NICE National Institute for Health and Care Excellence

NICE guidance

Entecavir for the treatment of chronic hepatitis B

Technology appraisal guidance
Published: 27 August 2008

www.nice.org.uk/guidance/ta153

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

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

1.1 Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

2 The technology

2.1 Entecavir (Baraclude, Bristol-Myers Squibb) is an oral nucleoside analogue. It works by inhibiting the viral DNA polymerase responsible for hepatitis B virus (HBV) replication. Entecavir has a marketing authorisation in the UK for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. For further information, see the summary of product characteristics.

2.2 Adverse events associated with the use of nucleoside analogues include lactic acidosis and severe hepatomegaly with steatosis. Additional adverse events reported for entecavir include headache, fatigue, dizziness and nausea. For full details of side effects and contraindications, see the summary of product characteristics.

2.3 The acquisition costs of entecavir (excluding VAT; BNF edition 55) are £378.00 for a 30-tablet pack (500 micrograms), £378.00 for a 30-tablet pack (1 mg) and £441.00 for a 210-ml pack (50 micrograms/ml) of the oral solution. Costs may vary in different settings because of negotiated procurement discounts. The optimal treatment duration is currently unknown. For people who have not previously received treatment with antiviral drugs for chronic hepatitis B, the recommended dose is 500 micrograms once daily. For people taking lamivudine who have evidence of viraemia or lamivudine resistance, the recommended dose is 1 mg, once daily. Dose reductions are required for people with renal impairment.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of entecavir and a review of this submission by the Evidence Review Group (ERG).

3.1 The manufacturer approached the initial decision problem by comparing entecavir monotherapy with interferon alfa-2a and -2b, peginterferon alfa-2a, lamivudine, adefovir dipivoxil and telbivudine. The population under consideration was adults with compensated liver disease and active chronic hepatitis B (that is, evidence of viral replication and active liver inflammation). The primary outcome measures outlined in the decision problem were virological response (HBV DNA), histological improvement (inflammation and fibrosis), biochemical response (for example, ALT levels), development of viral resistance and HBeAg/hepatitis B surface antigen (HBsAg) seroconversion rate. secondary outcome measures were survival and adverse affects of treatment.

3.2 The manufacturer's submission presented evidence on the clinical effectiveness of entecavir from five randomised controlled trials (RCTs) that compared entecavir with lamivudine. Three of the studies were carried out in people who had not previously received nucleoside analogue treatment. One trial compared entecavir with lamivudine in people with HBeAg-positive hepatitis B, another included only people with HBeAg-negative disease and another included a mixed group with either HBeAg-positive or HBeAg-negative chronic hepatitis B. The remaining two studies were in people with lamivudine-refractory disease; one included only people with HBeAg-positive disease and the other included people with either HBeAg-positive or HBeAg-negative chronic hepatitis B.

3.3 The results of the five RCTs (n = 2438) showed that entecavir was statistically superior to lamivudine in terms of the number of people with HBV DNA suppression, ALT normalisation and histological improvement after one year of treatment. There was no statistically significant difference between the treatments in the number of people with HBeAg-positive chronic hepatitis B achieving HBeAg seroconversion. The number of people with any adverse events or serious adverse events was similar for entecavir and lamivudine. The number of people who withdrew during the first year because of adverse events was similar for entecavir and lamivudine, except in one trial where significantly more

people in the lamivudine group withdrew from the study due to adverse events. The number of deaths during treatment was low (< 1% in all groups).

3.4 There were no trials that compared all treatment options in any one population; the manufacturer therefore conducted a series of network meta-analyses but only for the nucleoside-naive populations. The models used entecavir as the baseline treatment as it was common to all analyses, and all the models assumed fixed-treatment effects. The ERG identified as a strength of the mixed treatment comparison (MTC) that it was supported by a reasonably sound systematic review process; albeit noting caveats around the ambiguity about the number of trials that were included. The ERG considered the following as weaknesses of the MTC.

- Relatively few studies in some of the networks; for example, only two peginterferon alfa-2a RCTs were included, one in HBeAg-positive patients and one in HBeAg-negative patients.
- There was a paucity of outcome for year two treatment; the entecavir year two data were unpublished and would not have been subjected to external journal peer review that the data from the other trials included in the MTC would have undergone, and peginterferon alfa-2a was omitted entirely from the network as no year two data were identified.
- No definition of the criteria by which entecavir was judged to be 'significantly better' or 'equivalent' to other drugs.
- No assessment, or at least discussion or reflection on the results of the MTC, and the methodology used to construct it in general.
- No discussion on how the results of the MTC compared to the results of the manufacturer's systematic review of entecavir (that is, how mixed direct and indirect evidence compared with direct evidence).
- No discussion or rationale was presented for use of a fixed over a random-effects model.

3.5 The results of the meta-analyses showed that for HBeAg-positive chronic hepatitis B, entecavir had a significantly higher predicted probability of HBV DNA response than all comparators and an equivalent predicted probability of

seroconversion to all comparators at 1 and 2 years. Entecavir also had a significantly higher predicted probability of ALT normalisation than lamivudine (at both 1 and 2 years) and peginterferon alfa-2a (at 1 year), and was reported to be equivalent to telbivudine (at both 1 and 2 years). Entecavir had a significantly higher predicted probability of histological improvement compared to lamivudine at 1 year, and was reported to be equivalent to telbivudine. For HBeAg-negative disease, the network meta-analysis found that entecavir had a significantly higher predicted probability of HBV DNA response at 1 and 2 years compared with lamivudine and peginterferon alfa-2a, and was reported to be equivalent to telbivudine at both 1 and 2 years. Entecavir had a significantly higher predicted probability of ALT normalisation compared with all comparators at 1 year, but appeared similar to comparators at 2 years. Entecavir had a significantly higher predicted probability of histological improvement compared with lamivudine at 1 year, and was reported to be equivalent to telbivudine.

3.6 The available RCTs in people with HBeAg-positive, lamivudine-resistant disease were smaller so the manufacturer stated that the likelihood of no events occurring in one of the arms was much higher. The manufacturer therefore presented a 'simple' indirect comparison using lamivudine as the common reference. The results showed that entecavir and lamivudine/adefovir had similar rates of seroconversion and viral load reduction.

3.7 Head-to-head studies evaluating the relative rates of genotypic resistance were not available. Similarly a formal network meta-analysis of resistance rates was deemed by the manufacturer not to be possible because the data would come from non-RCT evidence and the patient populations were too heterogeneous to be combined in such an analysis. Instead, the manufacturer presented a descriptive analysis of the rates of genotypic resistance across available nucleoside analogues taken from the literature. This showed that entecavir had a lower rate of genotypic resistance than lamivudine, telbivudine and adefovir dipivoxil at 2, 3 and 4 years, and only a slightly higher rate than adefovir dipivoxil at 1 year (adefovir dipivoxil 0%, entecavir 0.2%).

3.8 The manufacturer's submission presented an economic analysis comprising two Markov models (one for HBeAg-positive disease and one for HBeAg-negative disease). The HBeAg-positive disease model consisted of 14 health states that were defined as untreated chronic hepatitis B, spontaneous HBeAg

seroconversion, HBsAg loss, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, post-liver transplantation, treated chronic hepatitis B, treatment-induced HBeAg seroconversion and death. The HBeAg-negative disease model also differentiated between response to initial treatment and response to salvage therapy, resulting in 15 health states. The models were designed to compare entecavir with lamivudine, peginterferon alfa-2a and telbivudine, and both had a lifetime horizon. The estimated treatment duration for entecavir was 2 years in the HBeAg-positive model and 5 years in the HBeAg-negative model. The estimates of efficacy used in the economic model were based on the indirect comparison.

3.9 The base-case analysis for people with HBeAg-positive disease resulted in an incremental cost-effectiveness ratio (ICER) of £14,329 per additional quality-adjusted life year (QALY) gained for entecavir compared with lamivudine. A comparison of entecavir with peginterferon alfa-2a resulted in an ICER of £8,403 per additional QALY gained. A comparison of entecavir with telbivudine resulted in telbivudine dominating entecavir.

3.10 The base-case analysis for people with HBeAg-negative disease resulted in an ICER of £13,208 per QALY gained for entecavir compared with lamivudine. A comparison of entecavir with peginterferon alfa-2a resulted in an ICER of £7,511 per QALY gained and a comparison of entecavir with telbivudine resulted in an ICER of £6,907 per QALY gained.

3.11 The base-case analysis for people with lamivudine-refractory disease, comparing entecavir with adefovir dipivoxil plus lamivudine, resulted in entecavir dominating.

3.12 The ERG questioned the clinical validity of some of the assumptions in the manufacturer's model, in particular the base-case treatment duration assumptions of 2 years for people with HBeAg-positive disease and 5 years for people with HBeAg-negative disease. Comparing entecavir with lamivudine, the ERG's exploratory scenario analyses found that increasing the treatment duration from 2 to 5 years for people with HBeAg-positive disease increased the ICER from £14,329 in the manufacturer's base case to £22,107 per QALY gained. Even longer treatment durations gave higher ICERs – £27,120 per QALY gained for 10 years' treatment and £30,334 per QALY gained for 20 years' treatment. The

ERG noted the scenario analysis used by the manufacturer in which the assumption of a lifetime treatment duration for people with HBeAg-negative disease was used. This resulted in an ICER of £16,850 and £11,100 per QALY gained when compared with lamivudine and peginterferon alfa-2a respectively, with entecavir dominating telbivudine.

3.13 The ERG also conducted exploratory scenario analyses of the HBeAg-negative model, assuming a lifetime treatment duration. In this scenario people who progressed to compensated cirrhosis continued receiving treatment unless (or until) they developed decompensated cirrhosis. The same rate of progression to decompensated cirrhosis was assumed for all alternative treatments (1.8% per year based on the estimate used for lamivudine in 'Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B' [NICE technology appraisal 96] – see section 6). This resulted in an ICER of £27,124 per QALY gained, when comparing entecavir with lamivudine.

3.14 The assumption that all people present for treatment in the pre-cirrhotic state of the disease was not supported by the ERG clinical specialists. The ERG scenario analyses for people with HBeAg-negative disease assumed that 90% of people start treatment with chronic hepatitis B without cirrhosis and 10% of people start treatment with compensated cirrhosis. This produced an ICER of £34,006 per QALY gained when comparing entecavir with lamivudine. When the proportion of people presenting with cirrhosis at the start of treatment is set to 20%, the ICER increases to £42,608 per additional QALY gained.

3.15 During the consultation period for this appraisal, the manufacturer submitted revised cost-effectiveness estimates for the HBeAg-negative population at the request of the Committee. This revised model considered lifetime treatment duration and assumed that treatment with entecavir continued when people progressed to compensated cirrhosis. (In the original model a 5-year treatment duration was used and it was assumed that treatment was discontinued when cirrhosis developed.) A 1.8% rate of progression from compensated to decompensated cirrhosis was used. The cost of adefovir dipivoxil treatment following the development of resistance in people who had not yet developed cirrhosis was also included and this treatment was assumed to be continued when the disease progressed to active cirrhosis. This revised base case gave an ICER for entecavir versus lamivudine of £20,463 per QALY gained. A further

scenario was modelled in which people who developed resistance to lamivudine after developing compensated cirrhosis were also assumed to switch to adefovir dipivoxil. This resulted in an ICER of £15,531 per QALY gained.

3.16 The Committee also requested that the assumption that all people with HBeAg-negative chronic hepatitis B are in the pre-cirrhotic state when they start treatment should be changed to reflect NHS practice. The manufacturer presented a modified analysis for different proportions of people starting treatment after developing cirrhosis, from none to 20%. Assuming that 10% of people start treatment with compensated cirrhosis, the ICER was £24,335 per QALY gained (assuming adefovir dipivoxil treatment costs for people with resistance but only in those without cirrhosis) and £17,083 per QALY gained (with adefovir dipivoxil treatment costs for all people with resistance). Assuming that 20% of people start treatment with compensated cirrhosis, the ICER was £29,176 per QALY gained (assuming adefovir dipivoxil treatment costs for people with resistance only in those without cirrhosis) and £19,023 per QALY gained (assuming adefovir dipivoxil treatment costs for all people with resistance).

3.17 For the purposes of clarification, the Committee requested that the manufacturer provide disaggregated outcomes from their simulation analysis, including the number of events of cirrhosis and hepatocellular carcinoma in each treatment group. For comparison, observational data on the relationship between HBV DNA and the incidences of cirrhosis and hepatocellular carcinoma in people with chronic hepatitis B were also provided by the manufacturer. In general, the incidences of cirrhosis and hepatocellular carcinoma were higher in the observational studies (mixed cohorts) than in the models for both HBeAg-positive and HBeAg-negative populations. However, the manufacturer suggested that this was not unexpected, given that the populations in the studies were untreated.

3.18 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of entecavir for the treatment of chronic hepatitis B, having considered evidence on the nature of the condition and the value placed on the benefits of entecavir 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 was advised by the patient experts about the impact of hepatitis B on their 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 impact of this in terms of costs, mortality and health-related quality of life. The Committee agreed that avoiding progression to cirrhosis or hepatocellular carcinoma was the most important goal in the treatment of chronic hepatitis B and that the relationship between any surrogate endpoints measured in clinical studies and these outcomes should be fully taken into consideration.

4.3 The Committee was advised by the clinical specialists of the relative importance of the different tests in the diagnosis and management of chronic hepatitis B. It was persuaded that measurement of viral load is an important predictor of future liver damage and can be used to identify patterns of viral resistance. However, it also acknowledged the significance of seroconversion in HBeAg-positive disease, which allows for the discontinuation of treatment to be considered. The Committee was convinced that it was appropriate to use various outcomes to predict the long-term effect of the disease and apply them when defining the economic model structure and practical continuation rules. However, it noted that the relationship between surrogate and long-term outcomes was not very explicit and that some clarification would be welcomed.

4.4 The Committee considered the treatment options available for people with chronic hepatitis B in the UK. The Committee discussed with the patient experts and clinical specialists the relevance of previous NICE guidance on chronic hepatitis B and where in the treatment pathway entecavir should be considered.

The Committee understood from the clinical specialists that in the treatment pathway entecavir could be seen as an alternative to interferon either as first-line treatment or where interferon is considered inappropriate (because of contraindication or intolerance) or as an alternative to lamivudine as second-line treatment. The Committee heard from the clinical specialists that in HBeAg-positive disease the rates of seroconversion achieved with entecavir were sufficiently high that it could be considered as an option for first-line treatment alongside interferon. However the Committee considered that, without having reviewed all the evidence on the range of possible treatment sequences, it was not in a position to recommend one treatment algorithm over another and that such a recommendation was beyond the scope of this appraisal. However the Committee agreed that a comparison with interferon alfa or peginterferon alfa-2a was of interest and should be taken into account when considering the cost effectiveness of entecavir.

4.5 The Committee discussed the clinical effectiveness of entecavir in treating chronic hepatitis B and considered all of the available evidence. It acknowledged that in RCTs entecavir had been demonstrated to be more effective than lamivudine in terms of surrogate endpoints. The Committee then considered the indirect comparison exercise undertaken by the manufacturer to compare entecavir with all of the other alternative treatments outlined in the scope, taking into account the ERG's remarks on the high degree of uncertainty of the indirect analysis results. The Committee was particularly concerned about the robustness of the results of the indirect comparison when considering the comparison between entecavir and peginterferon alfa-2a. On balance, the Committee considered that although the totality of the evidence submitted supported the clinical effectiveness of entecavir, it was not in a position to advise on the relative clinical and cost effectiveness of different sequential treatment strategies including peginterferon alfa-2a and those involving only oral antiviral agents.

4.6 The Committee understood the high degree of mutability of the hepatitis B virus and recognised that the development of viral resistance was likely to be a problem with all available drugs. However, it agreed with the clinical specialists that drugs with different mechanisms of action were important in the clinical management of chronic hepatitis B particularly because of their value in reducing the potential for the development of resistance to treatment. The Committee noted that the comparatively low rate of resistance reported for entecavir in the

original manufacturer's submission was from one RCT with a 4-year follow-up of a subgroup of people. The Committee noted that additional data from this trial provided by the manufacturer during the consultation period showed that a low rate of resistance was still achieved over a 5-year period. It therefore concluded that low rates of resistance could reasonably be expected to be maintained for a number of years, but appreciated that there was still some uncertainty over the longer term.

4.7 The clinical specialists indicated that entecavir monotherapy could be used in place of lamivudine monotherapy in the pathway of care. The Committee also appreciated that lamivudine monotherapy was not a preferred option, in particular because of the high rate of viral resistance seen in highly replicative disease. The Committee concluded that an important advantage of entecavir over lamivudine with respect to resistance was the likelihood that treatment-resistant strains would emerge much later in the course of treatment, and that the need for the addition of another agent, such as adefovir dipivoxil, would be deferred but not necessarily avoided completely.

4.8 The Committee discussed the limitations and the degree of uncertainty in the economic models presented. It first considered the model representing the clinical management of people with HBeAg-positive chronic hepatitis B and noted the base-case ICERs presented and the degree of uncertainty associated with them. The Committee noted that the ICERs were below £20,000 per additional QALY gained, except in the comparison with telbivudine in which entecavir was dominated. The Committee acknowledged that this result was driven only by the assumption that entecavir had no incremental benefits when compared with telbivudine and that this took insufficient notice of the different rates of viral resistance between the two treatments. The Committee noted that the probabilistic sensitivity analyses showed that, for a threshold of £20,000 per QALY gained, entecavir still had a 45% probability of being cost effective in this particular comparison. Reflecting additionally on the concerns about the indirect comparison used for quantification of differences in effectiveness between entecavir and its comparators, the Committee concluded that the cost effectiveness results for these should be treated with extreme caution; particularly for the comparison of entecavir with peginterferon alfa-2a.

4.9 The Committee agreed with the view that the model of HBeAg-positive chronic

hepatitis B could be limited to a relatively short treatment duration because some people could be expected to experience seroconversion and thus stop receiving treatment. The Committee considered the ERG's exploratory scenario analyses on extending the timeframe of treatment in the HBeAg-positive model and noted that an extrapolation to 5 years of treatment resulted in a cost-effectiveness estimate of £22,000 per QALY gained when comparing with lamivudine. Extrapolation to the extreme of 20 years resulted in cost-effectiveness estimates at the high end of the range usually considered appropriate for the NHS. The Committee noted that no results were available for these exploratory analyses using the comparators other than lamivudine.

4.10 In conclusion, having considered the direct and indirect evidence for clinical effectiveness and the results of the economic model submitted by the manufacturer, including the exploratory analyses of the ERG, the Committee concluded that entecavir could be considered as a cost-effective option for the treatment of people with HBeAg-positive chronic hepatitis B in whom antiviral treatment is indicated.

4.11 The Committee further considered the analysis in people with lamivudine-refractory disease, though found this less informative due to the data limitations. The Committee also noted advice from the clinical experts that pre-treatment with lamivudine and/or adefovir dipivoxil would decrease the number of mutations needed for the development of resistance to entecavir. The Committee considered that it was beyond the scope of this appraisal to provide recommendations on the optimum treatment pathway and was unable to make a specific recommendation about the clinical and cost effectiveness of entecavir in people who had developed resistance to other antiviral agents.

4.12 The Committee discussed the ICERs for entecavir in the HBeAg-negative population that had been derived from the original manufacturer's analysis, the ERG's analysis and the revised modelling provided by the manufacturer. Assuming a lifetime treatment duration and continuation of treatment with entecavir when the disease progressed to compensated cirrhosis, the cost-effectiveness estimate was just over £20,000 per QALY gained when all patients start in the pre-cirrhotic state, and £24,335 per QALY gained if 10% of patients are assumed to have cirrhosis at the start of treatment, when compared with lamivudine. The Committee noted the manufacturer's comments that progression

to cirrhosis could be linked to the development of viral resistance. Therefore, accepting the lower rate of resistance development with entecavir compared to lamivudine may mean that the rate of progression was also likely to be lower. The Committee therefore agreed that there was uncertainty about the likely rate of progression to cirrhosis when comparing lamivudine to entecavir, and that use of the 1.8% estimate could have resulted in an underestimation of the cost effectiveness of entecavir. However, the Committee noted that there was still uncertainty surrounding the model – namely the lack of evidence on which to assess the plausibility of efficacy estimates of therapies over a lifetime treatment duration, and that the cost effectiveness compared with other available treatments had not been evaluated.

4.13 The Committee reviewed the additional data on the relationship between the surrogate outcomes used and final effectiveness outcomes, provided by the manufacturer during consultation. The Committee was persuaded by the observational studies presented that the estimates of the number of cases of cirrhosis and hepatocellular carcinoma averted in the original and subsequent models were plausible.

4.14 On the basis of the evidence presented during the consultation period and the previous testimonies from experts about the need for alternative treatments to be made available for people with HBeAg-negative chronic hepatitis B, the Committee was persuaded that the use of entecavir in people with HBeAg-negative chronic hepatitis B in whom antiviral treatment is indicated is clinically and cost effective.

5 Implementation

5.1 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.

5.2 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.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic hepatitis B and the healthcare professional responsible for their care thinks that entecavir is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committee is a standing advisory committee of NICE. 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.

ProfessorDavidBarnett
Professor of Clinical Pharmacology, University of Leicester

DrDavidWBlack
Director of Public Health, Derbyshire County PCT

DrCarolCampbell
Senior Lecturer, University of Teeside

DrPeterClarke
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

DrChristineDavey
Senior Researcher, North Yorkshire Alliance R & D Unit

DrMikeDavies
Consultant Physician, Manchester Royal Infirmary

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

DrCatherineJackson
Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

DrPeterJackson
Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust

ProfessorPeterJones
Pro Vice Chancellor for Research & Enterprise, Keele University

MsRachelLewis
Practice Development Facilitator, Manchester PCT

ProfessorJonathanMichaels
Professor of Vascular Surgery, University of Sheffield

DrEugeneMilne
Deputy Medical Director, North East Strategic Health Authority

DrSimonMitchell
Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

DrRichardAlexanderNakielny
Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

DrKatherinePayne
Health Economics Research Fellow, University of Manchester

DrPhilipRutledge
GP and Consultant in Medicines Management, NHS Lothian

MrMilesScott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

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

ProfessorAndrewStevens
Chair of Appraisal Committee C

MrWilliamTurner
Consultant Urologist, Addenbrookes Hospital

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.

HelenTucker
Technical Lead

JanetRobertson
Technical Adviser

ChrisFeinmann
Project Manager

7 Sources of evidence considered by the Committee

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

- Shepherd J et al. Entecavir for the treatment for chronic hepatitis B, February 2008.

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). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups and other consultees had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups and other consultees also had the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor:

- Bristol-Myers Squibb (entecavir)
- Professional or specialist and patient or carer groups:
- Association of Clinical Microbiologists
- Association of Medical Microbiologists
- British Association for the Study of the Liver
- British Infection Society
- British Society of Gastroenterology
- Hepatitis B Foundation UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

- South Asian Health Foundation

Other consultees

- Department of Health
- Welsh Assembly Government

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

- Novartis (telbivudine)
- Department of Health, Social Services and Public Health Safety for Northern Ireland
- Gilead Sciences (adefovir dipivoxil)
- GlaxoSmithKline
- 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 Assessments Centre (SHTAC)

The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on entecavir 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

Update information

February 2014: Implementation section updated to clarify that entecavir is recommended as an option for treating chronic hepatitis B.

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