Complete Summary

GUIDELINE TITLE

Entecavir for the treatment of chronic hepatitis B.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Entecavir for the treatment of chronic hepatitis B. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 25 p. (Technology appraisal guidance; no. 153).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic hepatitis B

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology

Infectious Diseases
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost effectiveness of entecavir for the treatment of chronic hepatitis B

TARGET POPULATION

Patients with chronic hepatitis B e antigen (HbeAg)-positive and HbeAg-negative hepatitis B

Note: This guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or human immunodeficiency virus (HIV).

INTERVENTIONS AND PRACTICES CONSIDERED

Entecavir

MAJOR OUTCOMES CONSIDERED

- Clinical Effectiveness
    - Proportion of patients with undetectable viral load below the limit of quantification by polymerase chain reaction (PCR) at weeks 24 and 48
    - Proportion of patients achieving seroconversion
    - Proportion of patients with histological improvement
    - Proportion of patients with alanine aminotransferase (ALT) normalization
    - Viral resistance
    - Adverse events
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Southampton Health Technology Assessment Centre (SHTAC), University of Southampton (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Manufacturer's Approach

Description of Manufacturers Search Strategy

The manufacturer has replicated the search strategies used by SHTAC in the previous assessment report on adefovir and pegylated interferon alpha 2a which underpinned NICE's existing guidance (NICE Technology Appraisal 96; see the National Guideline Clearinghouse [NGC] summary Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B). The manufacturer states that the full range of databases used by SHTAC were not searched for the submission due to difficulties in access. The minimum database search criteria specified by NICE were searched by the manufacturer (i.e., Medline, Embase, Medline in Progress (MEIP) and Cochrane). In addition, two of the Centre for Reviews and Dissemination (CRD) databases were also searched (Database of Reviews of Effectiveness [DARE]; health technology assessment [HTA] database). The host system used for the electronic bibliographic searching was not reported in the submission. The ERG requested clarification and the manufacturer reported that Dialog Datastar was used to search Embase, and that Ovid and Dialog Datastar had been used to search Medline (refer to Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]).

The SHTAC strategy was extended by the manufacturer to incorporate entecavir, telbivudine, and lamivudine. The searches were limited to articles published in the English language. No time limits were applied to the clinical effectiveness searches, but the ERG requested clarification about the search dates of the various electronic bibliographic databases, as these vary according to which host system is used. The manufacturer responded with the information for each database (see Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]). Each database was searched from its inception, up to approximately 21st September 2007.

The manufacturer also ran a 'simple search strategy' specifically to identify articles relating to entecavir. This was a bibliographic reference chasing exercise to check for any missed trials. It is stated that this strategy was also run for telbivudine, although terms for this drug are not presented in the actual strategy itself.

The search strategy, as adapted for each bibliographic database, was not presented in the submission. However, the strategy for Medline, Embase and the Cochrane Library was supplied on request to the ERG (see Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]). The strategy contains a mixture of free text and index terms, although for the Embase search it

is not explicit whether index terms were used. It is not clear from the search example given by the manufacturer if all the component databases of the Cochrane Library were searched or if the Cochrane Database of Systematic Reviews (CDSR) alone was used. The ERG noticed what appeared to be a few errors with the syntax used in the strategy and requested clarification from the manufacturer. The manufacturer confirmed that these were typographical errors in the submission, rather than errors in the strategies themselves (refer to Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]). The strategies appear to be comprehensive although only the generic names of the drugs were included in the strategy, rather than including trade names and Chemical Abstract Service (CAS) registry numbers or applying field tags to search for these. It is not considered, however, that using these would have produced any additional references.

In terms of on-going trials the manufacturer reports searching clinicaltrials.gov (http://clinicaltrials.gov) and Current Controlled Trials (www.controlled-trials.com), as well as internal company databases. The National Research Register (NRR) is not reported as having been searched, although this is not a NICE pre-requisite. Conference proceedings have not been reported as individually searched, although the Cochrane Central Register of Controlled Trials (CCRCT) has been searched and this does include hand-searched conference proceedings.

In summary, the search process for clinical effectiveness studies reported by the manufacturer is generally comprehensive, with key databases searched using a combination of free-text and index terms. The search strategy is not, however, fully reproducible due to limitations in reporting.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on whether They Were Appropriate.

Three different sets of inclusion criteria are presented in the manufacturer's submission (MS), all of which were applied to the same set of search results.

- The first set is for the clinical effectiveness systematic review of entecavir studies. This is the focus of the clinical effectiveness evidence for entecavir in the submission.
- The second set was for studies screened for possible inclusion in the mixed treatment comparison (MTC).
- The third set relates to a 'systematic review of licensed therapies for chronic hepatitis B', which incorporates adefovir, pegylated interferon alpha 2a, lamivudine, telbivudine, and entecavir.

Only fully published RCTs were eligible (see the "Number of Source Documents" field); however, observational extension studies were permitted. All other observational studies were excluded. Studies published in abstract form were excluded, and unpublished studies conducted by the manufacturer were only included where a clinical study report was available. Reviews were only analysed for bibliographic checking.

Cost-Effectiveness

Critique of Manufacturer's Approach

Description of Manufacturers Search Strategy

The cost-effectiveness searches have satisfied most of the minimum database criteria set by NICE (namely, Medline, Embase, and MEIP). The manufacturer has exceeded the criteria by searching internal company databases, The Cochrane Library, the HTA databases, the TRIP database (Turning Research into Practice), and websites of organisations including NICE, The Scottish Medicines Consortium (SMC), The European Association for the Study of Liver Diseases (EASL), The American Association for the Study of Liver Diseases (AASLD), as well as a Google internet search. It is not explicitly stated whether the NHS Economic Evaluation database (NHS EED) was searched, but it is assumed it was accessed via the CRD databases which were mentioned by the manufacturer as having been searched. It is not stated whether the Health Economic Evaluation Database (HEED), one of NICE's database criteria, was searched.

The date of the searches is recorded as "during September 5th and October 10th 2007". The host system used for Embase and Medline is reported as www.embase.com. It is stated that no time limits were applied, so presumably all databases were searched back to their inception.

It is reported that all search terms were mapped to EMTREE terms and exploded, as well as included as free-text terms. However, the strategy is not reproducible as the mapped terms are not recorded. It would have been preferable to record the exact search strategy that included the free text terms and subject headings, so that it could be reproduced, or at least have clearly defined which terms were free text and which were index terms.

The search strategy is not entirely transparent and therefore not easily reproducible because the list of free text terms is given, but they have not necessarily recorded the mapped index terms. The range of free-text terms looks sensible but there is no overt truncation of free text terms, although it is thought that the Datastar Dialog platform can be programmed to identify plurals and variations of endings of words. There is no indication in the search strategy as to which fields have been searched (title, abstract, subject headings etc.). However, it does say that the mapped headings have been exploded.

Refer to sections 3.1.1 and 3.1.2 of the ERG report (see the "Availability of Companion Documents" field) for more information on search strategies and details on inclusion/exclusion criteria used in the study selection.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

5 randomized controlled trials (RCTs). The Evidence Review Group (ERG) did not identify any additional RCTs that are relevant for inclusion.

Comparator Studies

- Entecavir – 1 additional RCTs
- Lamivudine – 11 additional RCTs

- Telbivudine – 3 RCTs
- Pegylated interferon alpha 2a – 2 RCTs
- Adefovir in combination with lamivudine (in lamivudine refractory patients) – 3 RCTs

Economic Evaluation

Published literature: 9 studies identified by the manufacturer and 1 study identified by the ERG

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Southampton Health Technology Assessment Centre (SHTAC), University of Southampton (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Critique of Manufacturer's Approach to Validity Assessment

The manufacturer's submission (MS) provides a formal appraisal of the validity of the included trials using the quality assessment criteria developed by NICE. It is not stated whether the appraisal was conducted independently by more than one person.

Description and Critique of the Statistical Approach Used

The MS reports almost the same descriptions of the statistical methods used in the randomised controlled trials (RCTs) as reported in the published papers, but gives slightly more detail for one study.

Overall, the statistical approaches reported in the published papers and MS relating to comparisons of entecavir against lamivudine in the RCTs appear generally appropriate. However, the statistical methods are reported superficially and have not been scrutinised in detail by the ERG. Differences in mean proportions of entecavir and lamivudine treated patients were based on confidence intervals obtained from a normal approximation to the binomial distribution. Differences between means of continuous variables were tested using *t*-tests based on linear regression models that were adjusted for baseline characteristics or included baseline data as covariates.

According to the clinical study reports, data were analysed using two approaches. Non-completing patients were included in analyses as treatment failures (NC=F approach) and as missing data (NC=M approach). The data reported in the published papers are from the NC=F analyses. The MS does not clarify which analysis method was used; it refers sporadically to NC=F analysis for only some end-points in some RCTs.

P-values for baseline comparisons were given in only two of the published papers and exceeded 0.05 for all the reported variables. Published papers for the remaining trials provided baseline variance (standard deviation [SD]) estimates for selected variables and stated narratively that the treatment groups were well balanced at baseline for demographics and disease characteristics.

The MS presents results from the five RCTs separately, with little narrative summary and no meta-analysis undertaken of any of the five included trials for any of the outcomes to elucidate any overall effects of treatment. In general, the data presented in the year one data in the MS reflect the data reported in the published papers.

The manufacturer does not give any reasons for not undertaking a meta-analysis, but proceeds directly to a network meta-analysis.

Mixed Treatment Comparison (MTC)

The manufacturer reports the methodology used to conduct a network meta-analysis.

Separate networks were conducted for hepatitis B e antigen (HBeAg)-negative and HBeAg-positive, treatment-naïve patients at year one and year two (year two predicted probabilities are cumulative rather than annual values). It was not considered possible to create a network for lamivudine-refractory patients. The five RCTs comparing entecavir with lamivudine presented in the manufacturer's systematic review are included in the MTC, hence both direct and indirect evidence is used.

The model was constructed using a Bayesian hierarchical approach using WinBUGs 1.4 software. A burn-in period of 10,000 simulations was used to allow convergence, followed by 10,000 simulations for estimation. Entecavir is the baseline treatment common to all analyses, and absolute probabilities were estimated using the average rate observed across the entecavir arms at baseline. A fixed treatment effect model is used. However, no discussion or rationale is presented for use of a fixed over a random effects model except that 'this form of

analysis is discussed in more detail by a number of authors', citing journal articles on the methodology of MTC models.

Refer to Section 3 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

Economic Evaluation

Overview of Manufacturer's Economic Evaluation

The manufacturer's submission to NICE includes:

- A review of published economic evaluations of interferon alpha, pegylated interferon alpha 2a, lamivudine, adefovir and entecavir used as the first line treatment in nucleoside naïve chronic hepatitis B (CHB) patients. The MS also reviewed economic evaluations of adefovir and entecavir as a salvage therapy in patients who became resistant to lamivudine.
- A report of an economic evaluation undertaken for the NICE Single Technology Assessment (STA) process. Entecavir as a first line treatment is compared with lamivudine, pegylated interferon alpha 2a, and telbivudine as monotherapy treatments. The cost-effectiveness of entecavir in nucleoside treatment naïve CHB patients is estimated separately for two mutually exclusive sub-groups: HBeAg-positive patients and HBeAg-negative patients. In addition, the cost effectiveness of entecavir vs. a combination therapy of lamivudine with adefovir is estimated in HBeAg positive patients who have developed resistance to lamivudine. In this model it is implicitly assumed that entecavir is a second line (salvage) therapy in a sub-group of lamivudine-resistant patients and is compared to the alternative combination therapy of lamivudine with adefovir.

Sensitivity Analyses

The MS reports one-way sensitivity analyses for selected variables in the base case and results of probabilistic sensitivity analysis, and presents a range of estimates of the probabilities of entecavir being cost-effective under the assumptions of the various threshold values for HBeAg-positive and HBeAg-negative populations respectively. The means and measures of variation of costs and outcomes in the HBeAg positive population are also reported.

Model Validation

The principal validation of the model structure and key clinical assumptions appears to have been an opinion expressed by "expert clinical hepatologists and gastroenterologists". The mathematical logic and statistical calculations appear to have been reviewed by an independent statistician and a modeller not involved in the development or analyses (though no further detail is given on the scope of this or the clinicians' review nor the criteria used to establish the model's validity).

Refer to Section 4 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The manufacturer's submission presented an economic analysis comprising two Markov models (one for hepatitis B e antigen [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.

The base-case analysis for people with HBeAg-positive disease resulted in an incremental cost-effectiveness ratio (ICER) of 14,329 pounds sterling 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 8403 pounds sterling per additional QALY gained. A comparison of entecavir with telbivudine resulted in telbivudine dominating entecavir.

The base-case analysis for people with HBeAg-negative disease resulted in an ICER of 13,208 pounds sterling per QALY gained for entecavir compared with lamivudine. A comparison of entecavir with peginterferon alfa-2a resulted in an ICER of 7511 pounds sterling per QALY gained and a comparison of entecavir with telbivudine resulted in an ICER of 6907 pounds sterling per QALY gained.

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

The Evidence Review Group (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 pounds sterling in the manufacturer's base case

to 22,107 pounds sterling per QALY gained. Even longer treatment durations gave higher ICERs.

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. This resulted in an ICER of 27,124 pounds sterling per QALY gained, when comparing entecavir with lamivudine.

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 pounds sterling 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 pounds sterling per additional QALY gained.

During the consultation period for this appraisal, the manufacturer submitted revised cost-effectiveness estimates for the HBeAg-negative population at the request of the Appraisal Committee. This revised model considered lifetime treatment duration and assumed that treatment with entecavir continued when people progressed to compensated cirrhosis. 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 pounds sterling 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 pounds sterling per QALY gained.

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 pounds sterling 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 National Health Service (NHS).

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.

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 pounds sterling per QALY gained when all patients start in the pre-cirrhotic state, and 24,335 pounds sterling per QALY gained if 10% of patients are assumed to have cirrhosis at the start of treatment, when compared with lamivudine.

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.

Refer to Sections 3 and 4 of the original guideline document for details of the economic analyses provided by the manufacturer, the ERG comments, and the Appraisal Committee considerations.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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

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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of entecavir in the treatment of chronic hepatitis B

POTENTIAL HARMS

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.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organizations 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 the National Institute for Health and Clinical Excellence (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.

- "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 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (www.nice.org.uk//TA153) [see also the "Availability of Companion Documents" field]).
    - A costing statement explaining the resource impact of this guidance.
    - Audit support for monitoring local practice.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Entecavir for the treatment of chronic hepatitis B. London (UK): National Institute for Health and

Clinical Excellence (NICE); 2008 Aug. 25 p. (Technology appraisal guidance; no. 153).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Aug

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: 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

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Entecavir for the treatment of chronic hepatitis B. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 2 p. (Technology appraisal 153). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Entecavir for the treatment of chronic hepatitis B. Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 2 p. (Technology appraisal 153). Available in Portable Document Format (PDF) from the NICE Web site.
- Entecavir for the treatment of chronic hepatitis B. Audit support. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008. 4 p. (Technology appraisal 153). Available in Portable Document Format (PDF) from the NICE Web site.
- Entecavir for the treatment of chronic hepatitis B. Evidence Review Group report. Southampton Health Technology Assessments Centre (SHTAC); 2008 Feb. 120 p. (Technology appraisal 153). Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1660. 11 Strand, London, WC2N 5HR

PATIENT RESOURCES

The following is available:

- Entecavir for chronic hepatitis B. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Aug. 4 p. (Technology appraisal 153). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1661. 11 Strand, London, WC2N 5HR.

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