



Complete Summary

GUIDELINE TITLE

Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Feb. 37 p. (Technology appraisal; no. 96).

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Chronic hepatitis B

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the clinical effectiveness and cost effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alfa (PEG) for the treatment of adults with chronic hepatitis B infection (CHB)

TARGET POPULATION

Adults with chronic hepatitis B infection

Note: This guidance does not apply to people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or human immunodeficiency virus (HIV).

INTERVENTIONS AND PRACTICES CONSIDERED

1. Peginterferon alfa-2a
2. Adefovir dipivoxil

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
 - survival
 - health related quality of life
 - drug resistance
 - time to treatment failure
 - histological response (e.g., inflammation/fibrosis -- on biopsy)
 - biochemical response (e.g., liver function - aminotransferase)
 - virological response (e.g., seroconversion rate -- & viral replication - HBVDNA)
 - seroconversion (e.g., HBeAg loss/anti-HBe; HBsAg loss/anti-HBs)
 - adverse effects of treatment
- 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Searches of Unpublished Data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 assessment report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessments Centre (See the "Companion Documents" field.)

Search Strategy

A sensitive search strategy was developed, tested and refined by an information scientist. Specific searches were conducted to identify studies of clinical-effectiveness; cost-effectiveness; quality of life; resource use/costs; and epidemiology/natural history (see Appendices 2, 3 and 4 in the Assessment Report for search strategies [refer to the "Availability of Companion Documents" field]). The strategies were applied to the following electronic databases:

- Cochrane Systematic Reviews Database
- Cochrane Central Register of Controlled Trials
- NHS CRD (University of York) databases:
 - DARE (Database of Abstracts of Reviews of Effects)
 - Health Technology Assessment (HTA) database
 - NHS EED (Economic Evaluations Database)
- Medline (Ovid)
- PreMedline
- Embase (Ovid)
- EconLit (Silver Platter)
- National Research Register
- ISI Web of Science - Science Citation Index
- ISI Proceedings
- BIOSIS
- Clinical trials.gov
- Current Controlled Trials

Searches for clinical-effectiveness, cost-effectiveness, costs of illness, quality of life, and epidemiology/natural history studies were carried out for the period from 1995/1996 to the April 2005. All searches were limited to the English language.

In addition to database searches, the websites of the following organisations were searched for relevant publications: the Department of Health; Health Protection Agency; European Agency for the Evaluation of Medicinal Products; British Association for the Study of the Liver (BASL), European Association for the Study of the Liver (EASL), American Association for the Study of the Liver (AASL); British Society of Gastroenterology; Foundation for Liver Research; The British Liver Trust, The British Association for Sexual Health and HIV; The British HIV

Association; the European Medicines Agency; the U.S. Food and Drug Administration (FDA).

Finally, bibliographies of related papers were assessed for relevant studies; experts were contacted for advice and peer review, and to identify additional published and unpublished references; and manufacturer and sponsor submissions to the National Institute for Clinical and Health Excellence (NICE) were searched for studies that met the inclusion criteria.

Inclusion and Exclusion Criteria

Studies identified by the search strategy were assessed for inclusion through two stages. Firstly, the titles and abstracts of all identified studies were screened by one reviewer, and a random sample of 10% of these were checked by a second reviewer. Secondly, full text versions of relevant papers were retrieved, and an inclusion worksheet (see Appendix 5 of the Assessment Report [refer to "Companion Documents" field]) was applied by two independent reviewers. Any differences in judgement at either stage were resolved through discussion. The inclusion criteria, as specified in the study protocol, were set as follows.

Interventions

- Interventions (alone and in combination with other treatment options):
 - pegylated interferon alfa-2a
 - adefovir dipivoxil
- Comparators (alone and in combination with other treatment options):
 - pegylated interferon alfa-2a*
 - adefovir dipivoxil*
 - interferon alfa-2a
 - interferon alfa-2b
 - lamivudine
 - best supportive care

*Intervention was not compared with itself

Patients

- Adults with chronic hepatitis B infection, including those who were HBeAg-positive and HBeAg-negative, and with compensated or decompensated disease.
- The clinical effectiveness of treatment in different patient subgroups (e.g., genotype) were analysed where data allowed.

Types of Studies

- Systematic reviews of randomised controlled trials (RCTs) and RCTs comparing the different drugs with placebo or each other or best supportive care were included in the review of clinical effectiveness.
- With the exception of two RCTs which are not yet fully published, studies published as abstracts or conference presentations were not generally included in the primary analysis of clinical and cost-effectiveness. However,

- their key characteristics were recorded and described to provide context around the discussion of effectiveness and summaries are provided where appropriate (labelled as 'unpublished data').
- Full economic evaluations of the specified interventions in patients with chronic hepatitis B infection were included.
 - A range of designs for studies on health related quality of life, and epidemiology/natural history were considered.

Outcomes

See the "Major Outcomes Considered" field above.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

A total of 1085 references to clinical-effectiveness studies were identified. After screening, six fully published randomised controlled trials (RCTs) and one systematic review met the inclusion criteria.

Cost Effectiveness

Not stated

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 assessment report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessments Centre (See the "Companion Documents" field.)

Data Extraction Strategy

Data were extracted from the included clinical-effectiveness studies using a standardised template. Data extraction was undertaken by one reviewer and

checked by a second, with any disagreements resolved through discussion. Full data extraction forms of all the included studies can be seen in Appendices 6 to 11 of the Assessment Report (see "Companion Documents" field).

Quality Assessment Strategy

The quality of included systematic reviews and randomized controlled trials (RCTs) was assessed using the National Health Service (NHS) Centre for Reviews and Dissemination (University of York) criteria (see Appendix 13 of the Assessment Report [refer to the "Companion Documents" field]). Quality criteria were applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

Methods of Analysis/Synthesis

A narrative synthesis was undertaken with the main results of the included clinical-effectiveness and cost-effectiveness studies described qualitatively, and in tabular form. A meta-analysis was not possible due to heterogeneity in the interventions and comparators evaluated by the included clinical trials. Where data allowed, clinical and cost-effectiveness was assessed according to patient sub-types (e.g., according to genotypes).

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 Appraisal Committee considered evidence from four economic models: one by the Assessment Group, one by each of the two manufacturers involved, and one published analysis by Kanwal and colleagues (which was published after the Assessment Report's deadline for inclusion). The models have similar structures and parameters, and their results are in broad agreement.

Overall Results of the Models

The models show that interferon alfa or peginterferon alfa-2a therapies followed by lamivudine then adefovir dipivoxil, where necessary, appear to be cost effective relative to alternative strategies. In most of the analyses, strategies in which adefovir dipivoxil is used before lamivudine, or without lamivudine, in the sequence are dominated by the alternative strategies. The exceptions are Gilead's estimated incremental cost-effectiveness ratio of £29,400 per quality-adjusted life year for adefovir dipivoxil then lamivudine, compared with lamivudine then adefovir dipivoxil, and the Assessment Group's estimated incremental cost-

effectiveness ratio of £57,000 per quality-adjusted life year (for HBeAg-positive patients) for peginterferon alfa-2a then adefovir dipivoxil then lamivudine, compared with peginterferon alfa-2a then lamivudine then adefovir dipivoxil.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

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

Note: This guidance does not apply to people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or human immunodeficiency virus (HIV).

- Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications.
- Adefovir dipivoxil is recommended as an option for the treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative) within its licensed indications if:
 - treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
 - a relapse occurs after successful initial treatment, or
 - treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated.
- Adefovir dipivoxil should not normally be given before treatment with lamivudine. It may be used either alone or in combination with lamivudine when:
 - treatment with lamivudine has resulted in viral resistance, or
 - lamivudine resistance is likely to occur rapidly (for example, in the presence of highly replicative hepatitis B disease), and development of lamivudine resistance is likely to have an adverse outcome (for

example, if a flare of the infection is likely to precipitate decompensated liver disease).

- Drug treatment with peginterferon alfa-2a or adefovir dipivoxil should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a general practitioner is appropriate.

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 pegylated interferon alfa-2a and adefovir dipivoxil for the treatment of chronic hepatitis B

POTENTIAL HARMS

Pegylated Interferon Alfa-2a

Peginterferons have a range of adverse effects similar to those of interferons. These include influenza-like symptoms such as fever, chills, myalgias, arthralgias and headache, which are most likely to occur at the start of treatment and seldom require discontinuation of treatment. Depletion of platelets and white blood cells is common. Other adverse effects include depression, anxiety or emotional lability, which may be severe. Cardiovascular adverse effects include hypertension or hypotension, arrhythmias, oedema, myocardial infarction or stroke.

Adefovir Dipivoxil

The most commonly reported adverse effects for adefovir dipivoxil are gastrointestinal effects including nausea, flatulence, diarrhoea and dyspepsia. Increases in serum creatinine are common but usually mild to moderate. However, cases of renal impairment and acute renal failure have been reported.

For full details of side effects and contraindications, see the 'Summary of product characteristics'.

CONTRAINDICATIONS

CONTRAINDICATIONS

Interferons are contraindicated in patients with chronic hepatitis with decompensated cirrhosis of the liver.

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 THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- All clinicians who care for people with chronic hepatitis B should review their current practice and policies to take account of the guidance (see the "Major Recommendations" field).
- Local guidelines, protocols or care pathways that refer to the care of people with chronic hepatitis B should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in appendix C of the original guideline document.
 - For an adult with chronic hepatitis B (HBeAg-positive or -negative), peginterferon alfa-2a is considered as an option for the initial treatment, within its licensed indications.
 - For an adult with chronic hepatitis B (HBeAg-positive or -negative) adefovir dipivoxil is considered as an option for treatment, within its licensed indications, if:
 - treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
 - a relapse occurs after successful initial treatment, or
 - treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated.
 - Adefovir dipivoxil is not normally given before treatment with lamivudine.
 - Adefovir dipivoxil is normally used either alone or in combination with lamivudine when:
 - treatment with lamivudine has resulted in viral resistance, or
 - lamivudine resistance is likely to occur rapidly and development of lamivudine resistance is likely to have an adverse outcome.
 - Drug treatment with peginterferon alfa-2a and adefovir dipivoxil is initiated by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis.
- Local clinical audits also could include measures related to the existence of clear, long-term management plans for people with chronic hepatitis B; the

provision of written information to patients on the transmission and outcomes of the disease; the regularity of alanine aminotransferase (ALT) level checks; the clinical supervision of the patients' care; and the coordination of data collection for local audits with national audits that may include these patients.

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

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Feb. 37 p. (Technology appraisal; no. 96).

ADAPTATION

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

DATE RELEASED

2006 Feb

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 A E Ades, MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol; Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Mrs Elizabeth Brain, Independent Patient Advocate; Professor Gary Butler, Professor of Paediatrics, University of Reading and Royal Berkshire Hospital; Dr Karl Claxton, Health Economist, University of York; Dr Richard Cookson, Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia; Professor Christopher Eccleston, Director, Pain Management Unit, University of Bath; Professor Terry Feest, Professor of Clinical Nephrology, Southmead Hospital; Ms Alison Forbes, Health Consultant Associate, Eden Insight; Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford; Mr John Goulston, Director of Finance, Barts and the London NHS Trust; Mr Adrian Griffin, Health Outcomes Manager, Johnson & Johnson Medical; Dr Elizabeth Haxby, Lead Clinician in Clinical Risk Management, Royal Brompton Hospital; Dr Rowan Hillson, Consultant Physician, Diabeticare, The Hillingdon Hospital; Dr Catherine Jackson, Clinical Lecturer in Primary Care Medicine, Alyth Health Centre, Angus; Mr Muntzer Mughal, Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust; Ms Judith Paget, Chief Executive, Caerphilly Local Health Board; Dr Katherine Payne, Health Economist, The North West Genetics Knowledge Park, The University of Manchester; Dr Ann Richardson, Independent Research Consultant; Mrs Kathryn Roberts, Nurse Practitioner, Hattersley Group Practice, Cheshire; Professor Philip Routledge, Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff; Dr Debbie Stephenson, Head of HTA Strategy, Eli Lilly and Company; Professor Andrew Stevens (*Vice-Chair*) Professor of Public Health, University of Birmingham; Dr Cathryn Thomas, General Practitioner, Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham; Dr Norman Vetter, Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff; Dr Paul Watson, Medical Director, Essex Strategic Health Authority; Dr David Winfield, Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

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:

- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Feb. 2 p. (Technology appraisal 96). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B - a systematic review and economic evaluation. Assessment report. Southampton Health Technology Assessments Centre; 2005 May 27. 222 p. Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0975. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. Understanding NICE guidance - information for people with chronic hepatitis B, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Feb. 7 p. (Technology appraisal 96).

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

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0976. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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