NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

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

Final scope

Objective: To appraise the clinical and cost effectiveness of adefovir dipivoxil (Hepsera, Gilead) for the treatment of chronic hepatitis B virus (CHB) infection and peginterferon alfa-2a (Pegasys, Roche) for the treatment of CHB infection, and to provide guidance to the NHS in England and Wales.[i]

Background:
Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). HBV is transmitted horizontally by blood to blood contact (e.g. the sharing of blood contaminated needles and injecting equipment used by drug users) and sexual transmission. It is also transmitted vertically from mother to infant in the perinatal period. About 2-10% of those infected as adults, and up to 90% of children infected perinatally, become chronic carriers of the hepatitis virus with the hepatitis B surface antigen (HBsAg) persisting for longer than 6 months.

Chronic hepatitis B can be separated into two forms based on the presence of hepatitis B 'e' antigen (HBeAg) and antibody (anti-HBe).

- HBeAg-positive CHB is associated with an extremely high HBV replication rate and persistently or intermittently increased aminotransferase levels. This type can occur immediately after the acute phase or develop after several years.
- Some 5-15% of patients with HBeAg-positive CHB per year may have favourable outcome and transit to the 'inactive chronic hepatitis B surface antigen carrier' state.
- HBeAg-negative or anti-HBe-positive CHB is associated with persistent or intermittent elevations in alanine aminotransferase activity and necroinflammation and fibrosis on liver histology that are linked aetiopathogenetically to the underlying HBV replication. Patients with HBeAg-negative CHB harbour replication competent HBV variants that are unable to produce HBeAg due to mutations either at the pre-core or the basic core promoter region of the viral genome. This represents a potentially severe and progressive form of chronic liver disease with very rare spontaneous remissions, frequent progression to cirrhosis and increased risk of the development of hepatocellular carcinoma.

Seven major HBV genotypes are known to prevail in different parts of the world.

The prevalence of CHB in developed countries is estimated at 0.3% in the UK population. This equates to approximately 160,000 cases in England and Wales. Men are more likely than women to develop chronic infections, although the reasons for this are unclear.

Most people with hepatitis B may not have symptoms at all. About 25% of carriers of CHB develop serious liver disease, including chronic hepatitis and cirrhosis. Liver

cirrhosis could result in symptoms such as weight loss, fatigue, jaundice, nausea, vomiting and loss of appetite and can ultimately lead to liver failure and liver cancer. Only 55-85% of those with active HBV-related cirrhosis survive for more than five years. The severity of liver histological lesions is an important factor in the decision to treat. Liver biopsy prior to initiation of treatment thus provides important information on the prognosis and probability of response. A realistic therapeutic approach aims to sustain HBeAg loss and anti-HBe seroconversion in HBeAg-positive CHB and to sustain biochemical and virological remission in HBeAg-negative CHB.

Current treatment includes interferon alfa-2a and interferon alfa-2b given by injection, and oral lamivudine. Interferon alfa-2a and -2b show side effects such as flu-like symptoms, depression and headaches. The use of interferon-alfa-2a and -2b is generally regarded to be contra-indicated in patients with CHB and decompensated liver disease. Lamivudine could lead to the development of mutant hepatitis B virus during and after treatment; resistance emerges in 15-32% of people in the first year of treatment.

The technologies:

Adefovir dipivoxil is an oral prodrug of adefovir that is converted to adefovir diphosphate in the human body. Adefovir diphosphate inhibits viral polymerases and, after incorporation into viral DNA, causes DNA chain termination. Adefovir dipivoxil is indicated for the treatment of CHB in adults with compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis. Adefovir is also indicated for adults with decompensated liver disease.

Adefovir dipivoxil is effective in lamivudine-resistant CHB and has been investigated in combination with lamivudine. Patients treated with adefovir dipivoxil have very commonly experienced asthenia, and commonly experienced headache or gastrointestinal problems. Possibility of renal impairment has been uncommonly reported and could be related to the dose and the dosing interval but is more common in patients who are waiting for, or who have undergone, liver transplantation.

Pegylated interferon alfa-2a is the result of the conjugation of PEG reagent to interferon alfa-2a. Peginterferon alfa-2a possesses the in-vitro antiviral and antiproliferative activities that are characteristic of interferon alfa-2a. After subcutaneous administration, the terminal half-life of peginterferon alfa-2a is approximately 50-130 hours compared with values of 3-4 hours for interferon alfa-2a. Peginterferon alfa-2a has been submitted to regulatory authorities in Europe in July 2004 for the treatment of both HBeAg-positive and HBeAg-negative CHB. Marketing Authorisation is expected to be granted by May 2005.

The place of peginterferon alfa-2a in the treatment of hepatitis B will depend on the marketing authorisation. In a trial, peginterferon alfa-2a was used in a once-weekly dose, compared with the three times weekly regimen of interferon alfa-2a. In two other trials, peginterferon ala-2a was compared with lamivudine in patients with HBeAg-positive and HBeAg-negative CHB.

Intervention(s)	Adefovir dipivoxil and peginterferon alfa-2a, alone and, if evidence allows, in combination with other treatment options.
Population(s)	Adults* with chronic hepatitis B (CHB) * See "other considerations" and covering letter
Current standard treatments (comparators)	Alone or, if evidence allows, in combination with other treatments: • HBeAg-positive CHB and compensated liver disease: interferon alfa-2a, interferon alfa-2b, lamivudine, adefovir dipivoxil*, peginterferon alfa-2a* or non-drug treatment strategies (including watchful waiting) • HBeAg-positive & decompensated liver disease: lamivudine, adefovir dipivoxil* or non-drug treatment strategies • HBeAg-negative & compensated liver disease: lamivudine, interferon-alfa-2a, -2b, peginterferon-alfa-2a*, adefovir dipivoxil* or non-drug treatment strategies (including watchful waiting) • HBeAg-negative & decompensated liver disease: lamivudine, adefovir dipivoxil* or non-drug treatment strategies * intervention will not be compared with itself
Other considerations	The outcome measures to be considered include: • survival • health related quality of life • resistance • time to treatment failure • histological improvement (e.g. inflammation/fibrosis – biopsy) • biochemical response (e.g. liver function - ALT) • virological response (e.g. seroconversion rate – HBeAg/anti-HBe/HBsAg & viral replication - HBV-DNA) • adverse effects of treatment The role of biopsy in initiating treatment. The appropriateness of stopping rules particularly for people with HBeAg-negative CHB. Cost effectiveness of treatments should ideally be expressed in terms of incremental cost per quality adjusted life year.

	Costs will be considered from an NHS and Personal Social Services perspective. The time horizon of the economic evaluation will be based on the time period over which costs and benefits can reasonably be expected to be experienced. If evidence allows, consideration will be given to patient preferences in determining the benefit of treatment. If the evidence allows, subgroups for whom the technology may be particularly cost-effective will be identified, which may include users of alcohol and other substances, people with depression and other psychiatric disorders, transplantation candidates, post liver transplantation, people with co-infections (including HIV, HCV, HDV), pregnant and breast feeding women, healthcare workers, prisoners and asylum seekers. The interventions will be appraised according to their (anticipated) licensed indication(s). Guidance will only be issued in accordance with the marketing authorisation.

[i] The Department of Health remit to the Institute is "To appraise the clinical and cost effectiveness of adefovir dipivoxil and pegylated interferon alfa-2a in their licensed indications for the treatment of chronic hepatitis B virus (HBV) infection".