PUBLIC SUMMARY DOCUMENT
Product: ADEFOVIR DIPIVOXIL, tablet, 10 mg, Hepsera®
Sponsor: Gilead Sciences Pty Ltd and the Australian Liver Association
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission requested a change to the current PBS restriction for adefovir to allow concurrent use with lamivudine in lamivudine resistant patients being treated for chronic hepatitis B (CHB).

A parallel application sought to amend the definition of antihepadnaviral failure in the current restriction for adefovir to utilise the direct measure of serum HBV DNA level in replacement of the surrogate of elevated serum ALT levels. This Public Summary Document reflects this.

2. Background

A stakeholder meeting about combination antiviral treatments for hepatitis B was convened in May 2007. The PBAC Chair, Departmental members, clinical experts, representatives from the sponsor and a representative from the Australian Society for HIV medicine were all present. The purpose of the meeting was to seek advice on the most appropriate drug treatment for CHB patients, the prevention of the development of resistance to these treatments, the place of combination antiviral therapy and the use of antivirals in CHB patients undergoing cancer chemotherapy. This submission was presented to PBAC as a result.

3. Registration Status

Adefovir was registered on 16/9/2003 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 (ALT or AST) or histologically active disease.

4. Listing Requested and PBAC's View

HIGHLY SPECIALISED DRUGS PROGRAM
Private hospital authority required
Chronic hepatitis B in a patient who has failed antihepadnaviral therapy and who satisfies all of the following criteria:
(1) Repeatedly elevated HBV DNA levels one log greater than the nadir value or failure to achieve a 1 log reduction in HBV DNA within 3 months, whilst on previous anti-hepadnaviral therapy except in patients with evidence of poor compliance;
(2) 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.

For PBAC's view of the restriction, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The combination of adefovir and lamivudine is the preferred treatment option in CHB patients demonstrating resistance to lamivudine.

6. Comparator

The submission identified adefovir monotherapy in lamivudine resistant patients as the main comparator. This was considered appropriate.

7. Clinical Trials

The following studies examining the development of adefovir resistance in combination therapy (i.e. adefovir with lamivudine in lamivudine resistant patients) were cited by the submission:

- Lampertico el al (2007)
- Schiff et al (2007)
- Thiebault et al (2005)

Studies of adefovir monotherapy in lamivudine resistant patients included the following:

- Fung et al (2005)
- Yeon et al (2006)
- Lee et al (2006)
- Chen et al (2006)

Studies comparing monotherapy adefovir with adefovir plus lamivudine in lamivudine resistant patients included the following:

- Lampertico et al (2007)
- Van der Poorten et al (2006)
- Rapti et al (2007)

Long term safety studies of adefovir plus lamivudine in lamivudine resistant patients cited in the submission included:

- Lampertico et al (2007)
- Rapti et al (2007)

Studies of entecavir in lamivudine resistant patients cited in the submission included:

- Colonno et al (2007)
- Jardi et al (2006)

The request to amend the definition of antihepadnaviral failure in the current restriction was based on the following reasons:

- Serum HBV DNA level is the most direct measure of HBV replication available. During antiviral therapy a reduction in serum HBV DNA is associated with response to treatment and always precedes biochemical and histological response. Conversely, the first laboratory marker of viral resistance is a rebound of serum HBV DNA levels which precedes the rise in ALT and the increase in histological activity of the disease.
- In June 2007, the Medical Services Advisory Commmittee recommended the public funding of HBV DNA testing for regular monitoring of chronic HBV and chronic HBV treatment.

8. Clinical Claim

The submission claimed that it is safer and more effective to add adefovir to lamivudine therapy rather than to switch to adefovir monotherapy for the treatment of lamivudine resistant CHB. The submission claimed that the reason for this is because the combination of adefovir with lamivudine prevents the development of adefovir resistance.

The submission also claimed that the current definition of antihepadnaviral therapy failure has two limitations which compromise patient management:

- ALT is a surrogate measure of drug failure.
- Reliance on ALT as a measure of drug failure delays access to second line treatment which has been shown to reduce the efficacy and increase the risk of resistance to the second line treatment (Lampertico, 2006). This in turn has been associated with the development of irreversible decompensation, liver failure and patient death, particularly in patients with cirrhosis.

For PBAC's view of these claims, see Recommendations and Reasons

9. Economic Analysis

The submission estimated the cost offsets over a 5 year period of progression to a worse health state due to adefovir resistance compared to the cost of maintaining lamivudine in patients receiving adefovir. Cost offsets estimated via survey estimates of disease progression due to adefovir resistance produced similar values.

10. Estimated PBS Usage and Financial Implications

The submission estimated that there are currently less than 10,000 patients receiving lamivudine and that annually, 20% will become resistant to it. The extra costs borne by the PBS through increased use of lamivudine were estimated to be less than $10 million per year in each of the first five years after the change to the listing.

11. Recommendation and Reasons

The PBAC recommended a change to the current PBS restriction for adefovir to allow concurrent use with lamivudine in lamivudine resistant patients being treated for chronic hepatitis B. The PBAC accepted the clinical claim that it is safer and more effective to add adefovir to lamivudine therapy rather than to switch to adefovir monotherapy for the treatment of lamivudine resistant chronic hepatis B and that antiviral resistance was a major health issue for approximately 6,000 patients commenced on lamivudine.

The PBAC recognised an absence of data on the rate of adefovir resistance developing beyond 3 years and believed that such data would have been useful in guiding its recommendation. The PBAC noted that the cost offsets presented in the submission remained uncertain despite two cost offsets models being presented. Nonetheless, the PBAC believed that significant cost offsets were present and that the cost of the benefits gained would decrease over the years. The PBAC was of the view that the financial implications, at a worst case scenario, were modest and was prepared to accept the requested change to the existing listing largely on clinical grounds.

The PBAC also recommended an amendment to the definition of antihepadnaviral failure in the current restriction for drugs listed for use in hepatitis B to utilise the direct measure of serum HBV DNA level as an alternative to the surrogate of elevated ALT. The PBAC

acknowledged that serum HBV DNA levels are the most direct measure of HBV replication available and noted that serum HBV DNA testing for chronic hepatitis B patients is now available privately and likely to be soon funded under Medicare.

Recommendation
Amend the restriction and NOTE to read as follows:

Restriction: Private hospital authority required
Chronic hepatitis B in a patient who has failed antihepadnaviral therapy and who satisfy all of the following criteria:
(1) (a) 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 in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or serum HBV DNA positive); or
(b) Repeatedly elevated HBV DNA levels one log greater than the nadir value or failure to achieve a 1 log reduction in HBV DNA within 3 months, whilst on previous antihepadnaviral therapy except in patients with evidence of poor compliance;
(2) Female patients of childbearing age are not pregnant, not breastfeeding, 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.
NOTE**:**
Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.
Patients may receive treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

12. 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.

13. Sponsor's Comment

The Sponsor accepts the PBAC recommendation with no further comment.