NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Telbivudine for the treatment of chronic hepatitis B

> This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

This guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

1.1 Telbivudine is not recommended for the treatment of chronic hepatitis B.

1.2 People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Telbivudine (Sebivo, Novartis) is a synthetic thymidine nucleoside analogue. It works by inhibiting the viral DNA polymerase responsible for viral replication. Telbivudine is licensed for the treatment of chronic hepatitis B in adults with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

2.2 The most common side effects associated with telbivudine include dizziness, headache, cough, diarrhoea, nausea, abdominal pain, rash, fatigue and increased levels of blood creatine phosphokinase, ALT and amylase. Uncommon side effects include malaise,

arthralgia, myalgia, peripheral neuropathy and myopathy. For full details of side effects and contraindications, see the summary of product characteristics (SPC).

2.3   The recommended dose of telbivudine is 600 mg (one tablet) once daily, taken orally, with or without food. The optimal treatment duration is unknown (see the SPC for criteria for treatment discontinuation). Telbivudine costs £290.33 for 28 × 600-mg tablets (excluding VAT; 'British national formulary' edition 55). Costs may vary in different settings because of negotiated procurement discounts.

3   The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of telbivudine and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1   The manufacturer's decision problem specified telbivudine monotherapy as the intervention of interest in a population of adults with compensated liver disease and active chronic hepatitis B (that is, evidence of viral replication and active liver inflammation and/or fibrosis). The decision problem considered people with HBeAg-positive and HBeAg-negative chronic hepatitis B disease as separate subgroups. The manufacturer did not consider telbivudine in combination with other antiviral treatments, arguing that there was not enough evidence and that combination therapy was not within the current marketing authorisation for telbivudine. The comparator specified by the manufacturer was lamivudine as first-line oral antiviral treatment in HBeAg-positive and HBeAg-negative disease. The health outcomes considered were seroconversion rates of hepatitis B e antigen (HBeAg); virological response (a reduction in hepatitis B virus [HBV] DNA); histological

improvement (in inflammation and fibrosis); biochemical changes (for example, reduction in serum ALT); and development of viral resistance to treatment.

3.2   The manufacturer's submission presented evidence on the clinical effectiveness of telbivudine monotherapy based on the GLOBE trial, which was a randomised, double-blind trial comparing the efficacy, safety and tolerability of telbivudine (600 mg/day) with lamivudine (100 mg/day) for 104 weeks. In total, 1367 patients were recruited, of whom 921 had HBeAg-positive chronic hepatitis B (458 in the telbivudine arm and 463 in the lamivudine arm) and 446 had HBeAg-negative chronic hepatitis B (222 in the telbivudine arm and 224 in the lamivudine arm). Patients were recruited from 20 countries and were nucleoside-naive. Patients were randomised in a one-to-one ratio to receive telbivudine or lamivudine (each with matching placebo for blinding purposes) once daily as oral tablets. The primary endpoint was therapeutic response, which was defined as suppression of HBV DNA to less than 5 $\log_{10}$ copies/ml plus either clearance of detectable HBeAg or serum ALT normalisation.

3.3   In patients with HBeAg-positive disease, there was a statistically significantly higher therapeutic response rate in the telbivudine group (63.3%) compared with the lamivudine group (48.2%) at week 104. That is an absolute difference of 15.1 percentage points (95% confidence interval [CI] 8.6 to 21.6, $p < 0.0001$). The mean reduction in baseline HBV DNA level was statistically significantly greater in the telbivudine group (-5.74 $\log_{10}$ copies/ml) compared with the lamivudine group (-4.42 $\log_{10}$ copies/ml) at week 104 in patients with HBeAg-positive disease ($p < 0.0001$). In patients with HBeAg-negative disease, there was also a statistically significantly higher therapeutic response rate in the telbivudine group (77.5%)

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compared with the lamivudine group (66.1%). That is an absolute difference of 11.4 percentage points (95% CI 2.9 to 19.9, p = 0.0069). A statistically significant reduction in HBV DNA levels was also observed in patients with HBeAg-negative disease: the mean reduction in HBV DNA levels from baseline at week 104 in the telbivudine group was -5.00 $\log_{10}$ copies/ml compared with -4.17 $\log_{10}$ copies/ml in the lamivudine group (p = 0.0002).

3.4   In patients with HBeAg-positive disease, the proportion of patients with HBV DNA undetectable by polymerase chain reaction (PCR) assay at week 104 was statistically significantly higher in the telbivudine arm (55.6%) compared with the lamivudine arm (38.5%) (p < 0.0001). Virological breakthrough (defined in the trial protocol as an increase in HBV DNA to greater than or equal to 5 $\log_{10}$ copies/ml on two consecutive occasions in patients who had previously achieved post-baseline virological response) was statistically significantly lower in the telbivudine arm (23.3%) than in the lamivudine arm (37.1%) (p < 0.0001). Virological breakthrough (defined as > 1 $\log_{10}$ above nadir) was statistically significantly lower in the telbivudine arm (28.6%) than in the lamivudine arm (45.5%). HBV resistance (as defined in the trial protocol) was statistically significantly lower in the telbivudine group (21.7%) compared with the lamivudine group (34.1%) (p < 0.0001).

3.5   Similar treatment effects were observed in patients with HBeAg-negative disease. The proportion of patients with HBV DNA undetectable by PCR was statistically significantly higher in the telbivudine arm (82.0%) compared with the lamivudine arm (56.7%) (p < 0.0001). Virological breakthrough (as defined in the trial protocol) was statistically significantly lower in the telbivudine arm (8.4%) than in the lamivudine arm (19.7%) (p = 0.0013). Virological breakthrough (defined as > 1 $\log_{10}$ above nadir) was statistically

significantly lower in the telbivudine arm (12.2%) than in the lamivudine arm (30.4%). HBV resistance was statistically significantly lower in the telbivudine arm (8.4%) than in the lamivudine arm (20.2%) (p = 0.0008).

3.6   The ERG considered that on the whole the manufacturer's submission was an unbiased estimate of the anti-viral treatment effects of telbivudine. However, the ERG suggested that although the results from the GLOBE trial were statistically significant, the clinical significance of the results was open to question. On the basis of the proportion of patients who discontinued treatment because of disease progression or lack of efficacy (0.8% versus 2.6% for telbivudine and lamivudine, respectively), there is an absolute difference of approximately 2 percentage points between telbivudine and lamivudine. According to the ERG, although virological breakthrough (defined as $>1 \log_{10}$ above nadir) at 104 weeks in patients with HBeAg-positive disease was lower in the telbivudine arm (28.6%) than in the lamivudine arm (45.5%), it was still clinically high. In addition, it is not clear if the GLOBE trial was powered to detect differences in subgroups of race or serum ALT levels. Over-representation of HBeAg-positive patients in the trial may have affected the statistical validity of the results in the HBeAg-negative disease group. The ERG noted that effects of treatment on health-related quality of life were not measured in the GLOBE trial.

3.7   The manufacturer's submission presented an analysis of the cost effectiveness of telbivudine in patients with chronic hepatitis B whose serum ALT levels are more than or equal to twice the upper normal limit. Two Markov state-transition models were provided in the manufacturer's submission: a seroconversion model (applicable to only HBeAg-positive disease) and a viral load model (applicable

to both HBeAg-positive and HBeAg-negative disease). Both models used a lifetime horizon. The comparators included in the seroconversion model were lamivudine and adefovir dipivoxil as part of treatment algorithms (which included adefovir dipivoxil, lamivudine or telbivudine as a salvage therapy for patients whose disease develops resistance after the first drug) and best supportive care (BSC). The manufacturer did not compare telbivudine with adefovir dipivoxil or lamivudine as separate treatments in the seroconversion model. In the viral load model, the only comparator considered was lamivudine.

3.8   The viral load model submitted by the manufacturer assumed that patients entered the model in the chronic hepatitis state without cirrhosis. Health states associated with disease progression were divided by serum ALT and viral load levels, resulting in a large number of possible health states. Consequently the data available from the GLOBE trial to populate the viral load model were sparse. In an attempt to deal with this, the manufacturer used values of 0.0 and 0.5 (which they referred to as 'non-informative priors') to correct for the probabilities of health-state transitions for which there were one or more zero observations and no data available.

3.9   The results of the economic analysis were presented as incremental costs per quality-adjusted life year (QALY) gained for telbivudine relative to lamivudine in the viral load model. In the seroconversion model, a comparison between a set of treatment algorithms relative to BSC was made. The manufacturer's main submission did not report on univariate sensitivity analyses and the base-case results were taken from probabilistic sensitivity analysis. After the ERG identified errors in the manufacturer's original viral load model, the manufacturer presented amended base-case analyses.

3.10 The base-case analysis of the viral load model (based on probabilistic sensitivity analysis) comparing telbivudine with lamivudine and assuming a 'non-informative prior' of 0.0 produced an incremental cost-effectiveness ratio (ICER) of £15,377 per additional QALY gained for HBeAg-positive disease; the corresponding ICER with a 'non-informative' prior of 0.5 was £8,542 per additional QALY gained. For HBeAg-negative disease, the ICER for a comparison of telbivudine with lamivudine with a 'non-informative prior' of 0.0 was £20,256 per additional QALY gained. The corresponding ICER with a 'non-informative prior' of 0.5 was £27,801 per additional QALY gained.

3.11 Deterministic base-case analyses (requested from the manufacturer) of the viral load model comparing telbivudine with lamivudine, with a 'non-informative prior' of 0.0, produced an ICER of £12,278 per additional QALY gained for HBeAg-positive disease. The corresponding ICER, with a 'non-informative prior' of 0.5, was £8,669 per additional QALY gained. For HBeAg-negative disease, the ICER for a comparison of telbivudine with lamivudine was £20,383 per additional QALY gained with a 'non-informative prior' of 0.0; the corresponding ICER, with a 'non-informative prior' of 0.5, was £57,419 per additional QALY gained.

3.12 The manufacturer's economic analysis based on the seroconversion model (HBeAg-positive disease only) gave an ICER of £13,193 per additional QALY gained (95% CI £7,788 to £25,194) for a comparison of telbivudine alone (followed by BSC if appropriate) with BSC alone. A comparison of telbivudine followed by adefovir dipivoxil and then BSC against BSC alone gave an ICER of £15,684 per additional QALY gained (95% CI £9,491 to £28,151). Adefovir dipivoxil followed by telbivudine and then BSC compared with BSC alone gave an ICER of £18,388 per additional

QALY gained (95% CI £11,707 to £30,357). Adefovir dipivoxil followed by lamivudine and then BSC compared with BSC alone gave an ICER of £17,398 per additional QALY gained (95% CI £11,063 to £28,322).

3.13   The ERG considered that the seroconversion model structure used to assess the cost effectiveness of telbivudine was consistent with methods adopted in previous technology appraisals in chronic hepatitis B. However, the ERG identified a number of issues and uncertainties relating to the economic evidence presented by the manufacturer. It noted the economic models presented in the manufacturer's submission contained insufficient discussion of uncertainty; in particular, no univariate sensitivity analyses were presented in the main body of the submission for either model. Although the submitted viral load model included a worksheet that contained univariate sensitivity analysis, these results were not discussed in the submission itself. The ERG noted that there was no explanation of the results of the univariate sensitivity analysis, or of the rationale for the choice of variables included or excluded. Also, no explanation of the choice of variable ranges was given. Consequently it was not clear what the key drivers of the economic model were. In addition, there was no detailed discussion about the probabilistic sensitivity analysis conducted.

3.14   The ERG noted that evidence on the clinical and cost effectiveness of adefovir dipivoxil was not adequately identified. No attempts were made to justify or investigate the assumptions made about the clinical and cost effectiveness of adefovir dipivoxil. The ERG further noted that entecavir was not included as a comparator in the economic models; it did not consider that methodological concerns about indirect comparisons were an adequate reason for not including this comparator. In addition, little account was taken of

entecavir's possibly better resistance profile compared with telbivudine. Alternative approaches to populating the model were not considered; in particular, the possibility of developing statistical risk models to address the sparsity of observed data from the GLOBE trial. Impacts of the so-called 'non-informative priors' on the economic results could not be adequately assessed by the ERG.

3.15 The ERG noted discrepancies between the calibration factors in the risk equations used for the compensated cirrhosis and hepatocellular carcinoma states in the original and resubmitted viral load models, and the factors listed in the appendices to the manufacturer's submission. The ERG also noted that an excessive reliance on visual basic coding made it unclear which parameters had or had not been included in the economic analyses. Further, the ERG noted that the manufacturer's submission did not discuss the power of the GLOBE trial to detect statistically significant effects of treatment in the subgroup of patients with serum ALT levels greater than or equal to twice the upper limit of normal. Data used to populate the economic models were taken from this subgroup of patients. No information was provided on the baseline characteristics of this subgroup of patients. The ERG states that there is real uncertainty over the completeness of data (from the Globe study) used to populate the model and that the key clinical effectiveness data in the economic model could not be critically appraised. The ERG notes in its conclusions that sensitivity analyses undertaken by the ERG have been able to address a limited number of the concerns raised above.

3.16 The ERG carried out scenario analyses on the viral load model (with a 'non-informative prior' of 0.0) using non-constant age-specific utilities, increasing the proportion of cirrhotic patients at treatment initiation to 15% and applying model calibration factors

(for risk of advanced liver disease). The cumulative effects of varying these parameters for HBeAg-positive disease gave an ICER of £16,100 per additional QALY gained. The corresponding ICER for HBeAg-negative disease was £26,200 per additional QALY gained.

3.17   The ERG conducted exploratory scenario analyses on the seroconversion model:

- assuming no treatment with telbivudine for people with decompensated liver disease,
- removing treatment-resistant patients from the denominators used to calculate transition probabilities for HBeAg seroconversion,
- increasing the proportion of cirrhotic patients at the start of treatment to 15%, and
- assuming treated people with cirrhosis seroconvert at the same rate as people with treated non-cirrhotic chronic hepatitis B.

The cumulative effects of varying the first three parameters gave ICERs ranging from £20,200 to £22,500 per additional QALY gained for telbivudine followed by adefovir, compared with lamividune followed by adefovir, and telbivudine alone compared with lamivudine alone, respectively, in the HBeAg-positive group. Adding the last assumption results in ICERs ranging from £8,400 to £10,800 per additional QALY gained for the same comparisons.

3.18   The ERG conducted a probabilistic sensitivity analysis using the viral load model with a 'non-informative prior' of 0.0 only. It replaced constant health-state utilities with non-constant age-specific utilities and applied the model calibration factors for risk of advanced liver disease listed in the appendices to the manufacturer's submission. This reduced the probability of telbivudine being cost effective when compared with lamivudine with a mean of £29,500 per

additional QALY gained and a probability of being cost effective of 0.01 at a willingness to pay of £20,000 and 0.54 at £30,000 per additional QALY gained. The ERG also conducted a probabilistic sensitivity analysis using the seroconversion model, and the results differed from the manufacturer's analysis: in particular, lamivudine is optimal over a wider range of willingness to pay with lamivudine followed by adefovir being optimal over a cost-effectiveness threshold range of £22,000 to £24,000 per additional QALY, where telbivudine was the optimal strategy over this range in the manufacturer's probabilistic sensitivity analysis. At higher cost-effectiveness thresholds (greater than £25,000 per QALY gained), telbivudine followed by adefovir remained the optimal strategy.

3.19   Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx

4   Consideration of the evidence

4.1   The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of telbivudine for the treatment of chronic hepatitis B, having considered evidence on the nature of the condition and the value placed on the benefits of telbivudine by people with chronic hepatitis B, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2   The Committee discussed the decision problem and evidence presented in the manufacturer's submission. It discussed with the clinical specialists the importance and relevance of the various possible surrogate markers of disease expression and response to treatment. The Committee heard from the patient experts about the impact of hepatitis B on quality of life and the importance of having

a variety of treatments available. The Committee was also mindful of the long-term risk of progression to cirrhosis or hepatocellular carcinoma associated with chronic hepatitis B infection and the resulting impact in terms of costs, mortality and health-related quality of life. The Committee agreed that avoiding these adverse consequences was the most important goal in the treatment of chronic hepatitis B. It noted that the relationship between any surrogate endpoints measured in clinical studies and these final health outcomes should be taken fully into consideration.

4.3   The Committee was advised by the clinical specialists of the differences between HBeAg-positive and HBeAg-negative disease. It acknowledged that, in the main, rather than different infections, HBeAg-positive and -negative disease represent different stages of infection. This is because HBeAg-negative chronic hepatitis B most commonly develops when the virus that was originally suppressed following HBeAg/antibody seroconversion mutates and the infection re-emerges from immune control. The Committee also understood that hepatitis in the HBeAg-negative phase of the disease carries a high risk of progression to cirrhosis or hepatocellular carcinoma. Therefore, it is important to maintain a low viral load in patients with HBeAg-negative disease.

4.4   The Committee was advised by the clinical specialists of the relative importance of different tests in the diagnosis and management of chronic hepatitis B. It was persuaded that measurement of viral load (HBV DNA) is an important predictor of future liver damage, and can be used to identify patterns of viral resistance to treatment. The clinical specialists confirmed that, in HBeAg-positive disease, reductions in HBV DNA levels by antiviral treatment may accelerate seroconversion. They also stated that in HBeAg-positive disease, seroconversion could indicate that

treatment could be stopped, although current clinical practice is to continue for 6 months after seroconversion. The Committee understood that this endpoint of treatment did not apply to HBeAg-negative disease and that assessment of when to stop treatment was more difficult. In many cases treatment would need to be lifelong. The clinical specialists stated that serum ALT levels were usually correlated with HBV DNA levels and serum ALT levels would be expected to normalise with a reduction in HBV DNA levels. The Committee also heard from the specialists that, in HBeAg-positive disease, spontaneous HBeAg/antibody seroconversion is associated with high serum ALT levels and that high serum ALT alone, without histological evidence of liver disease, was not an indication for treatment. The Committee heard that it is current clinical practice to start antiviral treatment only on the basis of liver inflammation (confirmed by biopsy) irrespective of serum ALT levels. This is reflected in telbivudine's marketing authorisation.

4.5   The Committee considered the treatments available for patients with chronic hepatitis B in the UK. It discussed with the patient experts and clinical specialists the relevance of previous NICE guidance on chronic hepatitis B and where in the treatment pathway telbivudine should be used. The clinical specialists stated that telbivudine monotherapy could be used in place of lamivudine monotherapy. However, they also stated that lamivudine monotherapy was not a preferred option; in particular it was not considered suitable in highly replicative disease because of the associated high rate of emergence of viral resistance. Combination therapy was considered more appropriate in these instances.

4.6   The Committee considered evidence of telbivudine's efficacy in the subgroup of patients with serum ALT levels greater than or equal to

twice the upper limit of normal (identified from the GLOBE trial population in the manufacturer's submission). The Committee was advised by the clinical specialists that estimates of telbivudine's efficacy in this subgroup were uncertain because they were based on a post-hoc analysis. The Committee expressed concerns over the relevance of the GLOBE trial population to UK practice, but it was persuaded by the clinical specialists that the ethnic mixes of the trial and UK patient populations were similar.

4.7   The Committee discussed the ERG critique of the efficacy results from the GLOBE trial; in particular, concerns that health-related quality of life data were not reported. However it concluded, on the basis of the clinical evidence from the GLOBE trial and testimonies from the clinical specialists and patient experts, that telbivudine was likely to be more effective than lamivudine for several of the outcomes measured, notably the primary endpoint (suppression of HBV DNA to less than 5 $\log_{10}$ copies/ml plus either clearance of detectable HBeAg or ALT normalisation). The Committee also noted that based on 2-year data there was a lower rate of viral resistance to treatment than was seen with lamivudine. However, it noted that resistance to telbivudine was likely to be problematic in the long term and that comparisons with treatment strategies involving the addition of other antivirals, such as adefovir dipivoxil, were the most appropriate for the evaluation of cost effectiveness.

4.8   The Committee discussed the economic analysis presented in the manufacturer's submission, the ERG's critique of the submission and the exploratory analyses undertaken by the ERG. In particular, it discussed the complexity and lack of transparency of the economic models used. With regard to transparency, the Committee was impeded by the lack of detail provided in the manufacturer's submission about which parameters were used.

With regard to complexity, the Committee acknowledged that the natural history of the disease required a number of health states to be defined in the economic models. However, the Committee noted that the viral load model in particular involved such a large number of health states that the data available from clinical studies were not sufficient to support clearly the transition probabilities indicated. In addition, the methods used to deal with the sparseness of the data had led to uncertainty about the outputs of the manufacturer's economic models. The Committee considered that both this complexity and lack of transparency undermined the credibility of the economic results. The Committee noted that the manufacturer did not consider alternative approaches that might have reduced the complexity of the economic models, especially in the viral load model. This, together with appropriate risk modelling, might have reduced the data requirements for populating the economic models. The Committee noted that the economic results generated by the viral load model appeared sensitive to the choice of 'priors' and noted that the manufacturer did not present any univariate sensitivity analyses that identified the key drivers of cost effectiveness in either model. The Committee accepted that the sensitivity analyses presented by the ERG for both of the economic models showed a reduction in the probability of telbivudine being cost effective at willingness to pay thresholds of £20,000 and £30,000 per additional QALY gained; resulting in lamivudine being the preferred option in the range of cost effectiveness estimates that are usually seen to represent an efficient use of NHS resources.

4.9   The Committee considered that the transparency of the models (in particular, the viral load model for assessing the cost effectiveness of telbivudine for the treatment of HBeAg-negative patients) was reduced by the lack of detail in the manufacturer's submission

about which parameters were used. Additionally, the Committee was mindful that the manufacturer had commented during consultation that the concerns raised about the viral load model could not be rectified within the time constraints of the appraisal. The Committee noted the manufacturer's acceptance of the fact that this made it difficult to judge the cost effectiveness of the use of telbivudine in HBeAg-negative patients. The Committee concluded that, in light of the uncertainty about the cost effectiveness of telbivudine in HBeAg-negative chronic hepatitis B and the sensitivity analyses presented by the ERG, telbivudine could not be recommended as a cost-effective use of NHS resources.

4.10   In considering the cost effectiveness of telbivudine for treating HBeAg-positive chronic hepatitis B, the Committee was able to proceed further by considering the seroconversion model provided by the manufacturer. However, the Committee noted that although it was based on a model used in a previous appraisal, in this instance the selection of the parameters used was not transparent.

4.11   The Committee had serious concerns that the economic analysis based on the seroconversion model focused solely on a subset of the GLOBE trial population (specifically only people with serum ALT levels greater than or equal to twice the upper limit of normal). The Committee discussed the validity of clinical efficacy analysis based on this subgroup; it considered that validity of the results were dependent on the statistical integrity of the subgroup as well as its biological plausibility and clinical relevance. The manufacturer provided partial reassurance on the statistical integrity of this subgroup: randomisation of the GLOBE trial had been stratified into treatment-eligible groups with serum ALT levels greater than two and a half times the upper limit of normal. The

Committee was further mindful of comments from the manufacturer that the efficacy analyses of telbivudine in the subgroup of patients with serum ALT levels greater than or equal to twice the upper limit of normal was exploratory and the study was not powered to demonstrate differences between these subgroups. With regard to the clinical relevance of the subgroup, the Committee was mindful of comments from the clinical specialists that antiviral treatment of chronic hepatitis B was initiated principally on the basis of histological confirmation of liver inflammation, irrespective of serum ALT levels.

4.12　The Committee discussed the updated economic analysis based on the seroconversion model presented by the manufacturer. The Committee considered that although the adjustments made addressed some of the criticisms made by the ERG, the economic analysis was still based solely on the subgroup of patients with serum ALT levels greater than or equal to twice the upper limit of normal. Combined with the results of the sensitivity analyses presented by the ERG on the seroconversion model, the Committee considered that it therefore did not have a sufficient basis on which to recommend telbivudine as a cost-effective use of NHS resources in people with HBeAg-positive chronic hepatitis B. The Committee was also mindful that recommending a treatment that was somewhat more effective than lamivudine monotherapy would not necessarily be helpful in the context of highly replicative disease in which resistance was likely to develop rapidly, for which combination therapy was more appropriate.

4.13　Overall, the Committee agreed that there was evidence that telbivudine was likely to be more clinically effective and have a more favourable resistance profile than lamivudine monotherapy in patients with HBeAg-positive disease. However, it did not agree

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with the manufacturer that the evidence presented on the cost effectiveness of telbivudine in the subgroup of patients with serum ALT levels greater than or equal to twice the upper limit of normal could be used as a reliable basis for decision-making in patients with HBeAg-positive disease.

4.14   In light of the economic models and evidence presented, the Committee concluded that telbivudine, within its licensed indication, could not be recommended as a cost-effective use of NHS resources for the treatment of chronic hepatitis B.

5   Implementation

5.1   The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2   'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and

NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3   NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6   Related NICE guidance

Published

- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/TA96

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance (publication expected August 2008). Available from www.nice.org.uk/TAXXX

7   Review of guidance

7.1   The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the

light of information gathered by the Institute, and in consultation with consultees and commentators.

7.2   The guidance on this technology will be considered for review in February 2009. The review of 'Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B' (NICE technology appraisal guidance 96) is scheduled for consideration at this date.

David Barnett
Chair, Appraisal Committee
May 2008

Appendix A: Appraisal Committee members and NICE project team

A   Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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

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

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County PCT

Dr Carol Campbell

Senior Lecturer, University of Teesside

Dr Peter Clarke

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Dr Dyfrig Hughes

Reader in Pharmacoeconomics, Centre for the Economics of Health and Policy in Health, Bangor University

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

Dr Peter Jackson

Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust

Professor Peter Jones

Pro Vice Chancellor for Research & Enterprise, Keele University

Ms Rachel Lewis

Practice Development Facilitator, Manchester PCT

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Philip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services
Commissioning Team

Professor Andrew Stevens

Chair of Appraisal Committee C

Mr William Turner

Consultant Urologist, Addenbrookes Hospital

B   NICE project team

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

Ebenezer Tetteh

Technical Lead

Janet Robertson

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

A   The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- Hartwell D, Jones J, Harris P et al. Telbivudine as treatment for chronic hepatitis B, February 2008.

B   The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I II and III also had the opportunity to appeal against the final appraisal determination.

I   Manufacturer/sponsor:

- Novartis Pharmaceuticals UK Ltd (telbivudine)

II   Professional/specialist and patient/carer groups:

- Association of Clinical Microbiologists
- Association of Medical Microbiologists
- British Association for the Study of the Liver
- British Association for the Study of the Liver Nurses Forum (BASLNF)
- British Infection Society
- British Society of Gastroenterology
- Chinese National Healthy Living Centre
- Hepatitis B Foundation UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation

III   Other consultees

- Bury PCT
- Department of Health
- Welsh Assembly Government
- Worcestershire PCT

IV   Commentator organisations (did not provide written evidence and without the right of appeal)

- Bristol-Myers Squibb Pharmaceuticals Ltd (entecavir)
- Department of Health, Social Services and Public Health Safety for Northern Ireland
- Gilead Sciences (adefovir dipivoxil)
- National Collaborating Centre for Women and Children's Health
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Roche Products Limited (interferon alfa 2a, peginterferon alfa 2a)
- Schering-Plough Ltd (interferon alfa 2a, interferon alfa 2b)
- Southampton Health Technology Assessment Centre (SHTAC)

C   The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on telbivudine by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Howard Thomas, nominated by the British Society of Gastroenterologists – clinical specialist
- Dr Elizabeth Boxall, nominated by the Association of Clinical Microbiologists – clinical specialist
- Professor Geoffrey Dusheiko, nominated by the Royal College of Physicians – clinical specialist
- Penny Wilson Webb, nominated by Hepatitis B Foundation UK – patient expert
- Robert Windsor, nominated by Hepatitis B Foundation UK – patient expert