hepatitis Quality of Life Questionnaire; HRQoL = health-related quality of life; LS = least squares; NR = not reported; RCT = randomized controlled trial; SE = standard error.

Notes: Study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aCombined response was defined as undetectable HDV RNA (less than the lower limit of quantification, target not detected) or HDV RNA decrease of at least 2 log₁₀ IU/mL from baseline combined with ALT normalization.

^bIn MYR301, patients were randomized at a 1:1:1 ratio to receive delayed treatment with bulevirtide 10 mg (n = 51), immediate treatment with bulevirtide 2 mg (n = 49), or immediate treatment with bulevirtide 10 mg (n = 50). However, data related to the immediate treatment with bulevirtide 10 mg were not presented in this report because this dosage is neither approved nor used in Canadian clinical practice.

^cDelayed treatment: Baseline at randomization to before bulevirtide first dose at week 48 visit or to early termination before week 48 visit in the delayed treatment group. From week 48 onward, patients received bulevirtide 10 mg.

ⁱRated down 1 level for serious study limitations. Evidence is from 1 trial with a small sample size, raising concerns that prognostic balance may not have been achieved and the effect could be overestimated. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 20% between the groups was identified by the clinical experts consulted by CDA-AMC as a threshold of clinical importance for this outcome.

^eVirologic response was defined as undetectable HDV RNA or an HDV RNA decrease of at least 2 log₁₀ IU/mL from baseline.

^fIn the trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

^gRated down 1 level for serious study limitations. Evidence is from 1 trial with a small sample size, raising concerns that prognostic balance may not have been achieved and the effect could be overestimated. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 30% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

^hChange from baseline in liver stiffness was measured by FibroScan.

ⁱRated down 1 level for serious study limitations. Evidence is from 1 trial with a small sample size, raising concerns that prognostic balance may not have been achieved and the effect could be overestimated. There is no established MID for this outcome and the clinical experts consulted by CDA-AMC could not provide a threshold of important difference. In the absence of a known threshold, the null was used.

^jRated down 1 level for serious risk of bias due to assessor knowledge of treatment assignment. Rated down 2 levels for very serious imprecision: CIs were wide and included the potential for no difference and harm. There is no established MID for this outcome and the clinical experts consulted by CDA-AMC could not provide a threshold of important difference. In the absence of a known threshold, the null was used.

^kRated down 1 level for serious risk of bias due to assessor knowledge of treatment assignment. Rated down 2 levels for serious imprecision. The effect may be unstable because it is informed by few events. There is no established MID for this outcome and the clinical experts consulted by CDA-AMC could not provide a threshold of important difference. In the absence of a known threshold, the null was used.

Long-Term Extension Studies

No long-term extension study was submitted for this review.

Indirect Comparisons

Description of the Study

A sponsor-submitted ITC evaluated bulevirtide 2 mg relative to other comparators, including PEG-IFN and best supportive care or nucleos(t)ide analogue therapy in patients with chronic HDV infection. The following outcomes were reported to address the objectives of the network meta-analysis (NMA): undetectable HDV RNA, HDV RNA undetectable or reduced by at least 2 log₁₀ IU/mL (virologic response), combined response, ALT normalization at weeks 24 and 48, and AEs and treatment discontinuations due to AEs at week 48. The Bayesian NMA was conducted using both fixed-effect and random-effect models.

Efficacy Results

Combined Response

At week 48, results from the fixed-effects models suggested that bulevirtide 2 mg results in a favourable improvement in the combined response compared with both PEG-IFN (risk difference = ■; 95% credible interval [CrI], ■■■) and nucleos(t)ide analogue therapy (risk difference = ■; 95% CrI, ■■■). The corresponding random-effects models also indicated that bulevirtide 2 mg demonstrated a favourable improvement in the combined response compared with both pegylated interferon and nucleos(t)ide analogue therapy (risk difference = ■; 95% CrI, ■■■) and nucleos(t)ide analogue therapy (risk difference = ■; 95% CrI, ■■■). The point estimates were comparable across both the fixed-effects and random-effects models. Sensitivity analysis of the combined response was not feasible at week 48 due to the limited number of available studies.

Virologic Response

At week 48, results from the fixed-effects models indicated that bulevirtide 2 mg demonstrated a favourable improvement in the virologic response compared with both PEG-IFN (risk difference = ■; 95% CrI, ■■■) and nucleos(t)ide analogue therapy (risk difference = ■; 95% CrI, ■■■). However, the corresponding random-effects models yielded insufficient evidence to confirm a difference in the virologic response for the

bulevirtide 2 mg group compared with the PEG-IFN or nucleos(t)ide analogue therapy groups. The point estimates were comparable across both the fixed-effects and random-effects models.

ALT Normalization

At week 48, results from the fixed-effects models indicated that bulevirtide 2 mg suggested a favourable improvement in ALT normalization compared with both PEG-IFN (risk difference = ■; 95% CrI, ■■■) and nucleos(t)ide analogue therapy (risk difference = ■; 95% CrI, ■■■). The corresponding random-effects models yielded insufficient evidence to confirm a difference in the virologic response for the bulevirtide 2 mg group compared with the PEG-IFN or nucleos(t)ide analogue therapy groups. The point estimates were comparable across both the fixed-effects and random-effects models.

Undetectable HDV RNA

At week 48, results from the fixed-effects models suggested that bulevirtide 2 mg results in a favourable improvement in achieving undetectable HDV RNA compared with the nucleos(t)ide analogue therapy group (risk difference = ■; 95% CrI, ■■■). However, there was insufficient evidence to confirm a difference in achieving undetectable HDV RNA in the bulevirtide 2 mg group compared with the PEG-IFN (risk difference = ■; 95% CrI, ■■■). The corresponding random-effects models yielded insufficient evidence to confirm a difference in achieving undetectable HDV RNA in the bulevirtide 2 mg group compared with the PEG-IFN or nucleos(t)ide analogue therapy groups.

Harms Results

There was insufficient evidence to confirm a difference in the rates of AEs, serious AEs, or AEs leading to study withdrawal between bulevirtide at a 2 mg dose and treatment with PEG-IFN or nucleos(t)ide analogue therapy.

Critical Appraisal

The clinical experts consulted noted that, in the absence of approved treatments for HDV infection, some regimens included in the NMA — such as PEG-IFN and nucleos(t)ide analogues — were relatively appropriate comparators for bulevirtide. Although PEG-IFN can be used off-label to treat HDV infection, its use in clinical practice has become uncommon due to significant adverse effects, a global shortage, and limited availability in Canada. The clinical experts also noted that nucleos(t)ide analogues are used to manage HBV infection but have no direct effect on HDV infection. According to the clinical experts consulted, several comparators included in the NMA analyses are not relevant to the Canadian context, including bulevirtide plus tenofovir or PEG-IFN combined with adefovir, ribavirin, tenofovir, or entecavir. The literature search for the NMA was last updated by the sponsor in December 2021. The included studies were published between 2006 and 2019, indicating a temporal gap during which the treatment landscape has evolved. Potential bias may arise from an outdated literature search and the possible omission of relevant or unpublished evidence. The feasibility assessment for this NMA revealed considerable heterogeneity among the studies included in the analyses. There was considerable variation in study design, treatment duration and duration of follow-up, and regimen dosing, which may represent a potential source of heterogeneity. These sources of heterogeneity cannot be adjusted for within the NMA. Several important disease-specific characteristics were not reported in some studies within the network, which limits the ability to assess

heterogeneity between the studies. There were variations in patient populations across studies included in the NMA, particularly in baseline characteristics such as age, presence of cirrhosis, HDV RNA levels, ALT levels, and treatment history. The numerous sources of heterogeneity compromise the underlying transitivity assumption that must be met to produce valid conclusions from the NMA. Not all outcomes were reported across all studies included in the NMA. The network of interconnected studies was constructed using nucleos(t)ide analogues or delayed treatment as a common comparator. The clinical experts consulted considered this approach relatively appropriate because most patients with HBV and HDV coinfection receive nucleos(t)ide analogues for the management of HBV infection.

The network of evidence was sparse (i.e., few studies contributed to several comparisons); in many cases, there was only 1 study per link, which was insufficient to reliably estimate between-study variances. Bayesian fixed-effects models were used as a base-case analysis, with a random-effects model for the exploratory analysis. When heterogeneity is present, the CrIs of the fixed-effects model may be narrower and less conservative than the random-effects model, underestimating the uncertainty arising from between-study variation. The results of the random-effect models for most outcomes were affected by important imprecision, precluding a conclusion about which treatment may be favoured. The risk difference models were employed for the meta-analyses; however, their application may have limitations in this context. Specifically, the results of risk difference meta-analyses can be influenced by the nonreporting of zero-event outcomes. In addition, these models typically demonstrate lower statistical power and produce more conservative CIs compared to relative measures such as risk ratios, particularly when event rates are low. No patient-reported quality of life data, which was considered an important end point for this review, were evaluated. The NMA evaluated the comparative safety of bulevirtide relative to PEG-IFN and nucleos(t)ide analogues; however, the wide CrIs around these estimates indicate considerable uncertainty in the comparative safety outcomes.

Studies Addressing Gaps in the Evidence From the Systematic Review

SAVE-D Study

Description of the Study

SAVE-D was a multicentre, retrospective, real-world study (N = 244) to address the evidence gap regarding the effectiveness of bulevirtide beyond 48 weeks in patients with cirrhosis with and without clinically significant portal hypertension. Consecutive patients with HDV-related cirrhosis starting bulevirtide monotherapy were enrolled in the study. Chronic HDV infection was defined as RNA positivity for more than 6 months. Cirrhosis was defined either histologically (METAVIR score of F4), noninvasively by liver stiffness measurement greater than 12.5 kPa, or clinically (nodular liver surface, splenomegaly, thrombocytopenia).

Efficacy Results

All the enrolled patients (N = 244; 100%) had available assessments at baseline; of these, 87 (36%) had available assessments at week 96.

Key efficacy results evaluated at week 96 were:

- virological response (HDV RNA greater than or equal to 2 log decline₁₀ IU/mL): 79% of patients

- HDV RNA undetectable: 48% of patients
- biochemical response (ALT normalization less than 40 U/L): 64% of patients
- combined response (HDV RNA greater than or equal to 2 log decline or undetectable and ALT normalization): 54% of patients
- cumulative incidence of de novo HCC and liver decompensation: 3.0% and 2.8%, respectively.

Harms Results

Bulevirtide-related AEs were relatively mild, with a median bile acids increase from 15 μmol (IQR, 9 μmol to 32 μmol) at baseline to 36 μmol (IQR, 19 μmol to 66 μmol) at week 96 (all time points versus baseline $P < 0.001$). Mild and transient pruritus was also reported in 24 patients (10%).

Critical Appraisal

This was a single-arm, real-world study without a comparator, which means that comparative effectiveness conclusions relative to usual care could not be drawn. Further, the single-arm design does not allow for causal conclusions to be drawn. Major limitations of the SAVE-D study which increase uncertainty around effect estimates were the lack of investigation into possible missing outcome data between week 24 and week 96, which poses a high risk of bias; limited generalizability to Canada; and lack of reporting of HRQoL outcomes.

MYR203 Study

Description of the Study

MYR203 was a multicentre, open-label, randomized, comparative, parallel-arm phase II study to assess the efficacy and safety of bulevirtide in combination with PEG-IFN alfa versus PEG-IFN alfa alone in patients with chronic hepatitis B with delta-agent. Each treatment arm included 15 patients. The interventions relevant to this review were bulevirtide 2 mg subcutaneous monotherapy compared with PEG-IFN alfa alone.

Efficacy Results

The primary outcome of the study was HDV RNA response at week 72 (24 weeks post-treatment), defined as an HDV RNA value less than the lower level of detection, which is 10. Secondary outcomes were measured at 24 and 48 weeks, and comprised HDV RNA response, ALT normalization, combined response (negative HDV RNA and ALT normalization), and HDV RNA levels ($\log_{10}$ scale). Liver fibrosis measured with FibroScan was an additional secondary end point.

At week 72 (24 weeks post-treatment), for the primary efficacy end point of HDV RNA response, 0 of 7 patients (0.0%; 95% CI, 0% to 41.0%) treated with PEG-IFN alfa and 0 of 9 patients (0%; 95% CI, 0.0% to 33.6%) treated with bulevirtide 2 mg had an HDV RNA response at week 72. No patients (0 of 15 patients in each group) treated with PEG-IFN alfa only or bulevirtide 2 mg only had an HDV RNA response at week 72.

At week 48, the secondary end points for the PEG-IFN alfa and bulevirtide 2 mg groups differed by end point. The same number of patients (2 of 15; 13.3%; 95% CI, 1.7% to 40.5%) treated with PEG-IFN alfa and bulevirtide 2 mg had an HDV RNA response at week 48. For ALT normalization, 4 of 15 patients (26.7%; 95% CI, 7.8% to 55.1%) treated with PEG-IFN alfa and 11 of 15 patients (73.3%; 95% CI, 44.9% to 92.2%)

treated with bulevirtide 2 mg had ALT normalization at week 48. For combined response (negative HDV RNA and ALT normalization), 1 of 15 patients (6.7%; 95% CI, 0.2% to 31.9%) treated with PEG-IFN alfa alone and 2 of 15 patients (13.3%; 95% CI, 1.7% to 40.5%) treated with bulevirtide 2 mg alone had a combined response at week 48.

For liver stiffness, there was no statistically significant difference in the change from baseline between the group receiving bulevirtide alone compared to the PEG-IFN alfa group at any time point.

Harms Results

There were no deaths in the study and none of the AEs were considered suspected unexpected serious adverse reactions.

Critical Appraisal

Although MYR203 was an exploratory phase II trial, the very small sample sizes (baseline: n = 15 per group) and that all patients were recruited from Russia limits the generalizability of these findings to bulevirtide use in Canada. There was a risk of bias due to missing outcome data for the primary end point (HDV RNA response at 72 weeks), with declining sample sizes for the comparator PEG-IFN alfa (n = 7) and bulevirtide 2 mg (n = 9) groups. Additionally, HRQoL outcomes were not reported.

Economic Evidence

- Bulevirtide is available as a powder for solution for subcutaneous injection (2 mg/mL). At the submitted price of \$437.07 per vial, the annual cost of bulevirtide is expected to be \$159,641 per patient, based on the dosage recommended by Health Canada.
- Comparative clinical efficacy in the economic analysis was derived from the MYR301 trial, which compared bulevirtide with a delayed treatment group. Evidence submitted by the sponsor indicates that bulevirtide is likely to reduce HDV RNA detection, defined as an undetectable level of HDV RNA and/or by a reduction of HDV RNA by at least 2 log₁₀ IU/mL from baseline, and ALT normalization compared with delayed treatment among adult patients with HDV infection and compensated liver disease.
- The results of the CDA-AMC base-case analysis suggest the following:
 - Bulevirtide is predicted to be associated with higher costs to the health care system than best supportive care (incremental costs = \$1,297,909), primarily driven by increased costs associated with bulevirtide.
 - Bulevirtide is predicted to be associated with a gain of 4.01 life-years compared to best supportive care and may result in a gain of 3.38 QALYs compared to best supportive care.
 - The ICER of bulevirtide compared to best supportive care is \$383,943 per QALY gained.
 - Approximately 99.1% of the predicted incremental benefits were accrued based on extrapolation where there are no trial data. The model assumed treatment efficacy would be maintained over a

lifetime as responders would remain on life-long treatment. Because of the uncertainty in the long-term efficacy of bulevirtide and the optimal duration of treatment, these uncertainties suggest the CDA-AMC base-case analysis may overestimate the health benefits associated with bulevirtide.

- CDA-AMC estimates that the budget impact of reimbursing bulevirtide for the treatment of chronic HDV infection in adults with compensated liver disease will be approximately \$44,973,750 over the first 3 years of reimbursement compared to the amount currently spent on best supportive care. Because there are no drug costs associated with best supportive care, this amount reflects the estimated expenditure for bulevirtide. The actual budget impact of reimbursing bulevirtide will depend on the negotiated drug price of bulevirtide and the number of people eligible for treatment.

Request for Reconsideration

The sponsor and the public drug plans filed a request for reconsideration of the draft recommendation for bulevirtide for the treatment of chronic HDV infection in adults with compensated liver disease.

In their request, the sponsor identified the following issues:

- The sponsor stated that using ALT normalization as a renewal criterion in the clinical assessment of HDV progression does not align with the evidence and clinical practice.
- The sponsor stated that the initiation criteria do not align with the evidence provided. Specifically, the sponsor noted that a platelet count of equal to or greater than 60,000 cells/mm³ is not an appropriate marker to diagnose HDV infection. In addition, obtaining a positive PCR result for HDV RNA within the past 6 months is burdensome to patients and the health care system in Canada.

In their request, the drug plans identified the following issues:

- The drug plans sought clarification on whether normalization is a realistic expectation for patients with ALT levels approaching 10 times the upper limit of normal, and whether partial improvement — without normalization — would still be considered a clinically meaningful response that justifies continued treatment.
- The drug plans sought clarification on the discontinuation criteria regarding whether bulevirtide treatment should be discontinued in patients who require a liver transplant for reasons other than decompensated liver disease.

In the meeting to discuss the sponsor's and the public drug plan's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with chronic HDV infection
- feedback on the draft recommendation from 2 clinician groups, which included the Canadian Hepatitis B Network and the Hamilton Hepatology Clinical Group, and 5 independent clinicians.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Initial meeting date: August 27, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Minor reconsideration CDEC subpanel meeting date: December 9, 2025



Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Disclaimer: CDA-AMC has taken care to ensure that the information in this document was accurate, complete, and up to date when it was published, but does not make any guarantee to that effect. Your use of this information is subject to this disclaimer and the Terms of Use at cda-amc.ca.

The information in this document is made available for informational and educational purposes only and should not be used as a substitute for professional medical advice, the application of clinical judgment in respect of the care of a particular patient, or other professional judgments in any decision-making process. You assume full responsibility for the use of the information and rely on it at your own risk.

CDA-AMC does not endorse any information, drugs, therapies, treatments, products, processes, or services. The views and opinions of third parties published in this document do not necessarily reflect those of CDA-AMC. The copyright and other intellectual property rights in this document are owned by the Canadian Agency for Drugs and Technologies in Health (operating as CDA-AMC) and its licensors.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.