PUBLIC SUMMARY DOCUMENT

Product: Telbivudine, tablet, 600 mg, Sebivo®

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a section 100 (Highly Specialised Drug) listing for telbivudine for the treatment of patients with chronic hepatitis B who satisfy certain criteria.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Telbivudine was registered by the TGA on 23 February 2007 for the treatment of HBe-Ag-positive and HBeAg-negative chronic hepatitis B in patients who have compensated liver disease, evidence of viral replication and active liver inflammation and who are nucleoside analogue naïve.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug) Private hospital authority required

Patients aged 16 or older with chronic hepatitis B who satisfy all of the following criteria:
(1) Histological evidence of chronic hepatitis on liver biopsy (except in patients with coagulation disorders considered severe enough to prevent liver biopsy);
(2) Abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or HBV DNA positive);
(3) 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 telbivudine must be used as monotherapy.

The PBAC considered that any restriction should stipulate use in nucleoside naïve patients only as in the TGA indication does not include nucleoside-experienced patients.

5. Clinical Place for the Proposed Therapy

Telbivudine 600 mg will provide an alternative first-line therapy to lamivudine 100 mg and entecavir 0.5 mg in chronic hepatitis B (CHB).

6. Comparator

The submission nominated lamivudine as the main comparator and entecavir 0.5 mg as the secondary comparator.

The PBAC considered this was appropriate.

7. Clinical Trials

Direct comparison

The submission presented a direct comparison of telbivudine versus lamivudine, using the following trials:

- one direct randomised comparative trial comparing telbivudine 600 mg and lamivudine 100 mg in HBeAg-positive and HBeAg-negative patients with CHB and compensated liver disease at 52 and 104 weeks (trial NV-02B-007)
- one unweighted pooled analysis of data from the subgroup of Chinese patients in trial NV-02B-007 with all patients in trial NV-02B-015 (all enrolled patients were Chinese), in HBeAg-positive and HBeAg-negative patients with CHB and compensated liver disease.
- one direct randomised comparative trial comparing telbivudine 600 mg and lamivudine 100 mg in HBeAg-positive and HBeAg-negative patients with CHB and compensated liver disease who are currently receiving lamivudine treatment, over 52 weeks (trial NV-02B-019)

These trials had been published at the time of submission, as follows:

Trial ID	Protocol title / Publication title	Publication citation
NV-02B-007[a] Lai CL et al, 2005	Telbivudine (LDT) vs lamivudine for chronic hepatitis B: First-year results from the International phase III globe tribal.	Hepatology 2005; 748A
NV-02B-007[a] Lai CL et al, 2005	Maximal early HBV suppression is predictive of optimal virologic and clinical efficacy in nucleoside-treated hepatitis B patients: Scientific observations from a large multinational trial. (The globe study).	Hepatology 2005; 232A
NV-02B-019[a] Gane E et al, 2006	A randomised trial of telbivudine (LdT) versus lamivudine in lamivudine experienced patients – week 24 primary analysis.	AASLD abstract 2006. aasld2006.abstractcentral.com

[a] ongoing trial

Indirect comparison

The submission also presented an indirect comparison of telbivudine versus entecavir via the common reference of lamivudine, in the form of:

- one randomised comparative trial of telbivudine 600 mg versus lamivudine 100 mg in HBeAg-positive and HBeAg-negative CHB patients with compensated liver disease at 52 and 104 weeks (trial NV-02B-007)
- two randomised comparative trials of entecavir 0.5 mg versus lamivudine 100 mg in HBeAg-positive and HBeAg-negative CHB patients with compensated liver disease, each of 52 weeks duration (Chang et al, 2006 and Lai et al, 2006)

These trials had been published at the time of submission, as follows:

Trial ID	Protocol title/ Publication title	Publication citation
NV-02B-007[a] Lai CL et al, 2005	Telbivudine (LDT) vs lamivudine for chronic hepatitis B: First-year results from the International phase III globe tribal.	Hepatology 2005; 748A
NV-02B-007[a] Lai CL et al, 2005	Maximal early HBV suppression is predictive of optimal virologic and clinical efficacy in nucleoside-treated hepatitis B patients: Scientific observations from a large multinational trial. (The globe study).	Hepatology 2005; 232A
Chang et al (2006)	A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B	NEJM 2006; 354(10): 1001-10.
Lai et al (2006)	Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B.	NEJM 2006; 354(10): 1011-1020.

[a] ongoing trial

8. Results of Trials

Effectiveness

The primary outcome of trial NV-02B-007 was therapeutic response, defined as attainment of serum HBV DNA <5 $\log_{10}$copies/mL, at Week 52 and either HBeAg loss at Week 52 or ALT normalisation at Week 52.

Direct comparison

The results for the key trial NV-02B-007 showed that there were statistically significant differences in the proportion of HBeAg-positive subjects with therapeutic response at Week 52 (primary endpoint) and Weeks 76 and 104 for telbivudine 600mg versus lamivudine 100mg. There were also statistically significant advantages for telbivudine treatment compared with lamivudine treatment for some secondary outcomes.

These results showed that there was no statistically significant difference in the proportion of HBeAg-negative subjects with therapeutic response at Week 52 (primary endpoint) and Week 76 for telbivudine 600mg versus lamivudine 100mg. However, there was a statistically significant advantage for telbivudine compared with lamivudine for therapeutic response at Week 104. There were also statistically significant advantages for telbivudine compared with lamivudine for some secondary outcomes.

Indirect comparison

The relative risk results of comparable outcomes from trial NV-02B-007 and Chang et al (2006) showed that both telbivudine and entecavir resulted in a statistically significant difference in histological improvement and undetectable HBV DNA levels compared to lamivudine in HBeAg-positive patients. However, only entecavir resulted in a statistically significant difference in ALT normalisation compared to lamivudine in these patients.

The results from trial NV-02B-007 and Lai et al (2006), also showed that both telbivudine and entecavir resulted in a statistically significant difference in undetectable HBV DNA levels compared to lamivudine in HBeAg-negative patients. However, only entecavir resulted in a statistically significant difference in histological improvement and ALT normalisation compared to lamivudine in this patient group.

For PBAC's view on these results, see Recommendation and Reasons.

Virologic rebound

Chang et al (2006) reported virologic rebound in 2% (6/354) of HBeAg-positive entecavir-treated CHB patients versus 18% (63/355) of the lamivudine-treated patients during the first year of treatment. Lai et al (2006) reported virologic rebound in 2% (5/325) of the HBeAg-negative entecavir-treated patients versus 8% (25/313) of the lamivudine-treated patients by week 48. In both these trials, no patients with virologic breakthrough in the entecavir groups had evidence of resistance to entecavir on genotypic analysis at Week 48.

In trial NV-02B-007, 3.4% (15/438) of HBeAg-positive patients and 2.1% (4/192) of HBeAg-negative patients receiving telbivudine, compared to 10.4% (46/442) and 8.5% (16/187) respectively in the lamivudine groups, experienced virologic breakthrough. HBV resistance for patients treated with telbivudine was 3.0% (13/438) and 2.1%, (4/192) for the HBeAg-positive and HBeAg-negative patients respectively, compared to 8.2% (36/422) and 8.5% (16/187) respectively in the lamivudine groups.

The PBAC considered that overall, given the reported one year resistance rates for telbivudine and entecavir in the randomised trials it is extremely difficult to formulate any conclusions regarding the long term comparative resistance rates.

Toxicity

Direct comparison

At least one adverse event (AE) between baseline and Week 104 was reported in 81.0% (551/680) and 77.0% (529/687) of the telbivudine and lamivudine groups respectively in trial NV-02B-007. The proportion of serious AEs and treatment discontinuations were similar for telbivudine and lamivudine treatment. Rates of reported AEs were similar between telbivudine and lamivudine except for increased blood creatinine phosphokinases (84/680, 12.4% versus 51/680, 7.4% respectively).

Indirect comparison

The frequency of reported adverse events was similar between entecavir 0.5 mg and lamivudine 100 mg in HBeAg-positive 86.4% (306/354) versus 83.7% (297/355) respectively and HBeAg-negative CHB 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 majority of reported adverse events were mild to moderate in severity.

9. Clinical Claim

Direct comparison

The submission claimed that telbivudine has significant advantages in effectiveness over lamivudine and has similar or less toxicity.

The PBAC accepted that superiority over lamivudine was demonstrated in HBeAg-positive patients, but there was uncertainty about a similar conclusion for HBeAg-negative patients.

Indirect comparison
The submission described telbivudine as being no worse than entecavir in terms of effectiveness and toxicity.

The PBAC considered there was uncertainty about the efficacy in comparison with entecavir on some secondary outcomes.

10. Economic Analysis

The submission presented preliminary and modelled economic analyses for the comparison of telbivudine and lamivudine and a cost-minimisation analysis for the comparison of telbivudine and entecavir.

As the PBAC did not accept the clinical claim that telbivudine is no worse than entecavir, the cost-minimisation approach was not considered valid.

The submission presented a trial-based economic evaluation for the comparison telbivudine versus lamivudine. The choice of the cost-effectiveness approach was considered valid. The resources included were drug costs only. The outcomes were therapeutic response, histologic response, undetectable HBV DNA (<300 copies/mL) and ALT normalisation.

The submission presented a modelled economic evaluation for the comparison telbivudine versus lamivudine. The choice of the cost-utility approach was considered valid. The model measured lifetime healthcare costs associated with CHB and predicted survival in quality-adjusted life years, for the HBeAg-positive and negative cohorts, and for two different treatment arms, telbivudine and lamivudine. The resources included were drug costs, outpatient visits, pathology and imaging, inpatient hospitalisation and palliative care costs.

In the submission's base case modelled incremental discounted cost/extra discounted quality-adjusted life year, telbivudine was dominant (ie more effective and less costly) in both patient cohorts.

For PBAC's view of this result, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS (excluding co-payments) was estimated by the submission to be < $5 million in Year 5. The PBAC considered this figure may be a likely over-estimate.

12. Recommendation and Reasons

The PBAC noted there were statistically significant differences in the proportion of HBeAg-positive subjects with therapeutic response at Week 52 (primary endpoint) and Weeks 76 and 104 for telbivudine 600 mg versus lamivudine 100 mg in trial NV-02B-007. However the Committee considered it is unlikely that the difference in therapeutic response reported at Week 52 (primary endpoint) is clinically important because the statistical analysis plan implies that a difference of 15% is the minimum clinically important difference (the non-inferiority margin calculated for this outcome was -15%). Clinically important differences were reported at Weeks 76 and 104.

There was a statistically significant advantage for telbivudine treatment compared with lamivudine treatment in the proportion of HBeAg-negative subjects with therapeutic response at Week 104, but there was no statistically significant difference at Weeks 52 (primary

endpoint) and 76, in trial NV-02B-007. The PBAC considered it is unlikely that the difference in therapeutic response reported at Week 104 is clinically important.

The PBAC noted that the Pre-Sub-Committee Response had stated that while therapeutic response in the HBeAg-negative patients may not be considered clinically important at Week 104, there were other pre-specified secondary efficacy outcomes of clinical importance that were superior with telbivudine such as reduction in HBV DNA from baseline and HBV DNA non-detectable. Although the Response argued that these are more relevant outcomes because the primary goal of treatment for CHB, according to current treatment guidelines, is to eliminate or permanently suppress HBV replication, the PBAC considered that the pre-specified primary composite endpoint was the outcome of most interest. Consequently, the PBAC accepted that superiority over lamivudine was demonstrated in HBeAg-positive patients, but there was uncertainty about a similar conclusion for HBeAg-negative patients.

For the indirect comparison with entecavir, there was no statistically significant difference in histological improvement (primary outcome in Chang et al, 2006 and Lai et al, 2006 and the key secondary outcome in trial NV-02B-007) between telbivudine treatment and entecavir treatment for HBeAg-positive and HBeAg-negative CHB patients in the adjusted indirect comparison. Entecavir 0.5mg did appear to have greater efficacy for the following secondary endpoints: (i) HBV DNA undetectable levels in HBeAg-positive CHB patients; and (ii) ALT normalisation in HBeAg-negative CHB patients. Although the Pre-Sub-Committee Response argued that the lower limit of the confidence interval around the relative risk is very close to one and that the statistical advantage of entecavir over telbivudine may not be clinically important, the PBAC considered there was uncertainty about the claim that telbivudine is no worse that entecavir in terms of efficacy and safety.

The PBAC noted a number of issues concerning the modelled economic evaluation against lamivudine which cast doubts on the claim of dominance over lamivudine in the submission. These mainly resulted from the uncertainties surrounding the transition probabilities, their extrapolation in the model, and the regression equation used to determine the relationship between the surrogate treatment results and the development of cirrhosis and hepatocellular carcinoma.

The PBAC rejected the submission because of uncertainty about the cost effectiveness over lamivudine and uncertainty about the efficacy in comparison with entecavir on some secondary outcomes.

Recommendation
Reject

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

Novartis Pharmaceuticals is committed to securing a PBS listing for Sebivo for the treatment of Australian patients with chronic hepatitis B and is working towards a re-submission.