Scottish Medicines Consortium

entecavir, 0.5 and 1mg tablets (Baraclude®) No. (320/06)

Bristol-Myers Squibb Pharmaceuticals Ltd

8 September 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

entecavir (Baraclude®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis B virus 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.

Clinical studies have shown that entecavir is more effective than lamivudine in nucleoside-naïve HBeAg positive and negative patients and in lamivudine refractory patients.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the treatment of chronic hepatitis B virus (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. This indication is based on clinical trial data in patients with HBeAg positive and HBeAg negative HBV infection, nucleoside-naïve patients and patients with lamivudine-refractory hepatitis B.

Dosing information

Nucleoside naïve patients: 0.5mg daily with or without food.
Lamivudine refractory patients: 1mg daily on an empty stomach (two hours before or more than two hours after a meal.
Therapy should be initiated by a physician experienced in the management of chronic hepatitis B infection. The optimal duration of treatment is not known.

Product availability date

July 2006

Comparator medications

Anti viral agents: lamivudine, adefovir dipivoxil and interferon alfa -2a and -2b and peginterferon alfa-2a

Cost of relevant comparators

Product	Regimen	Cost per 6 months (£)	Cost per 48 weeks(£)
Entecavir	**0.5-1mg daily**	**2293**	**4234**
Adefovir dipivoxil	10mg daily	1916	3528
Lamivudine	100mg daily	509	937

Costs were accessed from eVadis on 4th July 2006. The optimum duration of treatment for lamivudine, adefovir and entecavir is unknown.

Summary of evidence on comparative efficacy

Entecavir is a guanosine nucleoside analogue, with selective activity against hepatitis B viral (HBV) replication. Once converted to the active triphosphate it competes with deoxyguanosine triphosphate, inhibiting HBV polymerase. This inhibition affects the three steps of viral replication: priming of HBV polymerase, reverse transcription of the negative strand DNA from the pregenomic messenger RNA, and synthesis of the positive strand HBV DNA.

There have been three pivotal, phase lll studies comparing entecavir to lamivudine in nucleoside-naïve HBeAg positive and HBeAg negative patients and in patients refractory to lamivudine. The study design, primary and secondary endpoints, inclusion and exclusion criteria were the same for the two nucleoside-naïve studies with the exception of HBeAg status. Both were randomised, double-blind studies to evaluate and compare the safety, tolerability and efficacy of entecavir 0.5 mg daily versus lamivudine 100 mg daily in patients with chronic hepatitis infection and compensated liver disease. Patients were included if they had detectable hepatitis B surface antigen (HbsAg), alanine transferase (ALT)>1.3-10x the upper limit of normal (ULN) and HBV DNA = 3 MEq/ml. Patients were excluded if they were co-infected with hepatitis C or D, human immunodeficiency virus (HIV) or had received lamivudine treatment lasting more than 12 weeks. The primary outcome measure was the proportion of patients with histologic improvement (=2 decrease in Knodell necroinflammatory score and no worsening in Knodell fibrosis score) at week 48. Secondary outcome measures included the reduction in HBV DNA, the proportion of patients with undetectable HBV (<300 copies/ml), decrease in Ishak fibrosis score, HBeAg loss and ALT normalisation. Patients were assessed for response at 48 weeks; complete responders stopped study treatment and were followed for 24 weeks to assess durability of response, partial responders continued blinded treatment for up to 96 weeks or until complete response was achieved and non-responders discontinued.

In the study of HBeAg positive patients, 709 patients were randomised and received treatment, and 628 patients had evaluable liver biopsies. Significantly more patients receiving entecavir had an improvement in liver histology, 72% versus 62% for entecavir and lamivudine respectively, difference 9.9% (95%CI: 2.6%, 17.2%), p=0.009. Entecavir was also superior to lamivudine for the secondary endpoints of the mean reduction in serum HBV DNA (-6.9 $\log_{10}$ copies /ml and -5.4 $\log_{10}$ copies /ml; p <0. 001), proportion of patients with undetectable HBV (67% versus 36%; p<0.0001) and normalisation of ALT (68% versus 60%; p=0.02) at 48 weeks. The benefits of entecavir were sustained after 24 weeks off therapy in most patients who had a complete response at 48 weeks.

In the study of HBeAg negative patients, 638 patients were randomised and treated, 583 patients had evaluable liver biopsies. Significantly more patients receiving entecavir had an improvement in liver histology, 70% versus 61% for entecavir and lamivudine respectively, difference 9.6% (95%CI: 2.0%, 17.3%), p=0.014. Entecavir was also superior to lamivudine for the secondary endpoints of the mean reduction in serum HBV DNA (-5.04 $\log_{10}$ copies/ml versus -4.53 $\log_{10}$ copies/ml, p<0.001), proportion of patients with undetectable HBV (90% versus 72%; p<0.001) and normalisation of ALT (78% versus 71%; p<0.05) at 48 weeks. Of those patients who discontinued treatment with a complete response at 48 weeks, 48% of entecavir and 35% of lamivudine patients had a sustained response for at least 24 weeks.

In a comparative, double-blind study, 286 HBeAg positive, lamivudine-refractory patients were randomised to entecavir 1mg or lamivudine 100mg daily for 48 weeks with a similar continuation/discontinuation protocol as for the nucleoside-naïve patient studies (complete

responders stopped treatment and were followed for 24 weeks, partial responders continued blinded treatment for up to 96 weeks or until complete response was achieved and then were followed for 24 weeks and non-responders discontinued but were eligible for a roll over study). Entecavir was superior to lamivudine for the co-primary outcomes of the proportion of patients with histologic improvement, as measured previously, (55% versus 28%, difference 27.3% (97.5%CI: 13.6%, 40.9%), p<0.0001), and undetectable HBV DNA with normalisation of ALT levels (55% versus 4%, difference 50.5% (97.5% CI: 40.4, 60.6), p<0.0001) at 48 weeks. Secondary outcomes included improvement in liver fibrosis, HBV DNA level, HBeAg seroconversion, HBV resistance. Durability of response after 24 weeks off therapy was also evaluated. Significantly more patients in the entecavir group achieved the secondary outcome of improvement in liver fibrosis and had significantly greater reduction in HBV DNA, but there was no significant difference in the proportion of patients with HBeAg seroconversion. Two patients in the entecavir group had a confirmed virological rebound at 48 weeks.

Summary of evidence on comparative safety

In the pivotal studies, entecavir was generally well tolerated and had a safety profile comparable to lamivudine. The overall frequency of adverse events and serious adverse events was comparable between entecavir 0.5 and 1mg and lamivudine 100mg with the most common adverse events being headache, upper respiratory tract infection, fatigue, nausea and cough. There was an increase in the rate of carcinogenesis in mice treated with up to 40 times the normal dose of entecavir and therefore the incidence of new diagnosis for neoplasms with entecavir treatment is being monitored. However the malignancy event rate in the clinical studies of lamivudine and entecavir was comparable. Hepatic flares in entecavir and lamivudine patients occurred with a similar frequency both on and off treatment in nucleoside-naïve patients.

Summary of clinical effectiveness issues

In two-stage analyses, entecavir has been shown to be non-inferior and superior to lamivudine for the treatment of HBV in nucleoside-naïve HBeAg positive and negative patients and in lamivudine-refractory patients with a similar adverse event profile. However there are no published studies comparing the sustained antiviral effect of entecavir versus adefovir, the other oral HBV therapy. Unlike lamivudine and adefovir, entecavir is not licensed in patients with decompensated liver disease and there is limited evidence at present in liver transplant patients. Patients co-infected with HIV and hepatitis C and D were excluded from the trials and therefore there is a lack of evidence base in these patients. The optimum length of treatment is unknown and sustainability of response after discontinuation of treatment has still to be fully established. Development of resistance to entecavir therapy in nucleoside-naïve patients has not been shown but resistance in patients who already carry important lamivudine mutations has led to virologic rebound.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis covering two sub-indications for entecavir. The first was an evaluation of entecavir vs lamivudine for the first line treatment of chronic HBV in nucleoside-naïve HBeAg positive and negative patients. The second analysis related to the second line use of entecavir vs lamivudine or adefovir in nucleoside-naïve patients who become resistant to lamivudine.

For the first evaluation, entecavir vs lamvudine trial data were used to separately assess cost-effectiveness for a cohort of HBeAg positive and HBeAg negative patients aged 35 years. Health outcomes were number of liver disease complications – compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (HCC) over a 10 year time horizon. These outcomes were estimated from an association between a surrogate secondary endpoint in the 48 week clinical trials, HBV viral load, and risk of medical complications, with this association derived from a published epidemiological study in untreated chronic hepatitis B patients (REVEAL study). This seems reasonable, although the results are sensitive to the relative risk of complications estimated from this study. Complication mortality estimates and costs were from published sources and a recent NICE technology appraisal of treatments for chronic hepatitis B, respectively, and utility data for the complications was derived from a study sponsored by the manufacturer in both members of the public and chronic hepatitis B patients. The base case results were an estimated incremental cost per QALY of £12,000 and £15,000 for HBeAg positive and patients and HBeAg negative patients, respectively.

An important driver of cost and outcomes in the model was the level of resistance to lamivudine.

The model assumed treatment was continuous for 10 years and the relative outcomes seen in the 48 week clinical trials would continue in a stable fashion for this time period. There seems to be considerable uncertainty concerning the duration of treatment in clinical practice, and a limitation of the analysis is that it did not explore scenarios of different (i.e. shorter) durations of treatment.

Using the same decision model for the analysis of second line use of entecavir in lamivudine-resistant patients, the comparators are continuation with lamivudine or adefovir. The base case cost per QALY saved was estimated at £9,000 and £17,000 respectively.

*Other data were also assessed but remain commercially confidential.**

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The estimated budget impact of introducing entecavir is £20k in 2006 (for 4 patients treated), rising to £150k by 2011 for 33 patients treated. The greater number treated is a combination of increasing market share and growth in incidence of chronic hepatitis B.

Guidelines and protocols

Treatment guidelines for chronic hepatitis B are published by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. The European guidelines recommend interferon as first choice in HBeAg positive and negative patients if there is no contra-indication to treatment and then either lamivudine or adefovir.

The National Institute of Clinical Excellence (NICE) guideline number 96; "Hepatitis B - (chronic) adefovir dipivoxil and pegylated interferon" was published in February 2006.

Additional information

In March 2005 after consideration of a full resubmission the Scottish Medicines Consortium recommended that: Adefovir dipivoxil (Hepsera®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis B in adults with either 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, or decompensated liver disease. Its use is restricted to patients who demonstrate lamivudine resistance.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 8 September 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

The undernoted references were supplied with the submission.

Chang T.-T., Gish R. G., de Man R., Gadano A., Sollano J., Chao Y.-C., Lok A. S., Han K.-H., Goodman Z., Zhu J., Cross A., DeHertogh D., Wilber R., Colonno R., Apelian D., the BEHoLD AI463022 Study Group. A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis. BN Engl J Med 2006; 354:1001-1010, Mar 9, 2006.

Lai C.-L., Shouval D., Lok A. S., Chang T.-T., Cheinquer H., Goodman Z., DeHertogh D., Wilber R., Zink R. C., Cross A., Colonno R., Fernandes L., the BEHoLD AI463027 Study Group. Entecavir versus Lamivudine for Patients with HBeAg-Negative Chronic Hepatitis B. N Engl J Med 2006; 354:1011-1020, Mar 9, 2006