PUBLIC SUMMARY DOCUMENT

Product: Adefovir Dipivoxil, tablet, 10 mg, Hepsera®

Sponsor: Gilead Sciences Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The resubmission requested an extension of the current Section 100 (Highly Specialised Drug) listing for patients with active chronic hepatitis B to include the treatment in combination with lamivudine of patients with advanced liver disease (evidence of cirrhosis on liver biopsy or a Child Pugh Turcotte score greater than 5) or after a liver transplant.

2. Background

The PBAC recommended listing for the second-line treatment of chronic hepatitis B on the basis of high but acceptable cost-effectiveness compared with on-going 'failed' lamivudine therapy (100 mg daily) at the July 2004 meeting. The Committee noted that there was a clinical need for this drug for patients who had failed therapy with lamivudine. The PBAC concluded that, on the balance of probabilities, adefovir would remain acceptably cost-effective within the relatively small second-line population with the greatest clinical need.

At its July 2006 meeting the PBAC considered a submission to extend the Section 100 (Highly Specialised Drug) listing for patients with active chronic hepatitis B to include the treatment in combination with lamivudine of nucleoside therapy naïve patients with advanced liver disease, and liver transplant patients with a history of hepatitis B virus (HBV) infection.

The PBAC rejected the submission because the patients in the pivotal clinical trial did not reflect the population requested in the restriction, the comparator in the key clinical trial was not relevant to the current PBS treatment algorithm, and the uncertainty between antiviral resistance and longer-term clinical outcomes. These problems led to uncertainty about the clinical claim and in the economic model.

3. Registration Status

Adefovir dipivoxil tablet 10 mg was registered on 16 September 2003 by the TGA for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease.

4. Listing Requested and PBAC's View

Private Hospital Authority Required
Patients with chronic hepatitis B who satisfy the following criteria:
(1) Active chronic hepatitis B (HBe antigen positive and/or serum HBV DNA positive) with advanced liver disease (either evidence of cirrhosis on liver biopsy or a Child Pugh Turcotte score greater than 5), adefovir may be used in combination with lamivudine.
(2) Active chronic hepatitis B (HBe antigen positive and/or serum HBV DNA positive) in patients who are failing antihepadnaviral therapy as demonstrated by repeatedly elevated

(greater than 1.2 times the upper limit of normal) serum ALT levels. Patients must have received concurrent antihepadnaviral therapy of greater than or equal to 6 months. Patients may receive PBS subsidised treatment of lamivudine in combination with adefovir for the initial 3 months only of PBS subsidised adefovir, unless patients have advanced liver disease (evidence of cirrhosis on liver biopsy or a Child Pugh Turcotte score greater than 5), in which case adefovir may be used in combination with lamivudine.
(3) Patients with a prior history of liver transplant for chronic hepatitis B. Adefovir may be used in combination with lamivudine.
(4) Female patients of childbearing age are not pregnant, not breastfeeding, and are using an effective form of contraception.
NOTE
Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.

See Recommendation and Reasons for the PBAC's view

5. Clinical Place for the Proposed Therapy

To allow for combination use with lamivudine in patients with chronic hepatitis B with advanced liver disease or with a prior liver transplant.

6. Comparator

The comparator was unchanged from the July 2006 submission i.e. lamivudine monotherapy followed by adefovir dipivoxil monotherapy as the main comparator for patients with lamivudine-sensitive HBV (treatment-naïve; treatment-experienced/lamivudine-sensitive; post-transplant/lamivudine sensitive) and adefovir dipivoxil monotherapy for patients with lamivudine-resistant HBV (treatment-experienced/lamivudine-resistant; post-transplant/lamivudine resistant).

7. Clinical Trials

No changes were made to the trial data presented in the previous submission. Please see the Public Summary Document on Adefovir Dipivoxil from the July 2006 PBAC meeting at www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-adefovir-july06.

8. Results of Trials

The re-submission provided new information to: (i) support the claim that the development of resistance in CHB patients with cirrhosis or post-liver transplant leads to clinically meaningful outcomes; (ii) support emerging data which suggests that the resistance rates for adefovir given sequentially in lamivudine resistant patients are higher than for treatment naïve patients given adefovir; and (iii) lower rates of resistance develop to lamivudine and adefovir when given concomitantly compared with sequential lamivudine and adefovir treatment.

9. Clinical Claim

The submission claimed that adefovir dipivoxil plus lamivudine combination therapy has significant advantages in effectiveness over the main comparator and is associated with similar or less toxicity.
See Recommendation and Reasons for PBAC's views.

10. Economic Analysis

An updated preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was valid. The variables included in the evaluation were the cost of adefovir, the cost of lamivudine and the proportion of patients that develop antiviral resistance.

The trial-based incremental discounted cost per extra patient avoiding lamivudine resistance was between $45,000 – 75,000 in Year 2.

The trial-based incremental discounted cost per extra patient avoiding adefovir resistance was between $105,000 – 200,000 in Year 2 and $34,079 in Year 4.

An updated modelled economic evaluation was presented. The base case modelled incremental discounted cost per extra patient with discounted dual resistance avoided was between $15,000- 45,000. The base case modelled incremental discounted cost per extra patient-year of discounted dual resistance avoided: <$15,000. The base case modelled incremental discounted cost per extra discounted life year gained was between $45,000 – 75,000.

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions per year was a total of 10,000 – 15,000 lamivudine prescriptions and < 10,000 adefovir prescriptions in Year 4, while the financial cost per year to the PBS was <$10 million in year 4 assuming all cirrhotic patients commence adefovir and lamivudine combination therapy when the current listing is revised.

12. Recommendation and Reasons

The PBAC agreed that entecavir is a potentially competing drug with adefovir and lamivudine combination, and comparison of the combination treatment with entecavir should have been presented.

The PBAC noted that while no changes had been made to the trial data presented in the previous submission (July 2006 PBAC meeting) new information had been provided to: (i) support the claim that the development of resistance in CHB patients with cirrhosis or post-liver transplant leads to clinically meaningful outcomes; (ii) support emerging data which suggests that the resistance rates for adefovir given sequentially in lamivudine resistant patients are higher than for treatment naïve patients given adefovir; and (iii) lower rates of resistance develop to lamivudine and adefovir when given concomitantly compared with sequential lamivudine and adefovir treatment.

The PBAC agreed that it is clinically important that treatments be made available to prevent the development of resistance to antiviral medications. The PBAC also noted from the hearing that there was a clinical need for combination therapy to be made available to high

risk patients. However, the new data presented did not assist the PBAC in forming a view about the cost effectiveness of combination therapy. The results were difficult to critically appraise given the lack of control, lack of blinding, possible confounding variables and selection bias inherent in the study designs.

The PBAC considered, on the available information, it had not yet been validated that the HIV treatment model of combination treatment, although plausible, should be the preferred approach for the treatment of hepatitis B in terms of cost-effectiveness.

The updated modelled economic evaluation applied the resistance rates and transition probabilities presented in earlier submissions. The PBAC noted the ESC advice with respect to uncertainties associated with the model, including the relevance of the model population to the population for whom PBS listing was sought.

Therefore, the PBAC rejected the application because of a lack of uncertain clinical effect and uncertain cost-effectiveness in the population for whom listing was requested.

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

The Sponsor disagrees with the PBAC opinion regarding clinical effectiveness of combination therapy in the context of drug resistant hepatitis B. The Sponsor however wishes to continue working with the PBAC to overcome issues of uncertainty regarding cost-effectiveness of combination therapy in patients with advanced liver disease and the post liver transplant patient population to achieve a PBS listing for combination therapy.