NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Telbivudine for the treatment of chronic hepatitis B

Draft scope (Pre-referral)

Draft remit/ appraisal objective

To appraise the clinical and cost effectiveness of telbivudine 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. Infection with HBeAg-negative chronic hepatitis B 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

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. Peginterferons are 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, courses usually last between 4 and12 months depending on the genotype of the virus. Interferons are contraindicated in decompensated liver disease.

Lamivudine and adefovir dipivoxil are nucleoside reverse transcriptase inhibitors. They 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 HBeAg-negative chronic hepatitis B, a circumscribed course of therapy is less likely to lead to long-term control of the infection, and long-term treatment is often needed. The main problem with long-term antiviral treatment is the emergence of resistance. 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

Telbivudine (Novartis Pharmaceuticals) is a nucleoside analogue. It works by inhibiting the viral DNA polymerase enzyme responsible for HBV replication, without inhibiting human cellular polymerases.

Telbivudine has no marketing authorisation in the UK. It is currently in clinical trials in people with HBeAg-positive compensated chronic hepatitis B.

Intervention(s)	Telbivudine alone or in combination with other therapies.
Population(s)	Adults with active chronic hepatitis B (evidence of viral replication and active liver inflammation)

Current standard comparators	• Interferon alfa-2a • Interferon alfa-2b • Peginterferon alfa-2a • Lamivudine • Adefovir dipivoxil If the evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy.
Outcomes	Outcomes to be considered include: • survival • health related quality of life • development of viral resistance • time to treatment failure • histological improvement (inflammation/fibrosis) • biochemical response (e.g. ALT) • virological response (HBV-DNA) • HBeAg/anti-HBe seroconversion rate • 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. 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. 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).

Questions for consultation

Given the large number of comparators and the different possible positions in treatment sequences for the drug, should telbivudine be appraised alongside other treatments in a multiple technology appraisal?