Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Angela Timoney FRPharmS

entecavir, 0.5mg and 1mg film-coated tablets and 0.05 mg/mL oral solution, Baraclude® SMC No. (747/11)

Bristol-Myers Squibb Pharmaceuticals Ltd

09 December 2011

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

entecavir (Baraclude®) is not recommended for use within NHS Scotland.

Indication under review: treatment of chronic hepatitis B virus (HBV) infection in adults with decompensated liver disease.

Entecavir demonstrated a superior virological response in adults with chronic HBV and decompensated liver disease compared with another nucleoside/nucleotide analogue. However there is no comparative evidence versus the relevant comparator.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 16 January 2012

Indication

Entecavir treatment for chronic HBV infection in adults with decompensated liver disease.

Dosing Information

The recommended dose for adults with decompensated liver disease is 1mg once daily, which must be taken on an empty stomach (more than 2 hours before or more than 2 hours after a meal). In patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.

Therapy should be initiated by a physician experienced in the management of chronic hepatitis B infection.

Product availability date

12 May 2011

Summary of evidence on comparative efficacy

Entecavir is a guanosine nucleoside analogue with activity against Hepatitis B Virus (HBV) polymerase. Entecavir has previously been accepted for use by SMC for the treatment of chronic HBV infection in adults with compensated liver disease, and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. This submission relates to a licence extension in chronic HBV to include patients with decompensated disease. These patients have significant liver-related morbidity and mortality, due to development of progressive liver failure and hepatocellular carcinoma (HCC).

The pivotal phase III study[1] compared entecavir with adefovir in patients aged ≥16 years with chronic HBV, (HBV DNA > 10^5 copies/mL), and decompensated liver disease, defined by a Child-Turcotte-Pugh (CTP) Score of ≥7, who had detectable hepatitis B surface antigen (HBsAG) for > 6months. Patients had positive or negative hepatitis B "e" antigen (HBeAg) and could have been pre or post liver transplant at baseline. They may have been nucleoside-naive or previously treated with lamivudine or with interferon-α (IFN-α), immunomodulators or other drugs with anti-HBV activity. Prior treatment with entecavir, adefovir or tenofovir was an exclusion criterion.

The study population was 74% male, and mainly Asian (54%) or white (33%) with a mean age of 52 years. The mean baseline HBV DNA level was 7.83 $\log_{10}$ copies/mL, 35% of patients were lamivudine resistant and 54% were HBeAg-positive. The mean model for end stage liver disease (MELD) score was 16.23 and CTP score was 8.59.

Patients were randomised in a 1:1 ratio to receive entecavir 1mg once daily or adefovir 10mg once daily for up to 96 weeks from the date the last randomised patient received their first dose of the study drug. All patients were followed for 5 years after their first dose of study drug for clinical outcomes. Published results are available for the 48 week analysis.

The primary efficacy endpoint was the mean change in serum HBV DNA level, from baseline, determined by Roche Amplicor® polymerase chain reaction (PCR) assay (log_{10} copies/mL) at week 24. The primary analysis showed a greater reduction in HBV DNA at week 24 for the entecavir group compared with the adefovir group (treatment difference -1.74 [95% CI -2.30to -1.18]; p<0.0001). This was supported by a sensitivity analysis to account for potentially confounding variables related to the patient (age, sex), virus (HBeAg status, genotype), or disease status (CTP score).

Mean change in serum HBV DNA level, from baseline, was greater for entecavir versus adefovir at all time points assessed to week 48. A higher proportion of patients in the entecavir versus adefovir group achieved HBV DNA <300 copies/mL at week 24 (49% versus 16%) and week 48 (57% versus 20%). The proportion of patients with serum ALT normalisation was significantly greater for entecavir compared with adefovir at weeks 24 and 48. Although adefovir produced higher rates than entecavir of HBeAg loss and seroconversion at week 24, these were comparable by week 48. HBsAg loss was demonstrated in five entecavir patients (one HBeAg-positive and four HBeAg-negative at baseline) and in no adefovir patients by week 48. Improvements from baseline in hepatic function, CTP and Model for End-stage Liver Disease (MELD) scores were comparable between treatment groups.

By week 48, five entecavir and 32 adefovir patients met criteria for resistance testing but no patients showed resistance in either group.

Efficacy Endpoints through week 48 – Treated patients (as randomised) – Study A1463048

	WEEK 24		WEEK 48	
Parameter	Entecavir 1mg (n=100)	Adefovir 10mg (n=91)	Entecavir 1mg (n=100)	Adefovir 10mg (n=91)
Mean change in serum HBV DNA level from baseline (log_{10}copies/mL) (non-completer = missing analysis)	-4.48	-3.40	-4.66	-3.90
Treatment difference (95% confidence interval [CI])	33% (20.2 to 45.2) p<0.0001		38% (24.8 to 50.3) p<0.0001	
HBV DNA Proportion undetectable (<300 copies/mL)	49%	16%	57%	20%
Treatment difference (95% CI)	-1.74 (-2.30 to -1.18) p<0.0001			
ALT normalisation (<1.0 x upper limit of normal [ULN]) in patients with abnormal baseline values	46/78 (59%)	28/71 (39%)	49/78 (63%)	33/71 (46%)
Treatment difference (95% CI)	19% (3.7 to 34.6) p=0.0193		16% (0.9 to 32.0) p=0.0425	
HBeAG loss	0/54 (0%)	7/51 (14%)	6/54 (11%)	9/51 (18%)
HBeAg seroconversion	0/54 (0%)	6/51 (12%)	3/54 (6%)	5/51 (10%)
HBsAg Loss	1/100 (1%)	0/91 (0%)	5/100 (5%)	0/91 (0%)

Summary of evidence on comparative safety

A safety analysis of the pivotal study found that the rates of adverse events (AEs), grade 3 to 4 AEs, serious AEs (SAEs) and discontinuation rates due to AEs were comparable between treatment groups. The most commonly reported AEs were hepatic failure and secondary complications of decompensated cirrhosis. SAEs were generally liver-related. The incidence of HCC was 12% in the entecavir arm and 20% in the adefovir arm. At the time of HCC diagnosis, 67% (8/12) of the entecavir-treated patients compared with 22% (4/18) of the adefovir-treated patients had HBV DNA <300 copies/mL. The mortality rate was numerically lower in the entecavir arm compared to the adefovir arm (23% [n=23] versus 33% [n=29]). [1]

A double-blind, randomised phase II study was also presented by the submitting company. [2] In the phase II safety study including entecavir and tenofovir previously described, the incidence of AEs, grade 3 to 4 AEs and SAEs related to study drug were low and similar across treatment groups.

Summary of clinical effectiveness issues

The 24 and 48 week data from the pivotal study demonstrated that entecavir has superior virological efficacy compared to adefovir in a decompensated population with mixed baseline characteristics as regards HBeAg positivity and lamivudine resistance. Within the initial 48 weeks of this study there was no clear definite advantage in terms of hepatic function improvement.

Entecavir should not be used as monotherapy to treat patients with lamivudine resistance in addition to decompensated liver disease. Approximately one third of patients in the pivotal study population were resistant to lamivudine and therefore did not correspond to the indication under review.

A key weakness in the submission is that entecavir has not been compared with the relevant comparator, tenofovir. Clinical experts consulted by SMC have advised that tenofovir has been the treatment of choice in patients with decompensated liver disease for some time.

Current guidance from the European Association for the study of the liver [2009] and the American Association for the Study of Liver Diseases [2009] recommend tenofovir or entecavir as first-line drugs for hepatitis B, due to their anti-viral potency and high genetic barrier to resistance profile, despite at the time of development there being limited safety data in patients with decompensated disease. In addition, the European Medicines Agency variation assessment report for entecavir states that tenofovir and entecavir are now widely acknowledged to be the gold standards for the treatment of patients with decompensated liver disease.

Summary of comparative health economic evidence

The submitting company presented a cost-effectiveness analysis comparing entecavir to adefovir in decompensated hepatitis B. A Markov model was used with four health states: decompensated disease, hepatocellular cancer, liver transplant, and dead. The time horizon used was 3 years on the basis that patients had limited survival.

Clinical data were taken from the main clinical trial and supplemented with data from the natural history model of hepatitis B constructed by the National Institute for Health and Clinical Excellence (NICE) in 2006. Trial results in terms of overall survival and cancer-free survival were extrapolated using parametric techniques and it was determined that sequential Weibull curves offered the best fit.

Resource use and costs were based on the NICE health technology assessment (HTA) model, suitably updated to current prices. The drug acquisition cost of entecavir assumes use of the film-coated tablets only. The submitting company reviewed the research literature and did not identify a set of consistent utility values to use in the model so the 'added cost per QALY gained' was not calculated; this was further justified on the grounds that survival was likely to be the most important thing to patients. The company noticed the evidence suggested adefovir had more renal toxicity and they therefore claimed not using QALYs was conservative.

The added cost of entecavir over adefovir over 3 years was £2,392, and the survival gain was 0.07 years (just over 25 days). The gain in cancer free survival was 0.09 years (slightly less than 33 days). The cost per life-year (LY) saved was £35,079. The cost per cancer-free survival year was £27,540.

One-way sensitivity analysis was performed. The most important factors identified were:

- Time horizon – over 5 years the cost per LY was £29k;
- Annual cost of decompensated cirrhosis – when these were increased by 25% the cost per LY rose to £38k and when they were reduced by 25% it fell to £32k.

The company presented two cost per QALY estimates of £43k and £102k within their sensitivity analysis but these carried several caveats.

In terms of limitations of the analysis, the following were noted:

- A key issue was that adefovir is not standard of care for these patients in Scotland and hence is not the relevant comparator;

- The time horizon at 3 years was too short to capture all the important costs and benefits;

- The basis for the extrapolation chosen was not presented;

- Benefits were measured in life-years; the justification was that consistent utility values were not available. There was a concern that the cost per life-year at £35k may translate into an even higher cost per QALY since any adjustment to the added survival for quality of life

being valued at less than 1 will decrease the denominator of the cost-effectiveness ratio (assuming entecavir has no quality of life benefit over adefovir). However, the NICE HTA model for hepatitis B, which the company used extensively in the submission, included a set of utility values which could however have been incorporated to give cost per QALYs. The company did not use these estimates but did provide some additional sensitivity analysis to show cost per QALY estimates using an alternative methodology. The results indicated a cost per QALY ratio of between £11,000 and £29,500 compared to adevofir.

Given these limitations, the economic case was not demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Association for the Study of the Liver (EASL) published "EASL Clinical Practice Guidelines: management of chronic hepatitis B" in 2009. The guidelines recommend that patients with decompensated liver disease should be treated in specialised liver units due to the complexity of anti-viral therapy and the potential for requiring liver transplantation. To prevent recurrent reactivation, treatment is indicated even if the HBV DNA level is low. The guideline recommends that either entecavir or tenofovir should be used due to their potency and good resistance profiles, despite the small amount of data for the safety in patients with decompensated disease. Clinical improvement may occur over three to six months, but some patients with advanced hepatic disease with a high Child-Pugh or MELD score may not benefit and require transplantation. In this situation treatment with a nucleoside/nucleotide analogue reduces the risk of HBV recurrence in the graft. The guidelines also note that adefovir is more expensive than tenofovir, is less efficacious, and engenders higher rates of resistance

The American Association for the Study of Liver Diseases updated their practice guidelines, "Chronic hepatitis B" in 2009. This guideline recommends that patients with decompensated cirrhosis should be promptly initiated with a nucleoside/nucleotide analogue, aimed at delivering a rapid suppression of HBV with a low-risk of resistance. Recommended treatment regimens are; lamivudine or telbivudine in combination with adefovir or tenofovir; or entecavir or tenofovir monotherapy (although safety and efficacy in patients with decompensated cirrhosis are lacking).

Both guidelines predate the licensing and publication of the key study of entecavir for the treatment of chronic hepatitis B in decompensated liver disease.

Additional information: comparators

Entecavir, adefovir, and lamivudine (in combination with a second agent that does not have cross-resistance to lamivudine) are licensed for the treatment of chronic hepatitis B virus infection in patients with decompensated liver disease. Lamivudine has not been reviewed by SMC for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Entecavir*	**1mg orally once daily**	**4,408**
Adefovir	10mg orally once daily	3,600
Tenofovir disoproxil (as fumarate)	245mg orally once daily with food	2,918
Lamivudine**	100mg orally once daily	1,015

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26 September 2011.

* Costs refer to entecavir oral tablets. Entecavir solution (50 micrograms/ml) is also available but costs more than three times as much as the tablets.

**In patients with decompensated liver disease, lamivudine should always be used in combination with a second agent without cross-resistance to lamivudine (e.g. adefovir, tenofovir). The cost per year quoted is for the lamivudine component only of any potential combination.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 28 patients. Based on an estimated uptake of 15% in year 1 and 26% in year 5, the impact on the medicines budget was estimated at £18k in year 1 and £35k in year 5. The net medicines budget impact was estimated at £4k and £8k.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Liaw YF, Raptopoulou-Gigi M, Cheinquer H et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: A randomised, open-label study. Hepatology (2011); 54: 91-100.

2. Liaw YF, Sheen IS, Lee CM et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology (2011); 53: 62-72

3. European Medicines Agency: CHMP variation Assessment Report for Baraclude (entecavir 2011. EMEA/H/C000623/II/0033 http://www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 11 November 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.