NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of tenofovir disoproxil fumarate within its licensed indication for the treatment of chronic hepatitis B

Background

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus. 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 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 hepatitis B virus.

Active infection can be described as HBeAg-positive or HBeAg-negative according to whether Hepatitis B 'e' antigen (HBeAg) is expressed. 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 estimated that about 180,000 people in the UK had chronic hepatitis B in 2002, but recent data from the Hepatitis B Foundation estimated that approximately 326,000 people are currently infected in the UK. 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 of chronic hepatitis B to cirrhosis occurs at an annual rate of 2–5.5% in HBeAg-positive chronic hepatitis B and an annual rate of 8-10% in HBeAg-negative chronic hepatitis B.

Options for the treatment of chronic hepatitis B have been specified in NICE Technology Appraisal guidance numbers 96 and 153. Three recombinant

interferons and one pegylated interferon have UK marketing authorisation for the treatment of chronic hepatitis B. 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, telbivudine and entecavir are nucleoside analogue and adefovir dipivoxil is a nucleotide analogue. All act by inhibiting the viral DNA polymerase responsible for HBV replication 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.

The technology

Tenofovir disoproxil fumarate (Viread, Gilead) is a nucleotide analogue which works by interfering with the viral DNA polymerase enzyme used for hepatitis B virus replication. It is administered orally at a dose of 300mg once daily. It is currently licensed for the treatment of HIV infection and is also used, but not specifically licensed, as a combination therapy with either emtricitabine or lamivudine, for people co-infected with HIV and hepatitis B virus.

Tenofovir disoproxil fumarate does not currently have a marketing authorisation for chronic hepatitis B. In March 2008, the CHMP issued a positive opinion for tenofovir disoproxil fumarate for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

Intervention(s)	Tenofovir disoproxil fumarate alone or combination with other therapies
Population(s)	Adults with active chronic hepatitis B (evidence of viral replication and active liver inflammation) and compensated liver disease. HBeAg-positive and HBeAg-negative disease will be considered separately

Standard comparators	• Interferon alfa-2a • Interferon alfa 2b • Peginterferon alfa-2a • Lamivudine • Adefovir dipivoxil • Entecavir
Outcomes	The outcome measures to be considered include: • HBeAg seroconversion rate • 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 • adverse effects of treatment • health-related quality of life.
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. The economic evaluation should incorporate key assumptions that were accepted by the appraisal committee in TA96 and TA153. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows, the appraisal will seek to identify subgroups (e.g. people with treatment resistant disease) of individuals for whom the technology is particularly clinically and cost- effective. If the evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy. 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'.
Related NICE recommendations	Related Technology Appraisals: NICE Appraisal Guidance No 96 - Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a (February 2006). Technology Appraisals in preparation Entecavir for the treatment of chronic hepatitis B. Earliest anticipated date of publication: August 2008 Telbivudine for the treatment of chronic hepatitis B. Earliest anticipated date of publication: August 2008