NICE National Institute for Health and Care Excellence

NICE guidance

Bulevirtide for treating chronic hepatitis D

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Bulevirtide is recommended as an option for treating chronic hepatitis D in adults with compensated liver disease only if:

- there is evidence of significant fibrosis (METAVIR stage F2 or above or Ishak stage 3 or above) and
- their hepatitis has not responded to peginterferon alfa-2a (PEG-IFN) or they cannot have interferon-based therapy.

Bulevirtide is only recommended if the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with bulevirtide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with hepatitis D also have hepatitis B. There are no other licensed treatments specifically for hepatitis D. Standard care usually involves treating symptoms and the hepatitis B. People with significant fibrosis (scarring) in their liver can be offered PEG-IFN, but it is not licensed for this use.

The company positioned bulevirtide for people with chronic hepatitis D who have tried PEG-IFN and whose condition did not respond to it, or for people who cannot have interferon-based therapy. The company also only positioned it for METAVIR stage F2 or above (which means they have significant fibrosis). Testing for METAVIR stage usually involves a biopsy, which is invasive and may have side effects, and many people decline it. But NICE's guideline on diagnosing and managing chronic hepatitis B recommends transient elastography (FibroScan), which is a non-invasive assessment. It also recommends that hepatitis D with significant fibrosis is defined by a METAVIR stage of F2 or above, or an Ishak stage of 3 or above.

Clinical trial evidence shows that bulevirtide is effective compared with standard care despite some uncertainties around how long it works for. Despite the uncertainties in the clinical trial evidence, the cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources. So bulevirtide is recommended.

2 Information about bulevirtide

Marketing authorisation indication

2.1 Bulevirtide (Hepcludex, Gilead) has a conditional marketing authorisation 'for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV RNA positive adult patients with compensated liver disease'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for bulevirtide.

Price

2.3 The list price of 2 milligram vials of bulevirtide is £6,500 for 30 vials (excluding VAT; BNF online accessed May 2023).

2.4 The company has a commercial arrangement. This makes bulevirtide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Gilead, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition, treatment pathway and positioning

Hepatitis D disease burden

3.1 Hepatitis D is an infectious disease of the liver caused by the hepatitis delta virus (HDV). Around half of all people who acquire HDV will develop chronic hepatitis D, defined as an infection lasting longer than 6 months. Hepatitis D only affects people who are already infected with the hepatitis B virus (HBV) because HDV needs the hepatitis B surface antigen to complete its replication. The patient expert explained the significant impact co-infection with hepatitis B and D has on their physical and mental health. They emphasised that the extreme lethargy associated with the condition affects their day-to-day functioning and ability to walk short distances. They also explained that changes to their lifestyle such as stopping smoking or eating healthily have had limited impact on improving the symptoms of their condition, which have been a constant burden for over 10 years. The committee noted the high disease burden of chronic hepatitis D.

Treatment pathway and unmet need

3.2 The treatment options for people with chronic hepatitis D are limited. Clinical experts explained that people with hepatitis D would have treatment according to the recommendations in NICE's guideline on diagnosing and managing chronic hepatitis B. People co-infected with hepatitis D, with evidence of significant fibrosis, can be offered a 48-week course of peginterferon alfa-2a (PEG-IFN). The clinical experts explained that using PEG-IFN to treat hepatitis D is off label, can have serious side effects, and is not effective for most people. They also said

that a large proportion of people would also have antivirals (tenofovir and entecavir) for their underlying hepatitis B infection. If hepatitis B is cured, the hepatitis D virus cannot survive. But hepatitis B has a low chance of being cured with current treatments. The clinical experts explained that bulevirtide is a first-in-class medicine that addresses an unmet need for effective and well-tolerated treatments. They added that there is regional variation in providing tests for HDV, even though NICE's guideline on diagnosing and managing chronic hepatitis B recommends that everyone with HBV should have one. The clinical experts added that even if bulevirtide was available, there may still be undiagnosed hepatitis D in people with undiagnosed hepatitis B. They also noted the limited number of laboratories testing for hepatitis D. But, if bulevirtide was available, there would be an extra incentive to identify people with HDV, which may arguably make access to diagnosis more equal across the country. The committee concluded that there is a significant unmet need for effective treatments in this population because the current options are limited.

Positioning of bulevirtide in the treatment pathway

3.3 The clinical evidence presented for bulevirtide came from MYR 301, a phase 3, multicentre, open-label, randomised trial evaluating the clinical efficacy and safety of bulevirtide in people with chronic hepatitis D and compensated liver disease. The marketing authorisation also specifies that bulevirtide should be considered for people with chronic hepatitis D and compensated liver disease. But the company positioned bulevirtide for a narrower population as a treatment for chronic hepatitis D with compensated liver disease and evidence of significant fibrosis, which it defined as a METAVIR fibrosis score of F2 or above. The condition should also have not responded well enough to PEG-IFN, or the person with hepatitis D should not be able to tolerate PEG-IFN or should have a contraindication. The company clarified that most people in MYR 301 had already had interferon treatment, and those who had not were likely to have a contraindication or not be able to tolerate it. The EAG accepted this but was concerned that the company's evidence included people not relevant to the decision problem it had specified. The company presented data from the full analysis set from MYR 301, which included people with all METAVIR fibrosis stages (F0 to F4). It explained that its

positioning addressed the area of highest unmet need. The clinical experts said that everyone with hepatitis D has an unmet need for treatments that prevent disease progression, and if bulevirtide was recommended, they would prefer to use it as an alternative to PEG-IFN. At consultation, the company noted that its proposed positioning aligned with the recommendations in NICE's guideline on diagnosing and managing chronic hepatitis B, which recommends that people with hepatitis D and significant fibrosis (defined by METAVIR stage F2 or above or Ishak stage 3 or above) should be offered a course of PEG-IFN. The committee considered that this positioning was appropriate.

Fibrosis staging

3.4 The clinical experts explained that it would be difficult to identify the company's proposed population in clinical practice. METAVIR staging is done using a liver biopsy, which is invasive and carries a morbidity and mortality risk. So, many people refuse this procedure. The committee agreed that, even if it accepted that it is clinically appropriate to limit bulevirtide to people with significant fibrosis, defined by a liver biopsy, it may not be possible to implement such a rule in practice. NICE's guideline on diagnosing and managing chronic hepatitis B recommends a non-invasive assessment, transient elastography (FibroScan), for everyone with HBV. Liver biopsy is only offered to confirm the level of fibrosis in adults with a transient elastography score of between 6 kPa and 10 kPa. The clinical experts explained that, in practice, clinicians would likely use transient elastography to determine eligibility for bulevirtide, along with serological tests and imaging. The committee heard that the company had collected transient elastography data in MYR 301. It considered that, if it was not possible to position bulevirtide as a first-line treatment, it would be useful for the company to present data using transient elastography rather than liver biopsy (METAVIR staging) to assess fibrosis. This is because this approach more closely reflects current clinical practice for determining fibrosis stage to identify eligible people. At consultation, the company reiterated the positioning in its base-case model of bulevirtide as a treatment for people with chronic hepatitis D, compensated liver disease and evidence of significant fibrosis (defined as a METAVIR score of F2 or above, based on liver biopsy). It identified 3 subgroups in MYR 301 that it considered aligned

with a METAVIR fibrosis stage of F2 or above, and 2 transient elastography cut-off scores that could rule out significant fibrosis. It considered these in a scenario analysis. The company noted that there is no agreement in clinical practice on cut-offs that can rule out significant or advanced fibrosis. So, it used external literature to inform these values. The company used a meta-analysis by Qi et al. (2018) and data from the European Association for the Study of the Liver (EASL; 2021 Clinical Practice Guidelines) to identify 2 transient elastography (FibroScan) thresholds of 7.25 kPa and 8.00 kPa that aligned with a METAVIR fibrosis stage of F2 or above. It applied these thresholds to the transient elastography scores collected in MYR 301. Based on its analyses, the company considered that most people in MYR 301 were in line with its proposed positioning of bulevirtide for a METAVIR fibrosis score of F2 or above. It carried out 3 scenario analyses covering each of the fibrosis stages it had identified. The company considered that these analyses showed that the transient elastography scores in MYR301 aligned with a METAVIR fibrosis staging of F2 or above. The EAG was unable to validate the threshold for the significant fibrosis source used in the EASL guideline. But it did consider that a value of at least 8.0 kPa is the most validated threshold to rule out advanced fibrosis (F3 or above). It was unclear about whether the company had used a systematic approach to identify the thresholds. The company clarified that it had not used a formal consensus approach to gather its clinical feedback on appropriate thresholds. The committee recognised there was still a high level of uncertainty about the most appropriate threshold for transient elastography fibrosis staging. It recalled at the first committee meeting that its preference had been for an elastography-based model (see section 3.8). The committee considered that it had not seen this detail, so this could not inform its decision making. It considered that using a non-invasive assessment through transient elastography (FibroScan) would be better than using an invasive liver biopsy assessment. The EAG noted that transient elastography is not very accurate at diagnosing significant fibrosis, but is likely to be used in clinical practice to identify people that will be eligible for bulevirtide. Because the response data from MYR 301 showed similar results for both subgroups and the full trial population, the EAG considered that this suggested including people with less severe liver disease had limited effects on the response rates. It preferred to use the full trial population. The company later updated its

base case to reflect response rates from the full trial population. The committee accepted this. It concluded that response rates should reflect the full trial population, and accepted that in clinical practice, fibrosis could be assessed by either transient elastography or a clinical biopsy.

Clinical effectiveness

Virological and biochemical response

3.5 The MYR 301 trial investigated 2 different doses of bulevirtide (2 mg and 10 mg) over 144 weeks and also bulevirtide 10 mg started at 48 weeks (that is, people had standard care until 48 weeks, at which point they started on bulevirtide). The company used 48-week data from the bulevirtide 2 mg arm and delayed treatment arm to reflect the intervention and comparator. The primary outcome of MYR 301 was combined virological and biochemical response at week 48. Virological response was defined as undetectable HDV RNA or a decrease in HDV RNA levels by 2log10 IU/ml or more from baseline. Biochemical response was defined as alanine aminotransferase (ALT) normalisation, that is, ALT levels in the normal range. In the MYR 301 trial, many more people on bulevirtide had a combined response than people who had standard care at 24 weeks and 48 weeks of treatment. This difference was statistically significant. The committee noted that people in the delayed treatment arm of the trial were allowed to continue with any treatment prescribed for their underlying hepatitis B. It agreed that this arm represented standard care in the UK. The committee acknowledged the large benefit for people who had treatment with bulevirtide at week 48 but noted that the 48-week treatment period in MYR 301 was quite short. At the second committee meeting, the company reiterated that longer-term data from MYR 301 is due to be published shortly. The committee considered that longer-term data would be useful to determine if response with bulevirtide is sustained beyond the 48-week treatment period. No additional data was provided by the company at the third committee meeting. The committee concluded that uncertainty still remained in identifying if response to treatment with bulevirtide would continue.

Surrogate outcomes

3.6 It is not feasible to assess the long-term complications of hepatitis D, such as decompensated cirrhosis, hepatocellular carcinoma and death directly in clinical trials, because these may take years to develop. Because of this, surrogate outcomes are used. The clinical experts said the surrogate outcomes of virological and biochemical response used in MYR 301 were reasonable markers of disease progression in hepatitis D. But they explained that some people's ALT levels may not normalise with treatment because of other reasons, such as fatty liver disease or alcohol use, and using the combined end point may disadvantage those with raised ALT if treatment was stopped in these people because of it. They added that undetectable HDV was also a good indication of treatment efficacy. The committee concluded that virological and biochemical response can be considered suitable surrogate outcomes for preventing the complications of liver disease.

Generalisability

3.7 Because MYR 301 did not include people in the UK, the company assumed that the baseline characteristics of people taking bulevirtide in the NHS would reflect the cohort reported by Spaan et al. (2020), a retrospective analysis of 107 people with hepatitis D in the UK. People in Spaan et al. had a baseline age of 35 years and 60% had cirrhosis. In MYR 301 the baseline age was 42 years and 47% had cirrhosis. The EAG said the baseline characteristics in Spaan et al. and MYR 301 were both clinically plausible, but the model was sensitive to these inputs in terms of the cost-effectiveness results and the severity modifier applied (see section 3.15). The company also presented data published by Public Health England (now the UK Health Security Agency [UKHSA]) on routine blood-borne virus testing. The median age between 2011 and 2020 was around 37 years. The committee noted that this data was provided after the technical engagement stage, so could not be fully reviewed by the EAG. Further to this, one of the clinical experts explained that they are the lead investigator of a study being done by the UKHSA on the epidemiology of HDV infection in the UK. The study is collecting data from the 10 laboratories doing HDV testing in the UK and data should be available on mean age at baseline. The committee agreed with using

UKHSA data but considered that data on mean (rather than median) age and the proportion with cirrhosis on diagnosis would be helpful. At consultation, the company updated its base case to reflect the average age of people diagnosed with hepatitis D in the UK based on the median age (35 years) from the UKHSA study. It considered that this data suggested that most people with chronic hepatitis D in the UK are young at diagnosis, so preferred to use the median age estimate. The EAG preferred the mean age. The committee agreed that the mean was the most appropriate measure of central tendency. The clinical expert noted that people with chronic hepatitis D would also be diagnosed with hepatitis B. The committee considered that relevant data on the age at diagnosis of hepatitis B would therefore help validate its concerns around the mean baseline age of people diagnosed with chronic hepatitis D (see section 3.16). It considered that, until more data becomes available, it was difficult to define the proportion with cirrhosis at baseline. It considered that the UKHSA data based on mean age at diagnosis was the most appropriate source to inform the baseline age. After the second committee meeting, the company updated its base case to reflect the cohort of people with hepatitis D in the UK that are currently alive (n=570). It considered that this reflected the age of people with hepatitis D who would use bulevirtide. The EAG explained that in the UKHSA study, mean age was captured in 2 different ways. It preferred to use the mean age from the full UKHSA dataset of people in the UK that had been diagnosed with hepatitis D, considering that this better reflected the age at diagnosis. The committee concluded that the baseline age that reflected the full UKHSA dataset of people diagnosed with hepatitis D was the most appropriate as it was also a bigger dataset (n=602).

Economic model

Company's modelling approach

3.8 The company presented a Markov model to estimate the cost effectiveness of bulevirtide compared with standard care. The model had 10 health states, representing METAVIR fibrosis stages F0 to F4, and more severe disease complications, including decompensated cirrhosis,

hepatocellular carcinoma, liver transplant, post-liver transplant and death. The model had a 24-week cycle length and used a lifetime time horizon. Because the company positioned bulevirtide for people with METAVIR stage F2 and above, the F0 to F1 states in the model were never occupied. The committee noted that using model health states based on METAVIR fibrosis staging may not be appropriate (see sections 3.3 and 3.4). The committee considered that, if the company amended its population and comparators to cover the entire marketing authorisation, then a model structure using METAVIR stages may be acceptable because data from the full trial population could be used. The committee concluded that, if the company is planning to position bulevirtide in a narrower population than the marketing authorisation, an elastography-based model (with effectiveness data from the relevant population alone) was preferred. At the second committee meeting the company maintained its base-case position using METAVIR staging (see section 3.4) and did not change its model to an elastography-based model. The committee concluded that it had not seen the evidence to change its original viewpoint and maintained its preference for an elastography-based model.

Transition probabilities

3.9 Initial transition probabilities in the model were determined by response status in MYR 301. Although the company positioned bulevirtide for people with METAVIR stage F2 and above, it used data from the full trial population to estimate probabilities of response, which included people with METAVIR stage F0 to F1. The EAG noted that people with less severe fibrosis may be more likely to have a better response, which may overestimate response rates in a population with METAVIR stage F2 and above. In the longer term, the company assumed that people with a combined response (from now referred to as combined responders) did not progress through fibrosis states or to more severe disease states, such as hepatocellular carcinoma, and could have fibrosis regression from 24 weeks onwards. The company assumed an 8.8% annual probability of regression from F4 to F3, and a 13.3% annual probability of regression from F3 to F2. The company assumed that people with a virological response only (from now referred to as virological responders) could progress, although at a slower rate than people whose condition

did not respond to treatment at all (from now referred to as non-responders). The clinical experts agreed with the company that combined responders would have a low risk of progression through fibrosis stages. But they argued that this would not be zero because this group could still have detectable levels of virus. They added that even combined responders may still be at risk of hepatocellular carcinoma. The clinical experts further explained that it is plausible that fibrosis regression could occur in combined responders but added that the company's assumed transition probabilities for fibrosis regression seemed high. The committee agreed with the clinical experts that combined responders would still be at risk of hepatocellular carcinoma and noted that in people with hepatitis B and hepatitis C, viral response reduces, but does not eradicate hepatocellular carcinoma risk. The committee noted that the EAG assumed a residual risk of hepatocellular carcinoma in its base case. It had noted a data analysis directly in people with HDV (Alfaiate et al. 2020) had found that all responders are likely to have hepatocellular carcinoma. This meant that combined and partial responders may have a chance of developing hepatocellular carcinoma. Because the risk for people whose condition responds to treatment is lower than those whose condition does not, the EAG preferred to assume that combined responders and partial responders would have the same probability of developing hepatocellular carcinoma. The committee felt that additional scenario analyses would be helpful to address the remaining uncertainties around transition probabilities. At consultation, the company did 3 exploratory analyses. In these analyses it assumed that progression through fibrosis states and to hepatocellular carcinoma in combined responders was 20% of that for partial responders. This had a small impact on the cost-effectiveness results and the company later included these assumptions in its revised base case. The committee was satisfied that this addressed the uncertainties it originally had around transition probabilities in the model.

Duration of response

3.10 The company's assessment of response was based on 48-week data from MYR 301, extrapolated for 1 additional model cycle to 72 weeks. The EAG preferred to limit the timeframe for assessing response to 48 weeks, without extrapolating data from MYR 301. It argued that the

company's extrapolations were uncertain because they assumed that response is maintained for all people who do not stop treatment from 48 weeks onwards. The committee considered the data on response at week 24 and week 48 and noted that some people lost response, while others gained response. But the trend is likely to be for people to lose response over time. The committee heard from the company that additional data from MYR 301, beyond 48 weeks, would soon be available. The committee considered that additional trial data would be helpful in resolving the uncertainty around ongoing response and gave the committee confidence in the response rates seen at 48 weeks. But, until this data is available, the committee agreed with the EAG that response should be limited to 48 weeks because this is aligned with the data currently available. At consultation, the company clarified that its revised base case now included the data from MYR 301 which was not extrapolated beyond 48 weeks. The trial results showed a trend for response rates to increase during the first 48 weeks of treatment, so it had chosen not to extrapolate data beyond 48 weeks. The clinical expert highlighted that it was very difficult to define how long people should be treated for because there was not enough data from the 48-week treatment period. People with hepatitis might initially see sustained response, but many may later relapse. The committee was still unclear about how long response would be sustained beyond the 48-week data. It considered that longer-term data would have been helpful to committee decision making and resolving the uncertainty over how long people would maintain a response beyond 48 weeks.

Treatment duration and stopping rules

3.11 The summary of product characteristics for bulevirtide says that treatment should be continued for as long as it is associated with a clinical benefit. The company assumed that treatment duration in the model depends on response status. Combined responders were assumed to remain on treatment indefinitely, whereas virological responders and non-responders stopped at 72 weeks and 48 weeks respectively. The EAG highlighted the mismatch between treatment duration in the model and in the trial; everyone in the trial could continue treatment, irrespective of response status. The clinical experts broadly agreed with the company's model assumptions for combined responders

and non-responders but were less sure of what would happen for virological responders. One clinical expert explained that if a person had a virological response but high ALT for reasons other than hepatitis, for example fatty liver disease or alcohol use, clinicians would be wary about stopping treatment. The clinical experts added that treatment would also likely continue for combined or virological responders who develop hepatocellular carcinoma, and that for people with convincing evidence of virus eradication, treatment would likely be stopped. The committee agreed with the clinical experts' assumptions. At consultation, the company confirmed its base-case analyses now included the assumption that combined responders with undetectable RNA at 48 weeks would stop treatment 52 weeks later. The committee considered that there was some uncertainty around the company's assumptions. In MYR 301, people could be treated with bulevirtide up to 144 weeks. But the company assumed that partial responders would have treatment for up to 72 weeks, then stop treatment if they had not had a complete response. If the condition had not responded at all to treatment at week 48, treatment was stopped. The committee noted that the study protocol for MYR 301 suggested that partial responders could continue treatment for longer than the 72 weeks assumed by the company. It also noted that there was no clear justification for why, if there was no response, treatment stopped at 48 weeks. The company did 3 exploratory analyses to test the effect of varying stopping rules, all of which increased the company's cost-effectiveness estimates, assuming:

- partial and non-responders stopped treatment at week 48
- partial and non-responders stopped treatment at week 72
- non-responders at week 48 would continue to be treated for a further 52 weeks.

The committee recognised that there was still ambiguity around how long treatment should be continued and when bulevirtide should stop because of lack of response. The company confirmed that this data had not been collected in MYR 301, so further data analyses would be needed. It later updated its base case so partial and non-responders stopped treatment at week 72. The committee accepted this but concluded that only further data collection would help resolve the uncertainty around treatment duration and stopping rules.

Utility gain for combined responders

3.12 The company applied a utility gain for combined responders to capture the benefit of having the combined outcome of virological and biochemical response. The committee noted that the utility gain for combined responders was a key driver of cost effectiveness. The company fitted a Tobit regression model to 48-week pooled data from MYR 301. Variables included in the model, informed by clinical experts, were cirrhosis status at baseline and response at week 48. The utility gain was applied in addition to utility for the F2 to F4 health states for people with a combined response. The committee heard from the clinical experts that it was plausible for people's symptoms and quality of life to improve with the reduction in viral load. It concluded that it was reasonable to assume a utility gain for combined responders. The committee was less certain about the size of the utility gain that should be applied. It noted the lack of justification for the Tobit approach and highlighted that the resulting utility gain from the regression model was not statistically significant. At consultation, the company explained its decision to use a Tobit regression analysis. It said that a large number of people in MYR 301 had the highest utility index score and this suggested that there was a ceiling effect, so other regression analyses would not be appropriate. The committee accepted this explanation. It recalled that, in previous appraisals of hepatitis C, combined response was associated with a smaller utility gain than assumed by the company. It considered that the size of the utility benefit for combined responders was uncertain and asked the company to explore this uncertainty by testing alternative estimates of utility gain. The company had searched existing NICE technology appraisal guidance on hepatitis B and C and found utility gains for people with a sustained virologic response ranging from 0.03 to 0.05. It did 2 scenario analyses, reducing the utility gain in its base case by 50% and 75%. These had a moderate impact on increasing the cost-effectiveness estimates. The EAG considered that these were arbitrary values. It preferred to test the impact of using the lowest and highest utility gains identified in previous NICE technology appraisal guidance on hepatitis. The clinical expert noted that hepatitis C and D are very different populations, with different risk factors and manifestations of disease. The committee also noted that there were some differences in the way utility gains had been assessed. In the

company's analysis, MYR 301 utility gains were assessed while people were still having treatment, whereas in previous technology appraisals these had been defined after treatment had stopped. The committee concluded that the utility gain for combined responders was still uncertain. It recalled that people's symptoms and quality of life improved as viral load reduced, so it preferred the EAG's scenarios incorporating the maximum utility gain for combined responders from previous technology appraisals. The company later included this in its base-case analyses.

Health-state utility values

3.13 The MYR 301 trial collected EQ-5D-3L data at baseline, week 24 and week 48. The company argued that the EQ-5D data did not demonstrate face validity because it did not reflect differences between people with and without compensated cirrhosis. It added that key symptoms of hepatitis such as fatigue, nausea and vomiting are not well reflected by EQ-5D-3L. The company could not identify appropriate utility values for people with chronic hepatitis D in the literature, so preferred to use utility values from a meta-analysis of people with chronic hepatitis B. The EAG did not agree with the company's view because the EAG's experts highlighted that the impact of different levels of fibrosis on quality of life is likely to be very small. The committee agreed with the EAG and noted that even histologically advanced liver disease is silent in many people and decompensation is often the presenting event. The committee concluded that utilities based on MYR 301 were appropriate.

Costs

3.14 Bulevirtide is available as a 2 mg powder for injection vial, reconstituted and self-administered daily. According to the summary of product characteristics, people self-administering should get training to minimise the risk of injection site reactions. The company explained that it would fund all homecare services, including training to self-administer, so these costs are not included in the model. The committee concluded that the model includes all relevant costs associated with bulevirtide treatment.

Severity modifier

3.15 The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company calculated absolute and proportional quality-adjusted life year (QALY) shortfall weights in line with NICE's health technology evaluations manual. Absolute QALY shortfall is the future health, including quality and length of life, that is lost by people living with a condition, compared with the expected future health without the condition over people's remaining lifetime. Proportional QALY shortfall represents the proportion of future health, including quality and length of life, that is lost by people living with the condition. The company estimated that a weight of 1.2 should apply to the QALY. In its calculation of QALYs accrued by a healthy individual in the general population, baseline age was 37 years (based on UKHSA data) and 59% were men (based on baseline characteristics from the MYR 301 study). QALYs for people on standard care were taken from the comparator arm of the model. The EAG considered that the company had calculated the QALY weighting appropriately but noted that the weighting was sensitive to the assumed age at baseline as well as the proportion with cirrhosis. At consultation, the company provided data from the UKHSA study to validate assumptions around age at diagnosis. It considered that applying the UKHSA data did not alter the eligibility for a severity modifier. It preferred to use the mean age from the UKHSA cohort of people in the UK with hepatitis D who are currently alive (see section 3.7). It had not been able to provide updated data on cirrhosis status because this was still being collected by the UKHSA. It carried out a post-hoc analysis of baseline fibrosis distributions from MYR 301 to inform its assumption that 55% of people would have compensated cirrhosis. The EAG preferred to use the estimates from primary data collected in MYR 301, of 47% with compensated cirrhosis. The committee had previously noted that many of the EAG's preferred assumptions around the natural history modelling of chronic hepatitis D may also affect the QALY weighting calculations because they affect QALYs accrued by people having standard care. At the second committee meeting the EAG confirmed that, according to its results for all of its preferred scenarios, the total QALYs for standard care meant that the severity modifier did not apply. The committee had originally requested validation of the model predictions for people on standard care using

external literature sources. At consultation, the company also provided sources to validate the outcomes used in its model for compensated cirrhosis, hepatocellular carcinoma and liver-related mortality. The committee had some concerns about the company's approach. The EAG had not been able to validate this data in the company's model and did not think that the company had used a systematic approach to identify literature to validate the model outcomes. The company had carried out a literature search to identify data on the risk of disease progression in hepatitis D. Because of limitations and heterogeneity in the identified studies, it applied hazard ratios from publications that compared evidence for hepatitis D co-infected with hepatitis B to evidence from people only infected with hepatitis B. The EAG preferred to use alternative sources of data that directly estimated the natural history of disease in hepatitis D. The company noted that hepatitis D is a rare disease and modelling its natural history has not yet been established. The committee preferred the EAG's approach to estimate the natural history of the disease in the population of interest. It recognised the limited evidence for hepatitis D and noted that the NICE health technology evaluations manual states that the committee may be able to make recommendations accepting a higher degree of uncertainty, especially in rare diseases. In the company's sensitivity analyses, the results showed that in all but 1 of the scenarios, the QALY shortfall was over 12 QALYs (see section 3.17). So, the committee agreed the 1.2 severity modifier should be applied.

Committee's preferred assumptions

3.16 The committee considered the differences between the company's and the EAG's base-case assumptions. The committee favoured the EAG's assumptions but noted that there were still some concerns around the high level of uncertainty, specifically:

- response rates beyond 48 weeks in MYR 301 (see section 3.10)
- treatment duration beyond 48 weeks in MYR 301 (see section 3.11)

The committee preferred the EAG's assumptions, which included:

- using the baseline mean age from the full dataset of people with hepatitis D in the UKHSA study (see section 3.7)
- 30% of people with hepatocellular carcinoma will be cured from hepatocellular carcinoma and accrue a utility of 0.81 (see section 3.7)
- fibrosis regression can only start from 96 weeks (see section 3.7)
- maximum utility gain for combined responders based on that reported in previous technology appraisals (see section 3.12)
- natural history modelling of fibrosis progression and hepatocellular carcinoma based on evidence directly in HDV (see section 3.15).

In addition, the committee considered that the assumptions should specifically include:

- combined responders will have a low but not zero probability of hepatocellular carcinoma and probability of fibrosis progression (see section 3.9)
- baseline cirrhotic distribution based on MYR 301 (see section 3.7).

Cost-effectiveness estimates

3.17 The company's deterministic incremental cost-effectiveness ratio (ICER) for bulevirtide compared with standard care was £23,083 per QALY gained, including the commercial discount for bulevirtide and a 1.2 QALY weight (see section 3.15). The EAG presented a range of ICERs using alternative assumptions. The highest ICER presented by the EAG was £33,677. This included the EAG's preferred assumptions, baseline age characteristics for cirrhotic distribution from MYR 301, and the mean age at diagnosis based on the mean from the full UKHSA dataset. The probabilistic ICERs were slightly higher than the deterministic ICERs. NICE's health technology evaluations manual states that above a most plausible ICER of £20,000 per QALY gained, decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider the following factors:

- the degree of certainty and uncertainty around the ICER

- aspects that relate to uncaptured benefits and non-health factors.

The committee recalled the uncertainty in response rates and response duration beyond 48 weeks. It recognised the small UK population with hepatitis D and noted the benefits of the technology in reducing risks of transmission. It recognised the limited evidence for rare diseases and noted that the NICE health technology evaluations manual states that the committee may be able to make recommendations accepting a higher degree of uncertainty, especially in rare diseases. It considered the results of the company's sensitivity analyses which had explored the impact of the EAG's preferred assumptions on the company's revised cost-effectiveness estimates. It recalled that the results showed that in all but one of the scenarios, the QALY shortfall was over 12 QALYs, so the 1.2 severity modifier should be applied. It further explored the results of each scenario. It accepted most of the EAG's preferred assumptions. These included:

- response data based on MYR 301 (see section 3.3)
- the UKHSA data set that reflected all people with hepatitis D (see section 3.7)
- complete responders having a low probability of fibrosis progression (see section 3.9)

- the natural history of fibrosis progression and developing hepatocellular carcinoma being based on evidence directly in a hepatitis D population (see section 3.15).

The committee considered that the clinical expert opinion that combined responders would have a lower risk of hepatocellular carcinoma was most appropriate. So, it preferred the company's assumption (see section 3.9). It also considered that the baseline fibrosis distribution should be based on that in MYR 301 (see section 3.15). The committee recognised that hepatitis D is a rare disease and that bulevirtide has an orphan designation. But it considered there were still high levels of uncertainty. It noted specifically that the clinical trial had only published data for a period of 48 weeks. It recalled that after the first committee meeting it had asked to see further data on the evolution of response beyond 48 weeks, to help to validate model predictions around ongoing response. The company did not provide an updated analysis from MYR 301. Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the £20,000 to £30,000 per QALY gained range normally considered a cost-effective use of NHS resources. Considering the committee's preferred assumptions (see section 3.16), the company's deterministic ICER was £24,853 per QALY gained. So, the committee was satisfied that the most likely cost-effectiveness estimates were within what NICE considers an acceptable use of NHS resources.

Other considerations

Uncaptured benefits

3.18 The committee also heard about several benefits of bulevirtide that were not captured by the QALY calculation. It noted the rarity of hepatitis D and that bulevirtide was the first licensed treatment in this area, addressing an unmet need, and was therefore innovative. The clinical experts pointed out that the treatment would reduce the viral load in infected people, prevent the spread of infection and reduce the stigma around this blood-borne virus. The committee noted that these benefits were not captured in the cost-effectiveness analysis. But the committee was satisfied its concerns around the degree of uncertainty around the

ICER had been factored into its decision making.

Equality issues

3.19 The committee noted that chronic hepatitis D disproportionately affects people from a Black African family background. It heard that migrant HDV infections are increasing and native HDV infections are decreasing because of HBV vaccination programmes. It accepted that bulevirtide would be a welcome option and could address these potential issues.

Conclusion

3.20 The committee recommended bulevirtide for treating chronic hepatitis D in people with a METAVIR fibrosis stage of F2 or above.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has bulevirtide and the doctor responsible for their care thinks that bulevirtide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Anna Willis and Victoria Gillis-Elliott
Technical leads

Rufaro Kausi
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Accreditation