bulevirtide 2mg powder for solution for injection (Hepcludex®)

Gilead Sciences Ltd

10 February 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

bulevirtide (Hepcludex®) is accepted for restricted use within NHSScotland.

Indication Under Review: for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

SMC restriction: to use in patients with evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to interferon-based therapy or who are ineligible to receive interferon-based therapy due to intolerance or contra-indication.

In an open-label, phase III study, combined virological and biochemical response at week 48 was significantly improved with bulevirtide compared with observation in patients with HDV infection.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Bulevirtide is a lipopeptide that binds specifically to the sodium (Na^+) taurocholate co-transporting polypeptide (NTCP) and blocks the entry of hepatitis B virus and hepatitis D virus into hepatocytes. It is administered as a subcutaneous injection at a dose of 2mg once daily. The optimum duration of treatment is unknown and treatment should be continued as long as associated with clinical benefit. [1, 2]

1.2. Disease background

Hepatitis D is an inflammation of the liver caused by the hepatitis delta virus, a satellite of hepatitis B virus requiring its presence for replication. It is thought that nearly 5% of patients with chronic hepatitis B are also infected with hepatitis D. Patients with hepatitis D have a more progressive course of liver disease compared with those infected with hepatitis B alone. It has been associated with faster progression to fibrosis and cirrhosis, an earlier onset of hepatic complications and need for liver transplant. In patients with hepatitis B and D, liver cirrhosis and cancer generally occur earlier and the mortality rate at 5 years is double that for patients infected only with hepatitis B.[2]

1.3. Company proposed position

The submitting company has requested that bulevirtide is restricted for use in adults with chronic hepatitis delta who have compensated liver disease, and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to interferon-based therapy or who are ineligible to receive interferon-based therapy due to intolerance or contra-indication. Clinical experts consulted by SMC indicated that transient elastography, using non-invasive Fibroscan, is generally performed in clinical practice with the results translated into the equivalent METAVIR stage.

1.4. Treatment pathway and relevant comparators

Guidelines recommend a 48-week course of off-label peginterferon alfa for patients with hepatitis D and evidence of significant fibrosis. However, this has been associated with limited efficacy in terms of sustained virological response (25 to 30% of patients) and later relapses (more than 50% of patients). Moreover, only about half of patients are suitable for peginterferon alfa because of contra-indications, intolerance or advanced liver disease. Bulevirtide is the first medicine to be licensed for the treatment of hepatitis D. Continued therapy with nucleoside/nucleotide analogues is recommended for patients with ongoing hepatitis B virus (HBV) RNA replication but these have negligible antiviral effect in hepatitis D virus replication.[2-4] Based on the positioning proposed by the submitting company, the most relevant comparator is best supportive care (BSC).

1.5 Category for decision-making process

Eligibility for interim acceptance decision option

Bulevirtide has conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA).

Eligibility for a PACE meeting

Bulevirtide meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of bulevirtide for the treatment of hepatitis D comes from the MYR 301 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	MYR 301[5, 6]
Study Design	An ongoing, randomised, multicentre, open-label, phase III study.
Eligible Patients	• aged 18 to 65 years • positive serum anti-hepatitis delta virus (HDV) antibody results or polymerase chain reaction (PCR) result for serum or plasma HDV RNA for ≥6 months before screening • positive PCR results for serum or plasma HDV RNA at screening • alanine aminotransferase (ALT) level >1 x upper limit of normal (ULN) but <10 x ULN • serum albumin >28g/L.
Treatments	Bulevirtide 10mg subcutaneously (SC) daily for 144 weeks, bulevirtide 2mg SC daily for 144 weeks or delayed treatment (observation until week 48 then bulevirtide 10mg SC daily to week 144).
Randomisation	Stratified by presence of cirrhosis. Randomised in a ratio of 1:1:1.
Primary outcome	The primary outcome was combined response at week 48 assessed in the full analysis set. Combined response was defined as an undetectable HDV RNA (below the limit of detection) or decrease in HDV RNA by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalisation (defined as ALT ≤ULN regardless of baseline ALT level).
Secondary outcomes	Undetectable HDV RNA at week 48 (between bulevirtide 10mg and 2mg). ALT normalisation at week 48. Change from baseline in liver stiffness at week 48, 96, 144, 192 and 240. HDV RNA decrease by ≥2 $\log_{10}$ IU/mL or undetectable HDV RNA at week 48 was an additional efficacy outcome.
Statistical analysis	A hierarchical testing procedure was applied to the primary and key secondary outcomes in the study with no formal testing after the first non-significant outcome in the hierarchy. The hierarchy tested the difference in the primary outcome (combined response) initially between the bulevirtide 10mg group and then the bulevirtide 2mg group versus delayed treatment, followed by the key secondary outcome of proportion of patients with undetectable HDV RNA tested between the bulevirtide 10mg and bulevirtide 2mg groups.

The primary outcome of combined response at week 48, tested hierarchically in the bulevirtide 10mg and then 2mg group versus delayed treatment, was significantly greater in both bulevirtide groups ($p<0.001$). Since only the bulevirtide 2mg dose has received marketing authorisation and is relevant to this submission, results for the bulevirtide 2mg and delayed treatments groups are presented in Table 2.2. Other secondary outcomes included the proportion of patients with ALT normalisation at week 48 and change from baseline in liver stiffness measured by elastography.

Sustained virological response (patients with undetectable HDV RNA 24 and 48 weeks after treatment stopped) was also a secondary outcome but has not yet been reached.[7, 8]

Table 2.2: Results for the primary and selected outcomes at week 48 in the full analysis set of MYR 301[7, 8]

Primary and selected secondary outcomes at week 48	Bulevirtide 2mg (n=49)	Delayed treatment (n=51)
Combined response	45% (22/49)[A]	2.0% (1/51)
Proportion of patients with ALT normalisation	51% (25/49)	12% (6/51)
LS mean change from baseline in liver stiffness (kPa)	-3.08	0.88
Proportion of patients with HDV RNA decrease by ≥2 log_{10} IU/mL or undetectable HDV RNA	71% (35/49)	3.9% (2/51)

[A] p<0.001 versus delayed treatment. ALT=alanine aminotransferase. kPA=kilopascal. Combined response= undetectable HDV RNA or decrease in HDV RNA by ≥2 log_{10} IU/mL from baseline plus ALT normalisation at week 48. ALT normalisation (ALT ≤ULN).

2.2. Evidence to support the positioning proposed by the submitting company

To support the proposed positioning, the company presented results of post hoc analysis for the bulevirtide 2mg and delayed treatment groups only in patients who had previously received interferon-based treatment. On request, the company clarified that no data were available on the level of response and tolerability to previous interferon-based therapy or for patients with evidence of significant fibrosis (METAVIR stage ≥F2). However, the company considered that since the NICE clinical guideline recommends that pegylated interferon is restricted to patients who have evidence of significant fibrosis (METAVIR fibrosis stage ≥F2, or Ishak stage ≥3), it was expected that any patient who had received interferon-based therapy would also have evidence of significant fibrosis.

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) outcomes were exploratory, and assessed using the EuroQoL 5 dimensions (EQ-5D-3L) questionnaire, the fatigue severity scale and the Hepatitis Quality of Life Questionnaire (HQLQ). At week 48, scores for the individual EQ-5D-3L domains, EQ-visual analogue scale (VAS), fatigue severity scale and HQLQ components were generally similar in all three treatment groups with the exception of EQ VAS and some components of the HQLQ. The HQLQ, for role-physical, hepatitis-specific limitations and hepatitis-specific health distress, indicated some improvement in the bulevirtide 2mg group compared with delayed treatment.[6, 9]

2.4. Supportive studies

The company presented supportive data from an open-label, randomised, multicentre, phase II study (MYR 202) in adult patients with chronic hepatitis D who had liver cirrhosis, or who had failed previous interferon treatment or for whom such treatment was contraindicated. Patients were randomised equally to bulevirtide 2mg SC daily (n=28), 5mg SC daily (n=32) or 10mg SC daily (n=30), all in combination with the nucleotide analogue, tenofovir 245mg orally daily, or tenofovir alone (n=28) for 24 weeks. All patients had compensated liver disease, 50% had liver cirrhosis at baseline and 57% had received interferon therapy. The primary outcome was HDV RNA response (defined as undetectable HDV RNA or a decrease in HDV RNA by ≥2 log_{10} IU/mL from baseline) at

24 weeks in all randomised patients who received at least one dose of study treatment. Significantly more patients in all three bulevirtide plus tenofovir groups achieved an HDV RNA response (54% with bulevirtide 2mg versus 3.6% with tenofovir alone). A higher proportion of patients also achieved a combined response at 24 weeks (21% versus 0%, respectively). Results at 48 weeks, 24 weeks after stopping bulevirtide, suggested that most patients lost HDV RNA response.[1, 2, 10]

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the MYR 301 study, by week 48, any treatment-emergent adverse event (AE) was reported by 82% (40/49) in the bulevirtide 2mg group and 76% (39/51) of patients in the delayed treatment group, and these were considered treatment-related in 49% and 0%, respectively. In the bulevirtide 2mg and delayed treatment group respectively, patients reporting a grade 3 or higher AE were 10% versus 5.9%, patients with a reported serious AE were 4.1% versus 2.0%. No patients in any group discontinued therapy due to an AE.[7, 8]

Frequently reported treatment-emergent AEs of any grade with an incidence >5% in the bulevirtide 2mg and delayed treatment group, respectively, were: headache (18% versus 0%), all injection site reactions (including erythema, pruritus, swelling, pain, haematoma etc: 16% versus 0%), pruritus (12% versus 0%), fatigue (10% versus 2.0%), nausea (6.1% versus 3.9.[6, 7]

An increase in bile salts due to inactivation of the NTCP channel has been observed with bulevirtide and is noted in the SPC. This increase is reversible upon discontinuation of treatment. In patients with renal insufficiency, the increase in bile salts may be more pronounced.[1, 2]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Bulevirtide is the first medicine to be licensed for the treatment of hepatitis D.
- Bulevirtide 2mg was superior to delayed treatment in MYR 301 with a 43% improvement in the primary outcome of combined response at week 48. This was supported by numerically favourable results for each component of combined response and other secondary outcomes.[7, 8]

4.2. Key uncertainties

- The components of the primary outcome are surrogate virological and biochemical outcomes. The surrogacy of decreases in plasma HDV RNA for clinical benefit in hepatitis D has not been established. However, elevated ALT is suggestive of ongoing necro-inflammation of the liver and ALT normalisation has been associated with a decrease in the rate of progression of fibrosis to cirrhosis in hepatitis B and C and is considered relevant for hepatitis D. Therefore

the regulatory authorities considered that combined response was an appropriate primary outcome to assess clinical benefit for this first medicine for hepatitis D.[4]

- Longer term data on sustained virological response and disease progression to clinically important disease specific events, including cirrhosis and liver transplant, are not available. Further data will be available in 2025 when the final MYR 301 study results are available.

- Evidence to support the positioning comes from post hoc analysis in the subgroup of patients who had previously received interferon but this was not pre-planned and included small patient numbers and should be treated with caution. The level of response or tolerance to previous interferon in these patients is unknown and it is unclear if they reflect the exact positioning. It is unknown how many patients in MYR 301 had contraindications to interferon but since interferon is likely to be offered to almost all eligible patients with compensated liver disease as recommended in guidelines, the subgroup of patients who had not received interferon may have been contraindicated. There were insufficient data to identify patients in this subgroup who had a METAVIR stage of ≥F2 and the company considered that, in line with UK guidelines, all patients who had received previous interferon would have significant fibrosis. However this has not been separately confirmed as study patients were not required to have a liver biopsy.[3] In addition, there were no study patients from UK centres and it is unclear if previous treatment with interferon would have followed these guidelines.

- Within the positioning, the company defined evidence of significant fibrosis as a METAVIR stage of ≥F2. METAVIR staging requires a liver biopsy. Clinical experts consulted by SMC indicated that transient elastography, using non-invasive Fibroscans, is generally performed in clinical practice with the results translated into the equivalent METAVIR stage.

- There is some uncertainty on the optimal duration of bulevirtide therapy and this will be investigated further in MYR 301.[2, 11]

4.3. GB/EMA conditional marketing authorisation specific obligations

The specific obligation for the European Union and consequently the MHRA (due to authorisation through the reliance route) is that the MYR 301 study assessing the efficacy and safety of bulevirtide in patients with chronic hepatitis D will be completed by 28 February 2025. Further results from MYR 301 could provide evidence on sustained virological response after completing 144 weeks of treatment with bulevirtide, as well as further insight in to the optimal duration of treatment. Further results on liver stiffness measured by elastography could provide data on the level of progression of liver disease.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that bulevirtide fills an unmet need in this therapeutic area since available treatment is currently limited to interferon.

Clinical experts consulted by SMC considered that bulevirtide is a therapeutic advancement due to no other treatments being available in this proposed positioning.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of bulevirtide would require training and support for patients to administer subcutaneously each daily. However, patient numbers were expected to be small.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of bulevirtide, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Less than 5% of patients with chronic hepatitis B are co-infected with hepatitis D. This is the most severe form of hepatitis with increased risk of progressive liver disease causing cirrhosis, hepatocellular carcinoma and liver failure. The disease and its symptoms have a significant physical and mental impact on patients.
- Treatment options are limited to the off-label use of interferon which has poor sustained efficacy and is not tolerated or is contraindicated in many patients. Liver transplant is the only other available treatment so there is a significant unmet need for further effective options. Bulevirtide is the first medicine to be licensed for the treatment of hepatitis D.
- Bulevirtide offers a novel treatment option for patients with hepatitis D and in responding patients may provide long term viral suppression, stabilise liver disease and reduce the risk of disease progression to cirrhosis and liver cancer. It may also result in some disease regression in advanced cases and prevent liver failure and the need for liver transplant. This may relieve the physical and emotional burden of the disease on patients and improve their quality of life.
- PACE clinicians noted that although off-label interferon is recommended, a significant proportion of patients with hepatitis D are likely to have contraindications to its use and would be eligible for bulevirtide. The patient group representatives were supportive of bulevirtide for all patients due to its improved tolerability compared with interferon.
- Bulevirtide requires daily subcutaneous injection. However self-administration was expected to be acceptable to patients given the potential benefits and its tolerability and have minimal service implications for training given the small patient numbers.

Additional Patient and Carer Involvement

We received a joint patient group submission from HIV Scotland and Hepatitis Scotland. HIV Scotland is a registered charity. Hepatitis Scotland is part of the Scottish Drugs Forum which is a registered charity. Hepatitis Scotland has not received any pharmaceutical company funding in the past two years. HIV Scotland has received 18.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from HIV Scotland participated in the PACE meeting. The key points of the joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	A lifetime time horizon was used. The mean baseline age was 36. Assuming a lifetime of 100 years, the time horizon used in the model was 64 years.
Population	The submitting company requested SMC considers bulevirtide when positioned for the treatment of adults with CHD who have compensated liver disease and evidence of significant fibrosis (METAVIR stage greater than or equal to F2), whose disease has responded inadequately to interferon-based (IFN- based) therapy, or who are ineligible to receive IFN-based therapy due to intolerance or contra-indication.
Comparators	Best supportive care (BSC). This consisted of current clinical practice for HDV patients and included non-specific treatments and care. This was generally defined as symptomatic treatment, alongside treatment for the underlying hepatitis B.
Model description	A Markov state transition model was presented with the following health states: METAVIR stages F0 to F4 (compensated cirrhosis), hepatocellular carcinoma (HCC), decompensated cirrhosis (DCC), liver transplant (LT), post-liver transplant (PLT), death. Non-responders discontinued treatment at 48 weeks, with partial responders discontinuing treatment at 72 weeks. Patients were distributed across F2 to F4 health states at baseline. Model transition probabilities were derived from literature. Transitions slowed for partial responders and mostly halted for complete responders. Fibrosis regression was included for complete responders. Mortality rates increased compared to general population for those in the HCC, DCC, LT and PLT health states. A 24-week cycle length was used.
Clinical data	Clinical effectiveness data were derived from MYR 301 using the bulevirtide 2mg and delayed treatment (for BSC) arms. Week 24 and week 48 responses rates for complete responders (composite response, HDV-RNA undetectability or ≥2-log10 IU/ml decline and ALT normalisation) and partial responders (virologic response, HDV-RNA undetectability or 2-log10 decline) were used in the model. The week 48 complete response rates were 44.9% for bulevirtide and 1.96% for BSC.
Extrapolation	MYR 301 data were not extrapolated beyond Week 48 in the base case. A scenario analysis extends beyond the trial follow-up period, with the combined and virologic rates for the 2mg bulevirtide and delayed treatment arms of MYR 301 extrapolated to 72 weeks. A 96 week extrapolation was also available.
Quality of life	EQ-5D-3L data were collected in MYR 301 at baseline, week 24 and week 48. A utility increment for bulevirtide was added to the BSC utility in the F0 to F4 health states. Utility values for all health states were derived from a meta-analysis of chronic hepatitis B utilities. The resulting utility values were 0.85 for F0 to F3 (BSC only), 0.76 for F4 (BSC only), 0.46 for DCC, 0.52 for HCC, 0.57 for LT, and 0.67 for PLT.
Costs and resource use	Medicine costs included acquisition of bulevirtide, adverse events, and monitoring. In addition, health state costs for HDV were applied to each health state in the model.[12, 13] Health states F0 to F4 also included the costs of antiviral therapy to treat underlying HBV infection.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case results are presented in Table 6.2. The incremental costs were primarily due to the acquisition cost for bulevirtide, with the majority of incremental quality adjusted life year (QALY) gain for bulevirtide obtained in the fibrosis health states.

Table 6.2: Base case cost-effectiveness results with PAS

Technologies	Total life year gain	Incremental cost-effectiveness ratio (ICER) (£/QALY)
BSC	7.90	
Bulevirtide	11.94	34,520

Abbreviations: BSC = best supportive care

6.3. Sensitivity analyses

A number of sensitivity analyses were provided and the key scenarios are summarised in Table 6.3. The scenarios with the largest impact on the ICER were the reduction in time horizon, exclusion of fibrosis regression and the changing the definition of complete responder. Alternate sources of health state utility values and the use of extrapolated response rates showed ICER results consistent with base case.

Table 6.3: Scenario analyses with PAS

	Structural assumption	Base-case	Other scenarios considered	ICER vs. BSC (£/QALY)
-	Base-case			34,520
1	Patients' baseline fibrosis status	F2-F4	F3-F4	32,737
2	Utility gain for responders	Included	Excluded	37,631
3	Fibrosis regression	Included	Excluded	39,583
4	Hazard ratios for progression in complete responders versus partial responders (except death)	Assumed zero	Assumed half	37,576
5	Definition of complete responder	Combined	Virologic	40,182
6	Extrapolation of 48-week MYR 301 response data	No	Yes	33,964
7	Source of health state utility values for F0-F4 health states	CHB meta-analysis	MYR 301	35,492
8	Source of health state utility values	CHB meta-analysis	Chronic HCV meta-analysis	35,788
9	Time Horizon	64 years	10 years	74,869
10	Time Horizon	64 years	20 years	46,702

11	MYR 301 48-week response data	Full-analysis set	Previously treated with IFN-based therapy	34,867
12	Response Rates	Full-analysis set	METAVIR score ≥F2	30,944
13	Response Rates	Full-analysis set	FibroScan score ≥7.25 kPA	34,486
14	Response Rates	Full-analysis set	FibroScan score ≥8.0 kPA	34,329

Abbreviations: BSC = best supportive care, CHB = chronic hepatitis B, INF = interferon, F0 = fibrosis stage 0, F1 = fibrosis stage 1, F2 = fibrosis stage 2, F3 = fibrosis stage 3, F4 = fibrosis state 4 (compensated cirrhosis), HCV = hepatitis C virus, LYG = life-years gained, QALYs = quality-adjusted life years.

6.4. Key strengths

• The economic analysis used individual patient data from the MYR 301 study for bulevirtide.

• Natural history transition probabilities were obtained through systematic review and meta-analysis of the relevant literature.

• Comprehensive selection of variables considered in one-way deterministic sensitivity analysis.

6.5. Key uncertainties

• The complete and partial response rates from the full analysis set of MYR 301 consisted of patients who were both naïve and experienced to previous IFN-based therapy. These may not be fully reflective of the medicine's positioning of inadequate response to IFN-based therapy, or ineligibility to receive IFN-based therapy due to intolerance or contra-indication. It was unknown how many patients in MYR 301 had contraindications, but based on guideline recommendations it is likely that patients naïve to IFN-based therapy may have been contraindicated. Regarding IFN-based therapy experienced patients, a sensitivity analysis using response rates from a post hoc clinical analysis for patients previously treated with IFN-based therapy showed ICER insensitivity (table 6.3 scenario 11). However, this sensitivity analysis was limited, as a breakdown by level of response and tolerability to previous IFN-based therapy was not available, in addition to small patient numbers. The METAVIR fibrosis stages of those previously treated with IFN-therapy was also not available to support the assumption, in line with clinical guidelines, that all patients previously receiving IFN-based therapy had significant fibrosis. Although these limitations were present, the analysis did provide indicative evidence to support limited uncertainty in the ICER when considering previous use of IFN-based therapy.

• MYR 301 observed response data at 24 and 48 weeks were used in the base case. Increases and decreases in the composite response rates were present in the bulevirtide 2mg and delayed treatment arms in the observed data. This increased uncertainty as those who obtained a complete response remained as complete responders for the duration of the time horizon with no accounting for potential loss of complete response over time. Further observed response data would ease this limitation.

• Given the response data from MYR 301 was only available to 48 weeks (with extrapolation to 96 weeks), the accuracy of reflecting differences in costs and QALYS over a 64 year time horizon may be uncertain. A 10-year time horizon increased the ICER to £74,869, with a 20-year time horizon increasing it to £46,702. These scenarios demonstrated a reduced QALY gain, relative to costs, for bulevirtide under shortened time horizons. The benefit of bulevirtide over an extended period would need to be realised to reduce uncertainty in the base case ICER.

• Clinicians consulted by SMC indicated that FibroScan scores would be used as a proxy for METAVIR stages to assess fibrosis in clinical practice. Scenario analysis using MYR 301 response data from patients with significant fibrosis assessed using FibroScan provided indicative evidence that ICERs would remain consistent with the base case when considering FibroScan scores as a proxy for METAVIR fibrosis stages (Table 6.3 scenarios 13 and 14).

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of bulevirtide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as bulevirtide is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted buelvirtide for restricted use in NHSScotland.

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published the "Hepatitis B (chronic): diagnosis and management" clinical guideline (CG) 165 in 2013, which was updated in 2017.[3] The guideline recommends that patients co-infected with chronic hepatitis B and hepatitis delta infection, who have evidence of significant fibrosis (defined as METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3), should be offered a 48-week course of peginterferon alfa-2a. Consider stopping peginterferon alfa-2a if there is no decrease in DV RNA after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually. Stop treatment after HBsAg seroconversion.

The European Association for the Study of the Liver (EASL) published "EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection"[2], which updates the previous guidance from 2012.[4, 14] The guideline stipulates that pegylated interferon alfa for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease. Pegylated interferon alfa treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated. However, the guidance notes that the success rate of these treatments is low. Nucleos(t)ide analogue therapy should be considered in HDV-HBV co-infected patients with ongoing HBV DNA replication, although the guidance notes that neither NAs nor ribavirin showed significant effects on HDV RNA levels in patients with HDV infection. The guideline also notes that several candidates are being evaluated in clinical trials mainly in combination with pegylated interferon alfa and/or nucleos(t)ide analogue including HBV/HDV

entry inhibitors (bulevirtide), drugs inhibiting the release of HBsAg (nucleic acid polymers) and inhibitors of the prenylation of the large HDV antigen. Whenever possible, enrolment in these new clinical trials should be considered.

These guidelines predate the availability of bulevirtide.

9. Additional Information

9.1. Product availability date

September 2022

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety. Bulevirtide 2mg powder for solution of injection (Hepcludex®).

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
bulevirtide	**2mg SC once daily**	**78,867**

Costs from eMC Dictionary of Medicines and Devices Browser on 7 November 2022. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 7 patients eligible for treatment with bulevirtide in year 1 and 9 patients in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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14. European Association For The Study Of The Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. Journal of Hepatology 2012; 57(1): 167-85.

This assessment is based on data submitted by the applicant company up to and including 09 December 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.