PUBLIC SUMMARY DOCUMENT

Product: Entecavir, tablets, 500 microgram and 1 mg, Baraclude®

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) listing for the treatment of chronic hepatitis B in adults 16 years and older with evidence of active liver inflammation. Listing for treatment of naïve patients was sought for the 500 microgram tablet, and for the 1 mg tablet, listing for patients who have failed lamivudine therapy.

2. Background

The PBAC had not previously considered an application for entecavir tablets.

3. Registration Status

Entecavir 500 microgram and 1 mg tablets were registered by the TGA on 12 April 2006 for the treatment of chronic hepatitis B virus infection in adults 16 years or older with evidence of active liver inflammation. This indication is based on histologic, virologic, biochemical and serological responses after 48 weeks of treatment in nucleoside-treatment naive and lamivudine-resistent adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease. Safety and efficacy have not currently been demonstrated for treatment periods longer than 48 weeks.

4. Listing requested and PBAC's View

Entecavir tablet 500 microgram
Section 100 (Highly Specialised Drug) Private hospital authority required
Patients with chronic hepatitis B who satisfy all of the following criteria:
(i) histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy);
(ii) abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive);
(iii) female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception.
Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.

Entecavir tablet 1 mg
Section 100 (Highly Specialised Drug) private hospital authority required

Patients with chronic hepatitis B who have failed lamivudine therapy and who satisfy all of the following criteria:
(i) abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive);
(ii) female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception.
Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.

The PBAC noted there is the potential for leakage outside the requested restriction as clinicians may initiate entecavir 1 mg in nucleos(t)ide-naïve patients in order to achieve maximal viral load suppression, given problems with the resistance development of antiviral therapies for chronic hepatitis B.

5. Clinical place for the proposed therapy

Entecavir 500 microgram tablet will provide an alternative first-line therapy to lamivudine, interferon-alfa and peginterferon-alfa in chronic hepatitis B.

Entecavir tablet 1 mg will provide those patients who have developed resistance to lamivudine therapy with an additional second-line therapy to adefovir dipivoxil, and a third-line therapy.

6. Comparator

The submission nominated (a) lamivudine as the main comparator in the first-line setting (nucleoside naïve patients), and (b) adefovir dipivoxil as the main comparator in the second-line (lamivudine resistant patients) setting,

7. Clinical Trials

For nucleos(t)ide-naïve patients - one randomised key trial comparing entecavir 0.5 mg with lamivudine 100 mg in HBeAg-positive patients over 48 weeks; one randomised key trial comparing entecavir 500 microgram with lamivudine 100 mg in HBeAg-negative/ hepatitis B virus (HBV) DNA-positive patients over 48 weeks; and one randomised supportive trial comparing entecavir 500 microgram with lamivudine 100mg in HBeAg-positive and HBeAg-negative/ HBV DNA-positive patients over 22 weeks.

For lamivudine resistant patients - an indirect comparison of one randomised trial of entecavir 1 mg and one randomised trial of adefovir 10 mg, with lamivudine 100mg as the common reference for HBeAg-positive patients over 48 weeks and one supportive randomised trial comparing entecavir 1 mg with lamivudine 100mg in HBeAg-positive and HBeAg-negative/ HBV DNA-positive patients for 24 weeks.

The studies published at the time of the submission are as follows:

Trial/First author	Publication title	Publication citation
AI463-027/ Shouval D.	Entecavir demonstrates superior histologic and virologic efficacy over lamivudine in nucleos(t)ide-naïve HBeAg(-) CHB : results of phase III trial ETV-027	Hepatology 2004, 40;4(Suppl 1): 728A**.**
AI463-022/ Sollano J.	Entecavir is well-tolerated for treatment of CHB: phase III safety analysis in nucleos(t)ide naïve and lamivudine-resistant patients.	Hepatology 2004, 40;4(Suppl 1): 665A.
AI463-026/ Sherman M.	Entecavir is superior to continued lamivudine-resistant, HBeAg(+) CHB : results of phase III study ETV-027.	Hepatology 2004, 40;4(Suppl 1): 664A**.**
Sollano J.	Entecavir is well-tolerated for treatment of CHB: phase III safety analysis in nucleos(t)ide naïve and lamivudine-resistant patients. Hepatology 2004, 40;4(Suppl 1) :665A	Hepatology 2004, 40;4(Suppl 1): 665A.
Chang T.	Sustained viral load and ALT reduction following 48 weeks of entecavir treatment in subjects with CHB who have failed lamivudine	Hepatology 2002, 36; 4: 300A.
Peters MG.	Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant CHB.	Gastroenterology. 2004; 126:91-101.

8. Results of Trials

Nucleos(t)ide-Naïve Patients

The results of the comparative randomised trial at Week 48, Chang et al (2006)[a], for HBeAg-positive disease were statistically significant differences in the proportion of subjects with histological improvement (primary endpoint) and the proportion of subjects with HBV DNA <400 copies/mL for entecavir 500 microgram versus lamivudine 100 mg. There were statistically significant advantages for entecavir 500 microgram compared with lamivudine for all secondary outcomes except improvement in hepatic fibrosis, improvement in hepatic cytoplasmic HBcAg, improvement in hepatic HBsAg, loss of HBeAg, HBeAg seroconversion, complete virologic response and complete virologic response and ALT normalisation. The 95% CI for the combined endpoint (complete virologic response and ALT normalisation), considered to be the most appropriate surrogate outcome appears to include clinically relevant effects but also includes no difference.

The results of the comparative randomised trial at Week 48, Lai et al (2006)[a], for HBeAg-

[a] a report was published in the interim period between preparation of the submission and the start of the evaluation.

negative/ HBV DNA-positive disease were a statistically significant difference in the proportion of subjects with histological improvement (primary endpoint) and the proportion of subjects with HBV DNA <400 copies/mL for entecavir 500 microgram versus lamivudine 100 mg (70.3% versus 60.6%, and 91.4% versus 73.5% respectively). The 95% CI for the combined endpoint (serum HBV DNA < 0.7 MEq/mL and ALT < 1.25 x ULN), considered to be the most appropriate surrogate outcome appears to include clinically relevant effects but also includes no difference.

Lamivudine Resistant Patients

For the results of the indirect comparison in HBeAg-positive disease, all comparable endpoints between the two randomised trials forming the basis of the indirect comparison were secondary outcomes. The 95% CI for the absolute risk difference between entecavir 1 mg and lamivudine, and lamivudine and adefovir overlapped, supporting the validity of the indirect comparison. However, Peters et al (2004) had relatively small sample sizes in each treatment arm and therefore confidence intervals were wide.

Both entecavir 1 mg and adefovir 10 mg resulted in a statistically significant increase in key outcomes compared to lamivudine 100 mg

For nucleos(t)ide-naïve patients, the frequency of reported adverse events was similar between entecavir 500 microgram and lamivudine 100 mg in HBeAg-positive (86.4%, 306/354 versus 83.7%, 297/355 respectively) and HBeAg-negative/ HBV DNA-positive chronic hepatitis B patients (75.7%, 246/325 versus 79.2%, 248/313 respectively). One malignant hepatic neoplasm in the lamivudine arm of Lai et al (2006) was considered to be possibly related to study medication. The submission did not justify why the reported benign and malignant neoplasms in the key trials were considered unrelated to study therapy.

For lamivudine resistant patients, the comparison of entecavir 1 mg and adefovir 10 mg was indirect and therefore it was difficult to interpret any differences in the frequency and type of reported adverse events. The PES Commentary advised of concern due to the lack of long-term follow-up data regarding the development of resistance to entecavir.

9. Clinical Claim

For nucleos(t)ide-naïve patients, the submission claimed that entecavir 500 microgram was significantly more effective than lamivudine 100 mg and had similar or less toxicity. For lamivudine resistant patients, the submission claimed that entecavir 1 mg was no worse than adefovir 10 mg in terms of effectiveness and toxicity.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

For nucleos(t)ide-naïve patients, a preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was considered valid. The resources included were drug costs only. The outcomes were histological improvement, undetectable HBV DNA (<400 copies/mL) and ALT normalisation. Histological improvement was the primary outcome reported in the key trials and formed the basis of the preliminary economic evaluation.

For lamivudine resistant patients, the choice of the cost-minimisation approach for these patients was considered valid.

The trial-based incremental cost per extra patient achieving histological improvement at 48 weeks for both nucleos(t)ide-naïve patients - HBeAg-positive patients and HBeAg-negative/ HBV DNA-positive patients were between $15,000 and $45,000. The trial-based ICERs incorporated drug costs only.

The modelled economic evaluation for nucleos(t)ide-naïve patients presented two models, one for HBeAg-positive patients and one for HBeAg-negative patients. The structure of the two models was the same, with the exception that the model for HBeAg-negative patients did not include seroconversion rates and therefore HBV DNA levels in this model were extrapolated on the basis of respective treatment effects and resistance rates. The resources included were drug costs, and non-drug and long-term medical costs associated with compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma.

The base case modelled incremental discounted cost per extra discounted life year gained was for both nucleos(t)ide-naïve patients - HBeAg-positive patients and for HBeAg-negative/ HBV DNA-positive patients between $15,000 and $45,000. The base case modelled incremental discounted cost per extra discounted QALY for both groups was higher, but within the same range.

11. Estimated PBS Usage and Financial Implications

The likely number patients taking the 500 microgram or 1 mg tablets was < 10,000 in Year 4. The financial cost per year to the PBS for nucleos(t)ide-naïve patients was < $10 million in Year 4 and for lamivudine resistant patients it was cost neutral in Year 4**.** The overall market for chronic hepatitis B was not expected to grow or to grow more rapidly as a result of listing entecavir.

12. Recommendation and Reasons

Entacavir 500 micrograms

The PBAC recommended the listing of entecavir 500 microgram tablet for the treatment of chronic hepatitis B infection in nucleos(t)ide naïve patients on the basis of acceptable cost-effectiveness compared with lamivudine 100 mg.

The PBAC recalled that previously it had considered the surrogate outcomes of viral load (HBV DNA), seroconversion of HBeAg and histological improvement more persuasive

than serum ALT improvements in assessing efficacy. The PBAC noted that entecavir is more effective than lamivudine on some surrogates (statistically significant differences at 48 weeks in the proportion of patients with histological improvement, and the proportion of patients with HBV DNA <400 copies/mL) and no worse than lamivudine on the composite endpoint. The PBAC accepted the biological plausibility of the relevance of reduction in viral load in the treatment of chronic hepatitis B.

The PBAC noted there is the potential for leakage outside the requested restriction as clinicians may initiate entecavir 1 mg in nucleos(t)ide-naïve patients in order to achieve maximal viral load suppression, given problems with the resistance development of antiviral therapies for chronic hepatitis B. The PBAC requested that usage of entecavir be monitored by the Department.

The PBAC also noted that, in theory, the development of resistance to antiviral agents may be reduced by the use of combination treatment with different antiviral agents. However no evidence on the clinical- or cost- effectiveness of this approach had been presented. The Committee therefore recommended that the use of PBS-subsidised entecavir in nucleos(t)ide naïve patients be restricted to monotherapy.

The PBAC noted the long-term risk of malignancy associated with entecavir and that the ADEC had recommended that the sponsor develop a risk management plan. The PBAC also noted the potential for the development of resistance. The Committee requested the sponsor provide an update on resistance rates and pharmacovigilance reports in 12 months.

The Committee further advised the Pharmaceutical Benefits Pricing Authority that the Authority may wish to consider entering into a risk sharing arrangement with the sponsor to take into account the potential for usage outside of the restriction and for the development of resistance.

Recommendation

Entecavir, tablet, 500 microgram
Restriction: Private hospital authority required (Highly Specialised Drug)
Patients aged 16 years or older with chronic hepatitis B who satisfy all of the following criteria:
(i) histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy);
(ii) abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive);
(iii) female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception.
Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.
NOTE:

PBS-subsidised entecavir must be used as monotherapy.
Pack size: 30

Recommendation and Reasons

Entecavir 1 mg

The PBAC recommended the listing of entecavir 1 mg tablet for the treatment of chronic hepatitis B infection in lamivudine resistant patients on a cost minimisation basis compared to adefovir with entecavir 1 mg for 48 weeks considered of equivalent effectiveness to adefovir 10 mg for 48 weeks.

The PBAC noted that in the indirect comparison of two randomised trials via lamivudine which formed the evidentiary basis for the submission, the comparable endpoints were all secondary outcomes. The point estimate was favouring entecavir and the 95% CI for the absolute risk difference between entecavir 1 mg and lamivudine 100 mg, and lamivudine and adefovir 10 mg overlapped, supporting the validity of the indirect comparison. Both entecavir 1 mg and adefovir 10 mg resulted in a statistically significant increase in key outcomes compared to lamivudine 100 mg.

The PBAC noted the long-term risk of malignancy associated with entecavir and that the ADEC had recommended that the sponsor develop a risk management plan. The PBAC also noted the potential for the development of resistance. The Committee requested the sponsor provide an update on resistance rates and pharmacovigilance reports in 12 months.

The PBAC also noted is the potential for leakage outside the requested restriction as clinicians may initiate entecavir 1 mg in nucleos(t)ide-naïve patients in order to achieve maximal viral load suppression, given problems with the resistance development of antiviral therapies for chronic hepatitis B. The PBAC requested that usage of entecavir be monitored by the Department.

The Committee advised the PBPA that the authority may wish to consider entering into a risk sharing arrangement with the sponsor to take into account the potential for usage outside of the restriction and for the development of resistance.

Recommendation

Entecavir, tablet, 1 mg
Restriction: Private hospital authority required (Highly Specialised Drug)
Patients aged 16 years or older with chronic hepatitis B who have failed lamivudine therapy and who satisfy all of the following criteria:
(i) Repeatedly elevated (> 1.2 ULN) serum ALT levels while on concurrent antihepadnaviral therapy of ≥ 6 months duration in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or serum HBV DNA positive);
(ii) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception.

Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.
NOTE:
Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.
NOTE:
PBS-subsidised entecavir must be used as monotherapy.
Pack size: 30

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment