

PUBLIC SUMMARY DOCUMENT

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

Sponsor: Gilead Sciences Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought 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 nucleoside therapy naïve patients with advanced liver disease, and liver transplant patients with a history of HBV infection.

2. Background

A submission for a Section 100 (Highly Specialised Drug) listing for adefovir dipivoxil tablet 10 mg was first considered by the PBAC at its December 2003 meeting. The PBAC rejected the submission because of uncertainty over the extent of clinical benefit and uncertain cost-effectiveness in the lamivudine-resistant hepatitis B population.

The Committee considered a re-submission at its July 2004 meeting and recommended listing for 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). The PBAC noted that there was a clinical need for this drug for patients who have failed therapy with lamivudine.

At the November 2005 meeting, the PBAC agreed to the sponsor's request to remove the requirement for a second liver biopsy based on adefovir dipivoxil's listing as second-line to lamivudine therapy which already requires patients to have a diagnosis of hepatitis based on a liver biopsy. In order to overcome the concern that some patients may have received non-PBS subsidised lamivudine therapy without having undergone a liver biopsy, the PBAC recommended the addition of a note to the adefovir restriction stating that patients should have had a liver biopsy at some point since original diagnosis.

3. Registration Status

Adefovir dipivoxil tablets 10 mg are TGA registered for marketing in Australia for:

The treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

4. Listing Requested and PBAC's view

Private Hospital Authority Required

Patients with active chronic hepatitis B (HBe antigen positive and/or serum HBV DNA positive) who satisfy the following criteria:

- (1) Advanced liver disease with either evidence of cirrhosis on liver biopsy or a Child-Pugh-Turcotte score > 5. Adefovir may be used as either as monotherapy or in combination with lamivudine; OR
- (2) Repeatedly elevated (greater than 1.2 times the upper limit of normal) serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration and no evidence of cirrhosis. Patients without evidence of cirrhosis may receive treatment in combination with lamivudine for the initial 3 months only of PBS-subsidised adefovir dipivoxil therapy. Patients who are immunosuppressed may receive treatment in combination with lamivudine for the initial 12 months of PBS subsidised adefovir therapy. Thereafter, PBS-subsidised adefovir dipivoxil must be used as monotherapy; Patients with prior liver transplant and history of HBV infection. Adefovir may be used as either as monotherapy or in combination with lamivudine.

NOTE:

Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.

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 30g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.

The PBAC considered that the wording of the requested restriction did not exclude the possibility of the use of adefovir monotherapy in patients with advanced liver disease or in patients with prior liver transplant and history of hepatitis B virus infection. Further, to remain consistent with the current listing the requested restriction should also specify that patients who have repeatedly elevated (greater than 1.2 times the upper limit of normal) serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration and no evidence of cirrhosis have failed lamivudine therapy. However, the PBAC noted that the Pre-Sub-Committee and Pre-PBAC Responses acknowledged that it would be inappropriate to allow adefovir monotherapy in patients with advanced liver disease and post-transplant, and indicated willingness to engage in further discussions about necessary amendments to the wording of any restriction.

5. Clinical place for the proposed therapy

Combination use with lamivudine in patients with advanced liver disease or with a prior liver transplant to reduce the risk of resistance development in these patients.

6. Comparator

The submission nominated the comparators for different disease stages as detailed in the table below.

Type of chronic hepatitis B population	Stage in the treatment pathway	Comparator
Advanced liver disease ^a	Nucleos(t)ide-naive	Lamivudine and sequential adefovir
Advanced liver disease ^a	Nucleos(t)ide-experienced	Lamivudine and sequential adefovir
Advanced liver disease ^a	Nucleos(t)ide-experienced and lamivudine resistant	Adefovir monotherapy
Post-liver transplant	Nucleos(t)ide-experienced	Lamivudine and sequential adefovir
Post-liver transplant	Nucleos(t)ide-experienced and	Adefovir monotherapy

	lamivudine resistant	
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^a defined as evidence of cirrhosis on liver biopsy or a Child-Pugh-Turcotte score >5. Advanced liver disease therefore includes patients with compensated cirrhosis and decompensated cirrhosis.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The scientific basis of comparison was:

- 1) One head-to-head randomised comparative trial (NUC20912) comparing adefovir and lamivudine given in combination, and lamivudine monotherapy in nucleos(t)ide-naïve chronic hepatitis B patients with compensated liver disease (this trial was not published at the time of the submission); and
- 2) data from a long-term resistance surveillance program conducted by the sponsor in chronic hepatitis B patients who have completed five clinical studies.

The PBAC was advised the subject group in the key trial was not representative of those for whom PBS listing was sought. The trial data was predominantly derived from HBeAg-positive (which usually is associated with better outcomes), compensated (better outcomes), nucleos(t)ide-naïve patients only (but not post transplant); whereas the population for whom PBS listing was sought is patients with advanced liver disease or with prior liver transplant. Additionally the key trial did not compare lamivudine and adefovir combination with lamivudine and sequential adefovir, the appropriate comparator for nucleos(t)ide-naïve chronic hepatitis B patients with compensated liver disease. The Pre-Sub-Committee Response argued that what is important is not the stage of the disease but the fact that these drugs in combination actually suppress Hepatitis B virus DNA turnover and reduce the amount of resistance.

8. Results of Trials

The results of the pivotal clinical trial showed proportionally more patients in the adefovir and lamivudine combination arm achieved undetectable HBV DNA, HBeAg loss and HbeAg seroconversion compared with the lamivudine arm at week 128 although statistical testing was not performed. Adefovir and lamivudine combination reported numerically greater effectiveness (although not statistically significant) for all virological, histological and biochemical endpoints at week 128 compared with lamivudine monotherapy.

There was a statistically significant difference between adefovir and lamivudine combination and lamivudine monotherapy in the development of YMDD resistance mutations at week 52 and week 104.

Serious adverse events were reported in higher numbers of patients in the lamivudine monotherapy group compared with the adefovir plus lamivudine combination group, mainly related to elevations in liver enzymes that may reflect differences in efficacy between monotherapy and combination therapy. However, hepatitis flares were reported in a greater proportion of subjects in the adefovir and lamivudine combination group than in the lamivudine monotherapy group.

9. Clinical Claim

The submission described adefovir and lamivudine combination therapy as having significant advantages in effectiveness over the main comparator and similar or less toxicity.

The PBAC accepted that adefovir and lamivudine combination therapy has significant advantages in effectiveness over lamivudine and similar or less toxicity, in terms of development of resistance as an intermediate indicator of effectiveness. However, the relevance of this result derived from a population that does not reflect the population for whom PBS listing is sought and from an incorrect comparator was considered uncertain.

10. Economic Analysis

A preliminary economic evaluation was presented. The resources included were drug costs only. The trial-based incremental cost per extra patient avoiding lamivudine resistance was estimated to be in the range of \$45,000 - \$ 75,000 in Year 2. The trial-based incremental cost per extra patient avoiding adefovir resistance was estimated to be in the range of \$105,000 - \$200,000 in Year 2.

A modelled economic evaluation was presented. The choice of the cost-effectiveness approach is valid, but it was not completely applied as the submission did not report these results in terms of the conventional measures, namely incremental cost per life-year gained or per QALY gained. The PBAC noted a modelled evaluation to final outcomes is necessary to calculate the cost/ QALY for the different populations requested in the extension to the PBS listing i.e. advanced liver disease and post-transplant patients. The risk of morbidity and mortality in these patient groups is likely to vary and therefore produce different ICERs.

The base case modelled incremental cost per extra patient with dual resistance avoided was estimated to be in the range \$15,000 - \$45,000. The base case modelled incremental cost per extra patient-year of dual resistance avoided was estimated to be < \$15,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated a total in the range of 10,000 – 50,000 lamivudine prescriptions and < 10,000 adefovir prescriptions in Year 4. The PES advised that these estimates are reasonable.

The submission estimated a cost of < \$10 million in year 4. There is potential for usage beyond the requested restriction as adefovir monotherapy and adefovir and lamivudine combination could be used to treat patients without advanced liver disease.

12. Recommendation and Reasons

The PBAC considered that the wording of the requested restriction did not exclude the possibility of the use of adefovir monotherapy in patients with advanced liver disease or in patients with prior liver transplant and history of hepatitis B virus infection. Further, to remain consistent with the current listing the requested restriction should also specify that patients who have repeatedly elevated (greater than 1.2 times the upper limit of normal)

serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration and no evidence of cirrhosis have failed lamivudine therapy. However, the PBAC noted that the Pre-Sub-Committee and Pre-PBAC Responses acknowledged that it would be inappropriate to allow adefovir monotherapy in patients with advanced liver disease and post-transplant, and indicated willingness to engage in further discussions about necessary amendments to the wording of any restriction.

The PBAC also noted that the subject group in the key trial was not representative of those for whom PBS listing was sought. The trial data were predominantly derived from HBeAg-positive, compensated, nucleos(t)ide-naïve patients only (but not post transplant); whereas the population for whom PBS listing was sought was for patients with advanced liver disease or with prior liver transplant. Despite arguments in the Pre-Sub-Committee and Pre-PBAC Responses that the stage of the disease is not relevant in the development of resistance and that the long term outcomes of the development of resistance would be worse in patients with advanced disease, insufficient evidence was presented to support these hypotheses.

Additionally the key trial did not compare lamivudine and adefovir combination with lamivudine and sequential adefovir, the appropriate comparator for nucleos(t)ide-naïve chronic hepatitis B patients with compensated liver disease. The PBAC considered that these issues with the subject group and the comparator in the clinical trial led to considerable uncertainty about the interpretation of the clinical trial results.

The results for the primary and secondary surrogate outcomes from trial NUC20912 (time weighted average change in serum HBV DNA from baseline to week 16 (primary outcome), proportion of patients with ALT normalisation after 1 and 2 years of treatment (secondary outcome) and proportion of patients with HBeAg loss and HBeAg seroconversion (secondary outcomes)) suggest that there are no differences between a regimen in which adefovir is added to lamivudine in comparison with lamivudine alone. Adefovir and lamivudine combination was statistically more effective than lamivudine monotherapy in the development of YMDD variant hepatitis B virus (secondary endpoint) at Week 104. The Pre-Sub-Committee Response stated that the outcome of trial NUC20912 most relevant to the current submission is the development of antiviral resistance (pre-specified, secondary outcome). The submission argued that combination therapy with lamivudine and adefovir will delay or prevent the development of clinically relevant antiviral resistance, and consequently will delay disease progression in treated patients. This assumed a relationship between the surrogate outcome of resistance and clinically relevant health outcomes, which although plausible and supported by the presenter at the hearing, was not substantiated by clinical trials.

The PBAC accepted that adefovir and lamivudine combination therapy has significant advantages in effectiveness over lamivudine and similar or less toxicity, in terms of development of resistance as an intermediate indicator of effectiveness. However, the relevance of this result derived from a population that does not reflect the population for whom PBS listing is sought and from an incorrect comparator was considered uncertain.

There were a number of uncertainties about the modelled economic evaluation, highlighted by the PES commentary and the ESC Advice. These mainly resulted from the clinical uncertainties, ie the concerns about the population in the model which does not represent the patients for whom PBS listing is sought; the modelling of intermediate

outcomes rather than final outcomes and the absence of comparative data concerning incremental LYG or incremental QALYs; and the uncertainty of the impact of resistance rates on longer-term clinical sequelae and the ICERs for different sub-groups of chronic hepatitis B patients, given the different baseline risks for morbidity and mortality in these sub-groups.

The PBAC therefore rejected the submission because the patients 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.

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 acknowledges the PBAC comments and concerns. The sponsor wishes to address these issues and will continue to work with the PBAC towards a mutually acceptable solution to the emerging problem of HBV drug resistance.