# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Appraisal consultation document

## Entecavir for the treatment of chronic hepatitis B

The Department of Health has asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct a single technology appraisal (STA) of entecavir for the treatment of chronic hepatitis B and provide guidance on its use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted by the manufacturer and the views put forward by non-manufacturer consultees and commentators, and by the clinical specialist and patient expert representatives nominated for this appraisal by non-manufacturer consultees and commentators. The Committee has developed preliminary recommendations on the use of entecavir for the treatment of chronic hepatitis B.

**This document has been prepared for consultation with the formal consultees.** It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk). This document should be read in conjunction with the evidence base for this appraisal (the evaluation report) which is available from www.nice.org.uk

**Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in section 1 are preliminary and may change after consultation**.

The process the Institute will follow after the consultation period is summarised below. For further details, see the 'Guide to the single technology appraisal process' (this document is available on the Institute's website, www.nice.org.uk).

- The Appraisal Committee will meet again to consider the original evidence and this appraisal consultation document in the light of the views of the formal consultees.
- At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.
- After considering feedback from the consultation process, the Committee will prepare the final appraisal determination (FAD) and submit it to the Institute.

- Subject to any appeal by consultees, the FAD may be used as the basis for the Institute's guidance on the use of the appraised technology in the NHS in England and Wales.

**The key dates for this appraisal are:**

Closing date for comments: 30 April 2008

Second Appraisal Committee meeting: 8 May 2008

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

**Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in section 1 are preliminary and may change after consultation.**

# 1 Appraisal Committee's preliminary recommendations

This preliminary guidance does not apply to people with chronic hepatitis B known to be co-infected with 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 hepatitis B in whom the hepatitis B e antigen (HBeAg) is detected (HBeAg-positive chronic hepatitis B).

1.2 The Committee is minded not to recommend the use of entecavir for the treatment of people with chronic hepatitis B in whom the hepatitis B e antigen (HBeAg) is not detected (HBeAg-negative chronic hepatitis B).

1.3 The Committee recommends that the Institute requests further clarification from the manufacturer of entecavir on the cost effectiveness of entecavir for the treatment of people with HBeAg-negative chronic hepatitis B, which should be made available for the second Appraisal Committee meeting, on the following issues:.

- the consideration of alternative treatment strategies which should include:
  - using a typical cohort of patients starting with entecavir that represents NHS practice in terms of prevalence of existing active cirrhosis

  - continuation of treatment with entecavir when patients progress to compensated cirrhosis
  - lifetime-treatment duration
- the relative effectiveness of entecavir in people with compensated cirrhosis.

# 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 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 hepalomegaly 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; 'British national formulary' 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 (appendix A) considered evidence submitted by the manufacturer of entecavir and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer approached the 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 (hepatitis B virus [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 therapy. 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 for the nucleoside-naive populations. The network meta-analyses, implemented as Bayesian hierarchical models, assumed that treatment effects were exchangeable on the log-odds scale. The models used entecavir as the baseline treatment as it was common to all analyses, and all the models assumed fixed-treatment effects. 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. The ERG warned that the results of the meta-analysis should be treated with caution mainly because the manufacturer had not evaluated whether there were important differences in the characteristics of the studies included and there had been no testing for statistical heterogeneity.

3.5 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 for 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 treatment produced higher rates of undetectable viral load, histological improvement and ALT normalisation than lamivudine, peginterferon alfa-2a and telbivudine.

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 to not 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 available 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 both comparators.

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 analyses found that increasing the treatment duration from 2 to 5 years for people with HBeAg-positive disease increased the ICER from £14,329 to £22,107 per QALY gained. Even longer treatment durations for these patients 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 and resulted in an ICER of £16,850 and £11,100 per QALY gained when compared with lamivudine and peginterferon alfa-2a respectively, and entecavir dominating telbivudine.

3.13 The ERG also conducted exploratory sensitivity analyses that assumed people with HBeAg-negative disease would be treated for their whole lifetime irrespective of whether their disease progressed compensated cirrhosis or not, and that people with compensated cirrhosis receiving treatment would have a similar progression to decompensated cirrhosis regardless of which treatment they received (1.8% per year based on the estimate used for lamivudine in the previous technology appraisal of adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B – see section 6 below). 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 experts. The ERG sensitivity 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 patients presenting with cirrhosis at treatment initiation is set to 20% the ICER increases to £42,608 per additional QALY.

3.15 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 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 use of different tests in the diagnosis and management of chronic hepatitis B and 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 patients in clinical management which allows for the consideration of discontinuation of treatment. 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 patients with chronic hepatitis B in the UK. The Committee discussed the relevance of previous NICE guidance on chronic hepatitis B and where in the treatment pathway entecavir should be considered with the patient experts and clinical specialists. The Committee understood that in the treatment pathway, entecavir could be seen as an alternative to interferon either as primary first-line therapy or where an interferon is considered inappropriate (by reason of contraindication or intolerance) or as an alternative to lamivudine as a second-line therapy The Committee heard from the experts 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 therapy alongside interferon. The Committee agreed therefore that a comparison with interferon-alfa or peg- interferon alfa-2a was of interest, in addition to comparisons with oral antiviral agents 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 and observational studies 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. On balance, the Committee considered that the evidence submitted supported the clinical effectiveness of entecavir.

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 are 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 had been taken from a sub-group group of people in the trials. It was advised by the clinical specialists that this lower rate of resistance was biologically plausible and was expected to be significantly lower than that achieved with lamivudine. However, the Committee remained unconvinced that this low rate of resistance could be expected to be maintained in the long-term. The Committee understood that the main 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.

4.7 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. 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. It also considered the analysis in people with lamivudine-refractory disease, though found this less informative due to the data limitations. The Committee agreed with the view that the model of HBeAg-positive chronic hepatitis B could be limited to a short treatment duration because a significant proportion of people could be expected to experience seroconversion and thus stop receiving treatment. The Committee considered the ERG's exploratory analyses on extending the timeframe of treatment in the HBeAg-positive model and noted that an extrapolation to five years of treatment duration resulted in a cost-effectiveness estimate of £22,000 per QALY and extrapolation to the extreme of 20 years still resulted in cost-effectiveness estimates in the range usually considered appropriate for the NHS. Therefore the Committee concluded that entecavir is a cost-effective option for the treatment of HBeAg-positive chronic hepatitis B.

4.8 The Committee then considered the model representing the clinical management of people with HBeAg-negative chronic hepatitis B and noted the base-case ICERs presented and the degree of uncertainty associated with them. The Committee noted that the ICERs derived from this model were also below £20,000 per additional QALY gained and appeared to be cost effective. However, the Committee was not convinced of the appropriateness of using an 5-year treatment duration and was persuaded by the testimony of the clinical specialists who said the majority of people with HBeAg-negative chronic hepatitis B will need to be treated for prolonged periods of time and often for their lifetime. The Committee took note of the ERG's exploratory analyses for the HBeAg –negative population which assumed a lifetime treatment duration plus the inclusion of treatment for patients with compensated cirrhosis and having a similar progression to

decompensated cirrhosis, which resulted in an increased ICER of approximately £27,000 per additional QALY gained. It also recognised that removing the assumption that no people will start treatment with compensated cirrhosis resulted in ICERs higher than £34,000 per additional QALY gained. On this basis the Committee was not convinced that the cost effectiveness of entecavir in people with compensated cirrhosis, whether present at the start of treatment, or developing following the initiation of treatment, had been fully explored. On the basis of these concerns, the Committee was unable to issue a positive recommendation regarding the use of entecavir in people with HBeAg-negative chronic hepatitis B. The Committee therefore recommended that the Institute requests further clarification from the manufacturer of entecavir on these issues (section 1.3) which should be made available for the second Appraisal Committee meeting.

4.9 The Committee would also welcome further information about the relationship between the surrogate outcomes used and the final effectiveness outcomes of the model. Presentation of the number of cases of cirrhosis and hepatocellular carcinoma averted in the model and comparison with results from observational studies would allow for further consideration of the validity of the cost effectiveness estimates.

# 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). [NICE to amend list as needed at time of publication]

- 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/TA096

**Under development**

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

- Telbivudine for the treatment of chronic hepatitis B. NICE technology appraisal guidance (publication expected August 2008).

# 7 Proposed date for 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 It is proposed that the guidance on this technology is considered for review in February 2009. The review of the NICE technology appraisal guidance 96 (2006) on adefovir dipivoxil and peginterferon is scheduled for consideration at this date. The Institute would particularly welcome comment on this proposed date.

David Barnett
Chair, Appraisal Committee
March 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**

Senior Research Fellow in Pharmacoeconomics, Centre for the Economics of Health and Policy in Health, University of Wales

**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.

**Helen Tucker**

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:

- Shepherd J et al, Entecavir for the 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:

- Bristol-Myers Squibb Pharmaceuticals Ltd (entecavir)

II Professional/specialist and patient/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

III Other consultees

- Department of Health
- Welsh Assembly Government

IV 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 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 Entecavir by attending the initial Committee discussion and providing written evidence to the Committee. They are 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