NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Entecavir for the treatment of chronic hepatitis B

Final Scope

Draft remit/ appraisal objective

To appraise the clinical and cost effectiveness of entecavir for chronic hepatitis B.

Background

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). It is transmitted through blood to blood contact (e.g. through sharing of blood-contaminated needles by drug users) and sexual contact. It is also transmitted vertically from mother to infant, during or soon after birth. Infected individuals develop an acute infection, which may or may not result in symptoms. The majority of those infected during adulthood make a full recovery and acquire immunity from future infection. Only about 2-10% of infected adults will develop chronic hepatitis B, defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with hepatitis B virus. In contrast almost 100% of infected neonates and about 50% of infected young children will develop chronic hepatitis B if infected with HBV.

Active infection can be described as HBeAg-positive or HBeAg-negative according to whether hepatitis B 'e' antigen (HBeAg) is secreted. HBeAg is an indicator of viral replication, although some variant forms of the virus do not express HBeAg. The response to treatment and rates of progression differ between the two forms. People can be infected with the so-called HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus. Chronic infection with mutant strains of hepatitis B virus that do not produce e' antigen (that is, HBeAg-negative) is associated with a fluctuating course and a poor prognosis.

The Department of Health estimates that about 180,000 people in the UK have chronic hepatitis B. There are about 7700 new cases of chronic hepatitis B each year. Of these, around 300 people were infected within the UK; the remainder (mainly immigrants to the UK) were infected abroad, generally in areas of high prevalence where the virus is frequently transmitted from mother to child.

The progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of progression of 8–20% in HBeAg-positive chronic hepatitis B and an annual rate of 8-10% in HBeAg-negative chronic hepatitis B.

Treatment

Current standard treatments for chronic hepatitis B have been specified in NICE Technology Appraisal guidance No. 96 (see Appendix 1). The first drugs to be licensed for the treatment of chronic hepatitis B were alfa interferons. Interferons are natural proteins that activate the immune system in response to viral infection. Three recombinant interferons and one pegylated interferon have UK marketing authorisation for the treatment of chronic hepatitis B.

Pegylated interferons are formed by attaching strands of polyethylene glycol (PEG) to the interferon molecules which slows the rate of absorption and excretion of interferon. Peginterferon alfa- 2a is administered once a week compared with three or more times a week for unmodified interferons. The side effects of interferons can be severe and this means that they are not suitable for long-term treatment in chronic hepatitis B. Treatment courses usually last between 4 and12 months. However, 48 weeks of treatment with peginterferon alfa-2a is the optimum period to obtain potential clinical benefits. Interferons are contraindicated in decompensated liver disease.

Lamivudine is a nucleoside analogue and adefovir dipivoxil is a nucleotide analogue. Both are nucleoside reverse transcriptase inhibitors and can be given either as a circumscribed course of treatment or as long-term viral suppressive therapy. In HBeAg-positive chronic hepatitis B, treatment is usually given for a year with the aim of bringing about HBeAg seroconversion. In chronic infections by HBeAg-negative mutant strains, a circumscribed course of therapy is less likely to lead to long-term control of the infection, and long-term treatment is often needed. Resistance to lamivudine occurs in more than 60% of cases after 3 years' treatment, while resistance to adefovir dipivoxil appears less likely. Adefovir dipivoxil and lamivudine are sometimes given in combination (see Technology Appraisal guidance No. 96).

The technology

Entecavir (Baraclude, Bristol-Myers Squibb) is an oral nucleoside analogue. It works by inhibiting the viral DNA polymerase responsible for HBV replication, without inhibiting human cellular polymerases.

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 levels and histological evidence of active inflammation and/or fibrosis.

Intervention(s)	Entecavir alone or in combination with other therapies.

Population(s)	Adults with compensated liver disease and active chronic hepatitis B (that is evidence of viral replication and active liver inflammation)
Current standard comparators	• Interferon alfa-2a • Interferon alfa-2b • Peginterferon alfa-2a • Lamivudine • Adefovir dipivoxil • Telbivudine
Outcomes	Outcomes to be considered include: • HBeAg/ HBsAg seroconversion rate • virological response (HBV-DNA) • histological improvement (inflammation and fibrosis) • biochemical response (e.g. ALT levels) • development of viral resistance • time to treatment failure • survival • health related quality of life • adverse effects of treatment.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should reflect the chronic nature of hepatitis B. Consideration should be given to alternative treatment continuation rules as appropriate. Costs will be considered from a NHS and Personal Social Services Perspective.

Other considerations	If evidence allows, the appraisal will seek to identify subgroups of individuals for whom the technology is particularly clinically and cost-effective. Subgroups may include people with HBeAg – positive, HBeAg negative and treatment resistant disease types. In line with the Technology Appraisal 96, this STA will not specifically consider people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV' If the evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy Guidance will be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: NICE Appraisal Guidance No 96 - Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a (February 2006).

Appendix 1: NICE Appraisal Guidance No 96 - Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a

This guidance does not apply to people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV.

1.1 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.

1.2 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.

1.3 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).

1.4 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.