1. Purpose of Application
The submission sought to extend the Section 100 (Highly Specialised Drugs Program) listing of tenofovir to include treatment of HBeAg-negative, treatment-naïve patients and treatment-experienced patients with chronic hepatitis B (CHB).

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:
Tenofovir has been listed under Section 100 since 1 October 2002 for treatment of patients with HIV infection.

This was the second submission to the PBAC requesting listing of tenofovir for treatment of CHB.

At its November 2008 meeting, the PBAC recommended extending the listing of tenofovir to include treatment of patients with HBeAg-positive chronic hepatitis B who are nucleoside analogue naïve on a cost minimisation basis with entecavir 0.5 mg tablets where the equi-effective doses are tenofovir 300 mg per day and entecavir 0.5 mg per day.

The Committee rejected the application for listing of tenofovir in HBeAg-negative nucleoside naïve CHB patients, considering insufficient evidence had been present to support the claim of non-inferiority to entecavir 0.5 mg. Based on the data provided, the Committee did not accept the claim that tenofovir is equally effective in nucleoside naïve HBeAg-negative patients to entecavir because this conclusion relied on the assumption that tenofovir is equally effective in nucleoside naïve HBeAg-negative and HBeAg-positive patients.

The Committee also rejected the application for listing of tenofovir for the treatment of CHB in nucleoside experienced patients. The PBAC considered the methods used in the submission for the direct comparison of tenofovir to adefovir to be flawed.

3. Registration Status
Tenofovir was first registered by the TGA on 13 August 2002 for use in combination with other antiretroviral agents for the treatment of HIV-infected adults. Evidence to support this indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of tenofovir in treatment-naïve adults and in treatment-experienced adults.

On 30 July 2008, the TGA approved indications were extended to include treatment of CHB in adults with evidence of active viral replication and active liver inflammation.
4. Listing Requested and PBAC’s View
Section 100 (Highly Specialised Drugs Program)
Private hospital authority required

**Treatment-naïve chronic hepatitis B patients who satisfy all of the following criteria:**
1. Histological evidence of chronic hepatitis on liver biopsy (except in patients for whom a liver biopsy is contraindicated).
2. Elevated HBV DNA and/or abnormal serum ALT levels in conjunction with documented chronic hepatitis B infection.

**Chronic hepatitis B in patients who have failed antihepadnaviral therapy and who satisfy all of the following criteria:**
1. Persistently elevated HBV DNA levels despite prior antihepadnaviral therapy of greater than or equal to 6 months duration or failure to achieve a 1 log reduction in HBV DNA within 3 months of commencing antihepadnaviral therapy except in patients with evidence of poor compliance; or
2. Repeatedly elevated serum ALT levels despite antihepadnaviral therapy of greater than or equal to 6 months duration with documented chronic hepatitis B infection.

**NOTE:**
Patients who have failed prior antihepadnaviral therapy may receive tenofovir treatment in combination with lamivudine.
Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.
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.
Female patients who are of child-bearing age should not be pregnant, should not be breast-feeding, and should be using an effective form of contraception.

The PBAC agreed with the requested restriction but with minor changes.

5. Clinical Place for the Proposed Therapy
Tenofovir will provide an alternative oral treatment for chronic hepatitis B in both treatment-naïve and treatment-experienced patients.

6. Comparator
As in the November 2008 submission, the re-submission nominated entecavir 0.5 mg as the comparator for treatment-naïve patients and adefovir as the comparator for treatment-experienced patients. The PBAC previously considered these comparators to be appropriate.

7. Clinical trials
*Nucleos(t)ide naïve HBeAg negative patients*
No new direct randomised trials comparing tenofovir with entecavir were identified.

The basis of the re-submission for tenofovir in nucleos(t)ide naïve HBeAg negative patients was a new comparison of the tenofovir 300 mg arm of one randomised trial (trial 0102) and the entecavir 0.5 mg arm of another randomised trial (Lai 2006). Participants
in both trials were HBeAg negative. The trials did not have a common comparator on which to construct an indirect comparison.

The re-submission also included the unpublished results of a *post hoc* subgroup analysis of the results of a mixed treatment comparison (MTC) meta-analysis as supplementary evidence.

*For a list of the studies presented, refer to the November 2008 Public Summary Document.*

**Nucleos(t)ide experienced patients**

The primary evidence presented in the re-submission for tenofovir in nucleos(t)ide experienced patients was the same as in the previous submission.

*Please refer to the November 2008 Public Summary Document for a list of these trials and studies.*

The re-submission presented additional supplementary evidence. The following table details those studies published or presented at the time of submission:

<table>
<thead>
<tr>
<th>Trial/First author</th>
<th>Protocol title/Publication title</th>
<th>Publication citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0102 LTE HBeAg negative patients</td>
<td>Two year tenofovir disoproxil fumarate (TDF) treatment and adefovir dipivoxil (ADV) switch data in HBeAg-negative patients with chronic hepatitis B (Study 102)</td>
<td>Marcellin P, Buti M, Krastev Z et al, 59th Meeting of the American Association for the Study of Liver Disease. San Francisco, California: 31 October–4 November 2008. Oral presentation #146</td>
</tr>
<tr>
<td>Hann 2008</td>
<td>Tenofovir (TDF) has stronger antiviral effect than adefovir (ADV) against lamivudine (LAM)-resistant hepatitis B virus (HBV).</td>
<td>Hann HW, Chae HB, Dunn SR, <em>Hepatol Internat</em> 2: 244–249</td>
</tr>
<tr>
<td>van Bömmel 2006</td>
<td>Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy.</td>
<td>van Bömmel F, Zöllner B, Sarrazin C et al, <em>Hepatol</em> 44: 318–325</td>
</tr>
<tr>
<td>van Bömmel 2007</td>
<td>Efficacy of tenofovir DF for the treatment of adefovir resistance.</td>
<td>van Bömmel F, Trojan J, Wasmuth H et al, 58th Meeting of the American Association for the Study of Liver Diseases. Boston,</td>
</tr>
</tbody>
</table>
8. Results of Trials

Nucleos(t)ide naïve HBeAg negative patients

The re-submission aimed to demonstrate the non-inferiority of tenofovir 300 mg to entecavir 0.5 mg by comparing two treatment arms from two separate trials, with no common comparator. The specified non-inferiority margin was 10-15 %. The results of the key comparison of the tenofovir 300 mg arm of trial 0102 and the entecavir 0.5 mg arm of Lai (2006), both in HBeAg negative CHB patients, with no common comparator, are presented in the following table.

Results of the common outcome measure across the two treatment arms from trials 0102 and Lai 2006

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0102</th>
<th>Lai 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;300 copies/mL</td>
<td>230/250 (92.0)</td>
<td>293/325 (90.2)</td>
</tr>
</tbody>
</table>

CI=confidence interval; DNA=deoxyribonucleic acid; HBV=hepatitis B virus; n = number with event; N = number in group; OR=odds ratio; RD=risk difference; RR=relative risk.

Nucleos(t)ide experienced patients

The re-submission presented the same primary evidence as was presented in the previous submission.

The results of the comparison for tenofovir versus adefovir in nucleos(t)ide-experienced patients (combined analysis for studies 0102 and 0103) are shown below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenofovir</th>
<th>Adefovir</th>
<th>ARD (95% CI)</th>
<th>RR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response*</td>
<td>37/51 (72.5)</td>
<td>15/24 (62.5)</td>
<td>10.0% (-12.9%, 33.0%)</td>
<td>1.16 (0.82, 1.65)</td>
<td>1.59 (0.57, 4.44)</td>
</tr>
<tr>
<td>HBV DNA &lt;400 copies/mL</td>
<td>46/51 (90.2)</td>
<td>17/24 (70.8)</td>
<td>19.4% (-0.6%, 39.3%)</td>
<td>1.27 (0.97, 1.67)</td>
<td>3.79 (1.06, 13.56)</td>
</tr>
<tr>
<td>Histologic</td>
<td>40/51</td>
<td>21/24</td>
<td>-9.1%</td>
<td>0.90</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Response (78.4) (87.5) (-26.5%, 8.3%) (0.73, 1.10) (0.13, 2.07)

**ARD**=absolute risk difference; **CI**=confidence interval; **DNA**=deoxyribonucleic acid; **HBV**=hepatitis B virus; **n**=number with event; **N**=number in group; **OR**=odds ratio; **RR**=relative risk.

Proportion of subjects with complete response at week 48, defined as HBV DNA levels <400 copies/mL and histologic improvement indicated by at least 2-point reduction in Knodell necro-inflammatory score without worsening in Knodell fibrosis score.

For the purposes of this *post hoc* comparison, the definition of “treatment experienced” CHB patients was any subject with greater than 12 weeks of prior nucleoside therapy.

The re-submission claimed that as the lower limits of the 95% confidence intervals (CIs) are -0.6% for the risk difference and 0.97 for the relative risk, it can be concluded that tenofovir is non-inferior to adefovir using either 15% or 10% non-inferiority margins.

The results of the mixed treatment comparison meta-analysis (Dakin 2008) are presented below:

### Key results of the meta-analysis of outcomes after one year of treatment: All treatment-naïve patients

<table>
<thead>
<tr>
<th>Treatment (number of trials)</th>
<th>% patients HBV DNA &lt;300 copies/mL (95% CrI)</th>
<th>OR vs. LAM (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside- and nucleotide-naïve HBV mono-infected patients – HBeAg-positive and HBeAg-negative patients combined</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (1)</td>
<td>94.65 (85.86, 99.03)</td>
<td>33.29 (6.876, 116.4)</td>
</tr>
<tr>
<td>Entecavir (3)</td>
<td>79.04 (68.22, 89.1)</td>
<td>4.666 (2.464, 9.374)</td>
</tr>
<tr>
<td>Telbivudine (3)</td>
<td>71.84 (58.64, 84.76)</td>
<td>3.161 (1.59, 6.505)</td>
</tr>
<tr>
<td>Telbivudine + lamivudine (1)</td>
<td>61.63 (29.56, 88.35)</td>
<td>2.588 (0.461, 9.044)</td>
</tr>
<tr>
<td>Adefovir (4)</td>
<td>62.17 (39.74, 84.73)</td>
<td>2.274 (0.744, 6.431)</td>
</tr>
<tr>
<td>Lamivudine (9)</td>
<td>46.88 (43.2, 50.43)</td>
<td>–</td>
</tr>
<tr>
<td>Adefovir + lamivudine (1)</td>
<td>45.39 (17.73, 75.3)</td>
<td>1.167 (0.246, 3.544)</td>
</tr>
<tr>
<td>Placebo (5)</td>
<td>6.21 (1.37, 15.26)</td>
<td>0.077 (0.016, 0.207)</td>
</tr>
</tbody>
</table>

**Crl**=credible interval; **DNA**=deoxyribonucleic acid; **HBV**=hepatitis B virus; **LAM**=lamivudine; **OR**=odds ratio

Relevant *p* values: Tenofovir is significantly better than lamivudine (*p*<0.05); tenofovir is significantly better than placebo (*p*<0.05); tenofovir is significantly better than adefovir (*p*<0.05); tenofovir is significantly better than telbivudine (*p*<0.05); tenofovir is significantly better than entecavir (*p*<0.05); telbivudine + lamivudine is significantly worse than tenofovir (*p*<0.05); adefovir + lamivudine is significantly worse than tenofovir (*p*<0.05)

**Abbreviations:** **Crl**, credible (Bayesian probability) interval; **OR**, odds ratio showing how many times higher the probability of this outcome is with the treatment in question, compared with lamivudine

### Resistance

The re-submission reported that, to date, no clinically relevant mutations associated with tenofovir have been identified.

The re-submission provided the results of an updated safety review, performed during the six months from May 2008 to October 2008. During this period, the sponsor reviewed three key safety areas, and subsequently updated their company core safety information to include angioedema as an undesirable event. No amendments were considered necessary in the other two key safety areas reviewed, agranulocytosis and immune reconstitution syndrome.
For PBAC’s comments on these results, see Recommendation and Reasons.

9. Clinical Claim

Nucleos(t)ide naïve HBeAg negative CHB patients
The re-submission described tenofovir as non-inferior in terms of effectiveness and non-inferior in terms of safety compared to entecavir 0.5mg in nucleos(t)ide naïve HBeAg negative CHB patients.

Nucleos(t)ide experienced patients
The re-submission described tenofovir as non-inferior in terms of effectiveness and non-inferior in terms of safety compared to adefovir in nucleos(t)ide experienced CHB patients.

For PBAC’s views, see Recommendation and Reasons.

10. Economic Analysis
The submission presented a cost minimisation analysis. The equi-effective doses were estimated as tenofovir 300 mg once daily, long-term therapy, entecavir 0.5 mg once daily, long-term therapy in treatment naïve patients, and adefovir 10 mg once daily, long term therapy in treatment experienced patients.

11. Estimated PBS Usage and Financial Implications
The submission estimated the likely number of patients/year to be less than 10,000 in Year 5 of listing.

12. Recommendation and Reasons
The PBAC recommended extending the listing of tenofovir on a cost-minimisation basis compared with entecavir 0.5 mg for treatment of chronic hepatitis B in nucleoside analogue naïve and on a cost-minimisation basis compared with adefovir 10 mg for patients who have failed previous antihepadnaviral therapy. The equi-effective doses are entecavir 0.5 mg once daily and tenofovir 300 mg once daily for long-term therapy in treatment-naïve patients, and adefovir 10 mg and tenofovir 300 mg for long-term therapy for treatment-experienced patients. The PBAC considered the submission’s assumptions for a weighted price based on 50 % utilisation in each treatment group as reasonable. 

The PBAC recognised there is a clinical need for an effective additional treatment for chronic hepatitis B, particularly in HBeAg-negative and treatment-experienced patients and noted that tenofovir is widely listed in international guidelines as treatment for hepatitis B. The clinician at the hearing indicated that to date, there have been no signs of resistance to treatment with tenofovir. The Pre-PBAC Response acknowledged that the data presented are limited, but no new trials addressing the PBAC’s concerns with appropriate comparators are planned.

The basis of the re-submission for tenofovir in nucleos(t)ide naïve HBeAg-negative patients is a comparison of the tenofovir 300 mg arm of one randomised trial (trial 0102) and the entecavir 0.5 mg arm of another randomised trial (Lai 2006). Participants in both trials were HBeAg-negative. The trials did not have a common comparator on which to
construct an indirect comparison. In the absence of a common reference, there is greater uncertainty with this data-set than with the data presented previously in treatment-naïve HBeAg-positive nucleoside patients, however the unadjusted comparison approach is the only analysis possible given the trial data available.

The PBAC previously considered that HBeAg status is both an effect modifier and an independent predictor of outcome. Therefore, the comparison of outcomes between HBeAg-positive patients from one study and HBeAg negative patients from another study is subject to considerable confounding with important differences between the baseline characteristics of the patients in the trials, in addition to HBeAg status, that may influence the outcome.

The PBAC considered that the approach used in the previous submission for the direct comparison of tenofovir with adefovir, in which the results of the subgroups of nucleoside experienced patients from a trial in HBeAg-positive CHB patients and a trial in HBeAg negative CHB patients were combined, was flawed. These data were presented again and the methodological approach did not address the PBAC’s concerns. Patient data from two separate RCTs are combined, resulting in a loss of randomisation, an obvious imbalance of HBeAg-positive patients between treatment arms and an under-representation of HBeAg-positive patients in the data. The Pre-Sub-Committee Response noted that the totality of the evidence provides an overall picture of the clinical efficacy of tenofovir in comparison with the appropriate comparators. The PBAC was advised that the data support the fact that tenofovir is an effective agent, but the performance against its comparators remains uncertain because of the limitations of the data available.

Other evidence presented in the submission, including the mixed treatment comparison meta-analysis by Dakin et al (2008), supported a finding that tenofovir is an effective treatment for chronic hepatitis B. The PBAC noted that the re-submission states that the Dakin 2008 meta-analysis shows that treatment with tenofovir is more likely to result in a HBV DNA level < 300 copies/mL than either entecavir or adefovir, and this result is statistically significant. However, due to the under-representation of data in HBeAg negative patients, the results of this post hoc analysis are likely to be dominated by the treatment effect in HBeAg positive patients.

Nevertheless, despite the deficiencies in the data, the PBAC accepted overall that tenofovir is likely to be no worse than entecavir 0.5 mg for treatment naïve patients and no worse than adefovir 10 mg for treatment experienced patients and that it represents an important alternative treatment option for patients with chronic hepatitis B.

**Recommendation**

TENOFOVIR DISOPROXIL FUMARATE, tablet, 300 mg

Extend the current recommended restriction to include the following:

**Restriction:**

<table>
<thead>
<tr>
<th>Section 100 (Highly Specialised Drugs Program)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private hospital authority required</td>
</tr>
</tbody>
</table>
Treatment, as sole PBS-subsidised therapy, of chronic hepatitis B in a patient 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;
(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.

Chronic hepatitis B in a patient who has failed antihepadnaviral therapy and who satisfies all of the following criteria:

(1)(a) Repeatedly elevated 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; 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 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. Patients may receive tenofovir treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

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
Gilead Sciences welcomes the PBAC recommendation to extend the listing of Viread to include patients with chronic hepatitis B, both treatment naïve and treatment experienced patients, in accordance with the proposed S 100 restriction.