PUBLIC SUMMARY DOCUMENT
Product: Telbivudine, tablet, 600 mg, Sebivo®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The application sought a Section 100 (Highly Specialised Drug) Private hospital authority required listing for patients with chronic hepatitis B who are nucleoside analogue naïve and 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

At the July 2007 meeting, the PBAC rejected a submission for telbivudine, which sought a section 100 (Highly Specialised Drug) listing for the treatment of patients with chronic hepatitis B, based on uncertainty about the cost effectiveness over lamivudine and uncertainty about the claim of similar safety and efficacy in comparison with entecavir.

At the November 2007 meeting the PBAC agreed that testing for hepatitis B could be carried out by serum HBV DNA testing for chronic hepatitis B patients, however it was not certain if funding under Medicare had been finalised at the time of the March 2008 meeting.

3. Registration Status

Telbivudine was registered by the TGA on 5 March 2007 and is indicated 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 Drugs Program)
Private hospital authority required
Patients aged 16 years or older with chronic hepatitis B who are nucleoside analogue naïve and 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.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Telbivudine would provide an alternative first-line oral treatment for chronic hepatitis B (CHB).

6. Comparator

The submission nominated lamivudine and entecavir as the main comparators. These were accepted by the PBAC as appropriate.

7. Clinical Trials

The re-submission provided an update of its search strategy. No additional trials were located by the updated search. The following trials were included in this submission:

- two direct randomised comparative trials comparing telbivudine 600 mg and lamivudine 100 mg in HBeAg-positive and HBeAg-negative patients with CHB and compensated liver disease, over 104 weeks (trial NV-02B-007 and trial NV-02B-015);
- one pooled unweighted analysis of data from the subgroup of Chinese patients in trial NV-02B-007 with data from patients (all Chinese) in trial NV-02B-015; and
- 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).

Details of the trials published at the time of the submission are available in the July 2007 Public Summary Document.

8. Results of Trials

Trial NV-02B-007

The PBAC previously considered 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 600 mg versus lamivudine 100 mg in trial NV-02B-007. However, the Committee considered it was 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.

The PBAC previously considered that 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.

Trial NV-02B-015

There were statistically significant advantages for telbivudine treatment compared with lamivudine treatment for the primary endpoint, mean hepatitis B virus (HBV) reduction from baseline in HBeAg-positive subjects. It appeared that clinically important differences were detected for mean HBV DNA reduction from baseline at Weeks 76 and 104, but not at Weeks 24 and 52 (non-inferiority margin, NIM = 1.0 $\log_{10}$copies/mL). Clinical importance was estimated by applying the NIM reported in the statistical analysis plan of the key trial, NV-

02B-007 (information regarding the NIMs in trial NV-02B-015 were not provided). The 95% CIs appeared to include clinically unimportant differences.

There were statistically significant and clinically important differences in the proportion of HBeAg-positive subjects with a therapeutic response (primary endpoint in the key trial, NV-02B-007) at Weeks 52 and 104 for telbivudine 600 mg versus lamivudine 100 mg in trial NV-02B-015 (NIM = -15%). The 99% CIs appeared to include predominantly clinically important differences.

There was no statistically significant difference in the primary endpoint, mean HBV DNA reduction from baseline in HBeAg-negative subjects between telbivudine 600 mg and lamivudine 100 mg. The HBeAg-negative subgroup was not of sufficient size to detect statistically significant differences in this endpoint (n=20 and 22), however the difference was numerically in favour of telbivudine. It appeared that clinically important differences were detected for mean HBV DNA reduction from baseline at Week 104, but not at Weeks 24, 52 and 76 (NIM = 1.0 $\log_{10}$copies/mL). The 95% CIs appeared to include clinically unimportant differences.

There was a statistically significant and clinically important difference in the proportion of HBeAg-negative subjects with a therapeutic response (primary endpoint in the key trial, NV-02B-007) at Week 52, but not at Week 104, for telbivudine 600 mg versus lamivudine 100mg in trial NV-02B-015, based on the NIMs reported in the statistical analysis plan of the key trial, NV-02B-007. The 99% CI for therapeutic response appeared to include clinically unimportant differences.

The re-submission presented new toxicity data from trial NV-02B-015. There were similar proportions of patients with greater than one adverse event (64.7%, 108/167 versus 60.6%, 100/165, respectively) and treatment discontinuations (1.2% versus 1.8%, respectively) for telbivudine and lamivudine treatment. Rates of reported on-treatment adverse events were similar between telbivudine and lamivudine except for nasopharyngitis (29.3% versus 23.6%, respectively). Although the incidence of adverse events and the proportion of patients with nasopharyngitis were numerically higher in the telbivudine arm versus the lamivudine arm in trial NV-02B-015, overall telbivudine and lamivudine appeared to have similar toxicity.

9. Clinical Claim

The re-submission described telbivudine as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over lamivudine. Based on the supporting data, the PBAC considered this description was reasonable for HBeAg-positive patients but was not reasonable for HBeAg-negative patients.

The data presented continue to support the conclusion that telbivudine may be non-inferior, rather than superior, to lamivudine in HBeAg-negative patients.

The re-submission did not provide additional evidence to address the uncertainty concerning the claim that telbivudine is no worse that entecavir in terms of efficacy and safety. The PBAC considered based on the supporting data, this description was not reasonable.

10. Economic Analysis

An updated modelled (stepped) economic evaluation was presented. 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 number of viral load (VL) levels was reduced from five in the original submission to two (VL<300copies/mL or VL≥300copies/mL) in the re-submission. The model used data from an extended period (two years) of trial NV-02B-007 compared to one year of trial data in the original submission. The model extrapolated an ongoing treatment effect on viral load for a further two years post trial period (occurred for a lifetime in original submission). The base-case economic evaluation was defined using a twenty-year duration, and duration of viral load shifts of four years (two years during the trial and extrapolation for a further two years – with an assumption of continuing treatment effect). All transition probabilities between viral load categories were assumed to equal zero after this period. The model was allowed to continue for a lifetime. The model used six-monthly cycles.

For the base case modelled incremental cost per extra quality-adjusted life year (QALY), telbivudine was claimed to be dominant (i.e. more effective and less costly) in the HBeAg-positive patient cohort. The incremental cost per QALY in the HBeAg-negative cohort was in the range of $15,000 to $45,000.

The PBAC considered there was some uncertainty associated with the economic modelling for the HBeAg-positive cohort including the duration of the model (20 years). However, the PBAC noted that while telbivudine was dominant in the 20 year base case compared to lamivudine, the incremental cost effectiveness ratio (ICER) at 10 years also remained acceptable though somewhat uncertain at between $15,000 and $45,000 per extra QALY gained.

In the HBeAg-negative patient group, the PBAC also noted the ICER for the base case (model duration 20 years) was between $15,000 and $45,000 per extra QALY gained compared with lamivudine, and when the duration of the model was reduced to10 years the ICER increased to greater than $200,000 and was considered unacceptably high.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be less than 5,000 in Year 5, and a net financial cost per year to the PBS of less than $5 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of telbivudine for the treatment of chronic hepatitis B in patients who are nucleoside analogue naïve and who are hepatitis B antigen positive based on a high but acceptable incremental cost effectiveness ratio compared to lamivudine.

The PBAC noted the re-submission had requested listing in the nucleoside naïve population only as suggested by the Committee at the July 2007 meeting, and that it had previously accepted that superiority in efficacy over lamivudine had been demonstrated in HBeAg-positive patients. The PBAC considered that based on the data provided in the submission lamivudine and telbivudine appeared to have similar toxicity.

The PBAC considered there was some uncertainty associated with the economic modelling for the HBeAg-positive cohort including the duration of the model (20 years). However, the PBAC noted that while telbivudine was dominant in the 20 year base case compared to lamivudine, the incremental cost effectiveness ratio at 10 years also remained acceptable though somewhat uncertain at between $15,000 and $45,000 per extra QALY gained.

With respect to the submission's claim that telbivudine is non-inferior in terms of comparative safety and efficacy compared with entecavir, the PBAC considered there was still uncertainty about the efficacy in comparison with entecavir on some secondary outcomes.

With respect to the comparison of telbivudine and lamivudine in HBeAg-negative patients, the re-submission provided additional evidence for HBeAg-negative patients in trial NV-02B-015, but as the sub-group population was small, statistically significant differences in HBV-DNA reduction from baseline were not detected. Overall, the data presented continue to support the conclusion that telbivudine may be non-inferior, rather than superior, to lamivudine in HBeAg-negative patients.

In this patient group the PBAC also noted the ICER for the base case (model duration 20 years) was between $15,000 and $45,000 per extra QALY gained compared with lamivudine, and when the duration of model was reduced to 10 years duration the ICER increased to over $200,000.

Therefore, the PBAC rejected the listing of telbivudine for HBeAg-negative patients based on an unacceptably high and uncertain cost-effectiveness ratio compared to lamivudine.

Recommendation

TELBIVUDINE, tablet, 600 mg.

Restriction: Section 100 (Highly Specialised Drugs Program)
Private hospital authority required
Treatment, as sole PBS-subsidised therapy, in a patient with HBeAg-positive chronic hepatitis B who is nucleoside analogue naïve and satisfies 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) (a) Abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection; or
(b) Elevated HBV DNA levels in conjunction with documented chronic hepatitis B infection; and
(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.

Pack size: 28

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 welcomes the PBAC's decision to recommend telbivudine for the treatment of patients with HBeAg-positive chronic hepatitis B, and will work with the PBAC to secure a recommendation for HBeAg-negative patients.