Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for tenofovir disoproxil fumarate

Proprietary Product Name: Viread

Sponsor: Gilead Sciences, Australia & New Zealand

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	Extension of Indications
Decision:	Approved
Date of Decision:	17 September 2013
Active ingredient:	Tenofovir disoproxil fumarate
Product Name:	Viread
Sponsor's Name and Address:	Gilead Sciences, Australia & New Zealand Level 6, 417 St Kilda Road Melbourne VIC 3004
Dose form:	Tablet
Strength:	300 mg
Container:	Bottle
Pack size:	30
New Approved Therapeutic use:	Viread is indicated for the treatment of chronic hepatitis B in paediatric patients 12 years of age and older with compensated liver disease and with evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels or evidence of active inflammation.
Route of administration:	Oral
Dosage:	One 300 mg tablet daily
ARTG Number:	90370

Product background

Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir (TFV), which is a nucleotide reverse transcriptase inhibitor (NtRTI) and a hepatitis B virus (HBV) polymerase inhibitor.

At the time of this application, Viread tablets containing TDF 300 mg were approved for the following indications:

> *Viread in combination with other antiretroviral agents is indicated for the treatment of HIV-infected adults and paediatric patients 12 years of age and older.*
>
> *Viread is indicated for the treatment of chronic hepatitis B in adults (see CLINICAL TRIALS).*

This AusPAR describes the application by Gilead Sciences, Australia & New Zealand to extend the indications for Viread to include:

> *the treatment of chronic hepatitis B in paediatric patients aged 12 years of age and older.*

Viread when used for the treatment of chronic hepatitis B (CHB) in paediatric patients 12 years of age and older was granted Orphan Drug status by the TGA on 22 March 2012.

Regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods (ARTG) in August 2002.

At the time the current application was considered by the TGA, a similar application (that is, Viread for the treatment of CHB in paediatric patients) had been approved in the European Union (November 2012) and the USA (August 2012).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The sponsor had stated that worldwide, approximately 350 to 400 million people have CHB, and that following acute HBV infection, the risk of progression to chronic HBV infection is inversely proportional to the age at which the infection was acquired. The sponsor had stated that 90% of children infected with HBV in the first year of life and 30% to 50% of children infected between ages of 1 and 4 years develop CHB, leading to large number of adolescents with CHB, which is in turn a major cause of chronic hepatic insufficiency, cirrhosis, and hepatocellular carcinoma.

The sponsor had stated that there was an unmet treatment need in adolescents with CHB, and that although there are 5 drugs that are currently approved by the Food and Drug Administration (FDA) for treatment of CHB in children and adolescents <18 years old in the United States (US) (lamivudine [age 2 to 17 years], adefovir [age 12 years and older], entecavir [age 16 years and older], telbivudine [age 16 years and older], and interferon-alpha [age 5 to 18 years]), there are limitations to these agents. The sponsor cited the development of viral resistance with long-term use of lamivudine, the limited safety and

efficacy data of entecavir and telbivudine in patients < 16 years of age, cross-resistance between entecavir and lamivudine necessitating a higher dose of entecavir in patients with lamivudine-refractory HBV infection, side effects such as growth impairment with interferon-alpha, and inconvenient injectable dosage form of interferon alpha.

The sponsor had stated that TDF had demonstrated efficacy and safety in the treatment of CHB infection in adults in 2 previous studies (GS-US-174-0102 and GS-US-174-0103). Extrapolating from these results, the sponsor had hypothesised that TDF would be effective as a treatment for CHB in adolescents, and hence Study GS-US-174-0115 (the study submitted in this application) was initiated in adolescents with CHB to test the hypothesis.

> **Evaluator comments**: The clinical rationale is sound and logical. In Australia, there are 7 drugs that are currently approved for the treatment of CHB in adults: 2 are cytokines (interferon alpha, pegylated interferon), 3 are nucleoside analogues (lamivudine, entecavir, telbuvidine) and 2 are nucleotide analogues (adefovir, tenofovir). Out of these, 4 are currently approved for use in children and adolescents <18 years old: lamivudine (age 2 years and older), adefovir (age 12 years and older), entecavir (age 16 years and older), and telbivudine (age 16 years and older).

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 pivotal efficacy and safety study, Study GS-US-174-0115
- 1 Week-72 virology study report of study GS-US-174-0115 (results of this virology report have been incorporated into the main study report of Study GS-US-174-0115)
- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety

Paediatric data

The submission included paediatric efficacy and safety data, as this application is for the extension of indication for the treatment of CHB in paediatric patients aged 12 years and older.

Good clinical practice

The clinical study reviewed in this evaluation was in compliance with CPMP/ICH/135/95 *Note for Guidance on Good Clinical Practice*.

Pharmacokinetics

Not applicable.

Pharmacodynamics

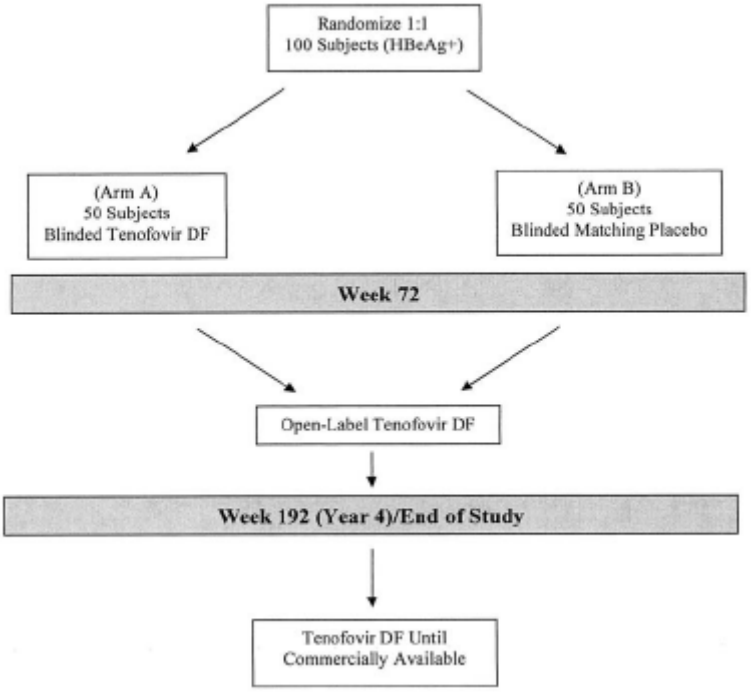
Not applicable.

Efficacy

Studies providing efficacy data

One study was provided. Study GS-US-174-0115 was a randomised, double-blind, placebo-controlled, multi-centre study evaluating the efficacy, safety and tolerability of TDF versus placebo in TDF-naïve adolescents (12 to 17 years of age, inclusive) with CHB. Subjects were randomised in a 1:1 ratio to 1 of 2 treatment groups: TDF 300 mg orally (PO) once daily or matching placebo PO once daily. After 72 weeks of blinded randomised treatment, subjects could switch to open-label TDF treatment for an additional 2.5 years (additional 120 weeks). A schema of the study design is presented in Figure 1.

Figure 1. GS-US-174-0115 Study Schema



The clinical study report (CSR) submitted for this application presents only the results for the 72 week double-blind phase.

The primary objective of the study was to compare the antiviral efficacy, safety and tolerability of TDF 300 mg once daily versus placebo once daily in adolescents (aged 12 to 17 years, inclusive) with CHB infection. The secondary objectives of the study were to evaluate the biochemical and serological responses to TDF versus placebo in adolescents with CHB infection, and to evaluate the incidence of drug resistance mutations.

Evaluator's conclusions on clinical efficacy for the extension of indication of TDF for treatment of CHB in paediatric patients 12 years of age and older

Overall, the study design, study inclusion and exclusion criteria, and study endpoints were appropriate and in line with recommendations of the TGA-adopted European Medicines Agency (EMA) *Guideline on the clinical evaluation of medicinal products intended for treatment of hepatitis B* (CHMP/EWP/6172/03, February 2006). The primary and secondary endpoints allowed evaluation of virological response (HBV deoxyribonucleic acid (DNA) < 400 copies/mL and HBV DNA < lower limit of quantitation (LLoQ) of the polymerase chain reaction (PCR) assay [169 copies/mL]), biochemical response (normal alanine transaminase (ALT) and normalised ALT), serological response (antibody to hepatitis B surface antigen (HbsAg) loss and seroconversion, and hepatitis B early antigen

(HBeAg) loss and seroconversion) as well as composite or combined responses of virological, biochemical and serological responses. These are consistent with current clinical practice guidelines recommendations on treatment objectives of CHB.

The baseline demographic and disease characteristics of the study population were comparable between treatment groups.

Main efficacy results are summarised in Table 1 and Table 2.

Table 1. GS-US-174-0115: Summary of Key Efficacy Results at Week 72

	TDF 300 mg (12–17 years)[a] (N = 52)	PLB (12–17 years)[a] (N = 54)	P-value[b]
Primary Efficacy Endpoint			
HBV DNA < 400 copies/mL, n (%) (DBEE Analysis)	46/52 (88.5%)	0/54 (0.0%)	< 0.001
HBV DNA, n (%)			
HBV DNA < 169 copies/mL (DBEE Analysis)	44/52 (84.6%)	0/54 (0.0%)	< 0.001
Mean (SD) Change from Baseline in HBV DNA (Log_{10} copies/mL) (FAS)	-5.36 (1.952)	-0.92 (1.944)	–
Secondary Efficacy Endpoints			
ALT, n (%)			
Normal ALT (DBEE Analysis)	40/52 (76.9%)	21/54 (38.9%)	< 0.001
Normalized ALT[c] (DBEE Analysis)	26/35 (74.3%)	13/42 (31.0%)	< 0.001
Mean (SD) Change from Baseline[b] in ALT (U/L)	–58 (121.3)	–13 (143.8)	–
Serology, n (%)			
HBeAg Loss (DBEE Analysis)	10/48 (20.8%)	7/48 (14.6%)	0.41
Seroconversion to anti-HBe (DBEE Analysis)	10/48 (20.8%)	7/48 (14.6%)	0.41
HBsAg Loss (DBEE Analysis)	1/52 (1.9%)	0/54	0.32
Seroconversion to anti-HBs (DBEE Analysis)	1/52 (1.9%)	0/54	0.32
Genotypic Analysis, n (%)			
Changes from Baseline at Conserved Sites within the HBV Polymerase/Subjects Evaluated	1/52 (1.9%)	5/54 (9.3%)	–

a Age group is based on the randomization stratification (12–14 or 15–17 years of age).
b P-values for categorical data from a two-sided Cochran-Mantel-Haenszel test, controlling for strata (12–14 years or 15–17 years at the time of randomization).
c Study baseline is defined as the first dose date of DB study drug. Study week is windowed week relative to study baseline

PLB = placebo; DBEE = Double-Blind Efficacy Evaluation SD = standard deviation; FAS = full analysis set

Table 2. Summary of composite efficacy endpoints, Study GS-US-174-0115

	TDF 300 mg (12–17 years) (N = 52)	Placebo (12–17 years) (N = 54)	P-value
composite endpoint of HBV DNA < 400 copies/mL and normal ALT, n/N (%), DBEE analysis	37/52 (71.2%)	0/54 (0.0%)	< 0.001

	TDF 300 mg (12–17 years) (N = 52)	Placebo (12–17 years) (N = 54)	P-value
composite endpoint of HBV DNA < 400 copies/mL and normal ALT and HBeAg loss[a], n/N (%), DBEE analysis	7/48 (14.6%)	0/48 (0.0%)	< 0.007
composite endpoint of HBV DNA < 400 copies/mL and normal ALT and HBeAg seroconversion[a], n/N (%), DBEE analysis	7/48 (14.6%)	0/48 (0.0%)	< 0.007
composite endpoint of HBV DNA < 400 copies/mL and normalised ALT[b], n/N (%), DBEE analysis	26/35 (74.3%)	0/42 (0.0%)	< 0.05
composite endpoint of HBV DNA < 400 copies/mL and normalised ALT and HBeAg loss[c], n/N (%), DBEE analysis	7/33 (21.2%)	0/42 (0.0%)	0.002
composite endpoint of HBV DNA < 400 copies/mL and normal ALT and HBeAg seroconversion[c], n/N (%), DBEE analysis	7/33 (21.2%)	0/42 (0.0%)	0.002

[a]among subjects who were HBeAg positive at study baseline

[b]among subjects with abnormal ALT at baseline

[c]among subjects who were HBeAg positive with abnormal ALT at study baseline

Efficacy analyses showed results in favour of TDF over placebo in terms of virological response (HBV DNA suppression) and biochemical response (ALT levels). However, no statistically significant differences were found between TDF and placebo in the incidences of HBeAg loss or seroconversion, and of HBsAg loss or seroconversion.

Efficacy results in terms of HBV DNA suppression at Week 72 showed that the proportion of subjects with HBV DNA < 400 copies/mL was statistically significantly higher in the TDF group compared to the placebo group (88.5% versus 0.0%; p<0.001), as was the proportion of subjects with HBV DNA below the LLoQ for the PCR assay of 169 copies/mL at Week 72 (84.6% versus 0.0%; p<0.001). Mean change from baseline in HBV DNA levels at Week 72 was -5.36 $\log_{10}$ copies/mL in the TDF group compared with -0.92 $\log_{10}$ copies/mL in the placebo group. The proportions of TDF-treated subjects with HBV DNA < 400 copies/mL and < 169 copies/mL increased from baseline to Week 48 and then was maintained through to Week 72. The mean change from baseline in HBV DNA levels in the TDF group also showed the same trend over time from baseline to Week 72.

The sponsor had provided a comparison of the virological response rates in this study with those of adult subjects with CHB treated with TDF in two Phase III studies (studies GS-US-174-0102 and GS-US-174-0103). The virological response rates in this study through Week 48 were generally comparable with those of the adult CHB subjects.

Subgroup analyses by age range subgroups (12 to 14 years versus 15 to 17 years) showed that the results were consistent across the age subgroups. The proportions of subjects with HBV DNA < 400 copies/mL, and HBV DNA < 169 copies/mL at Week 72 were similar between the 2 age subgroups within the TDF group (HBV DNA < 400 copies/mL: 90.0% in the age subgroup of 12 to 14 years versus 88.1% in the age subgroup of 15 to 17 years;

HBV DNA < 169 copies/mL: 90.0% versus 83.3%). Other subgroup analyses showed that the percentages of TDF-treated subjects with HBV DNA < 400 copies/mL and with HBV DNA < 169 copies/mL at Week 72 were greater in subjects with baseline abnormal ALT compared to those with baseline normal ALT (HBV DNA < 400 copies/mL: 97.1% versus 70.6%, double-blind efficacy evaluation (DBEE) analysis; HBV DNA < 169 copies/mL: 94.3% versus 64.7%, DBEE analysis), and also greater in subjects without prior oral HBV medications compared to those with prior oral HBV medications (HBV DNA < 400 copies/mL: 95.0% versus 84.4%, DBEE analysis; HBV DNA < 169 copies/mL: 95.0% versus 78.2%, DBEE analysis). No statistical test of significance was performed on these results. However, results showed that within the subgroup of subjects who had prior oral HBV medications, a much higher proportion of TDF-treated subjects than placebo-treated subjects achieved HBV DNA < 400 copies/mL (84.4% versus 0.0%) and HBV DNA < 169 copies/mL (78.2% versus 0.0%).

Efficacy results in terms of ALT levels showed that the proportion of subjects with normal ALT at Week 72 was statistically significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p<0.001). Mean ALT change from baseline at Week 72 was −58 U/L in the TDF group, compared with −13 U/L in the placebo group. The proportion of TDF-treated subjects with normal ALT and with normalised ALT increased from baseline to Week 16 and then was maintained through to Week 72. The mean change from baseline in ALT levels in the TDF group also showed the same trend over time from baseline to Week 72. Results for the proportion of subjects with normal ALT at Week 72 were consistent across the age subgroups (80.0% in the age subgroup of 12 to 14 years versus 76.2% in the age subgroup of 15 to 17 years). However, the proportion of subjects with normalised ALT at Week 72 was numerically higher in the age subgroup of 12 to 14 years (85.7%; 6/7) than in the age subgroup of 15 to 17 years (71.4%; 20/28).

The sponsor had provided a comparison of the biochemical response rates in this study with those of adult subjects with CHB treated with TDF in two Phase III studies (studies GS-US-174-0102 and GS-US-174-0103). The biochemical response rates in this study through Week 48 were generally comparable with those of the adult CHB subjects.

Efficacy results in terms of serological responses (HBeAg loss or seroconversion; HBsAg loss or seroconversion) showed that the difference between the TDF and placebo groups in the proportion of subjects who were HBeAg positive at study baseline and who then experienced HBeAg loss or seroconversion to anti-HBe by Week 72 was not statistically significant. All subjects were HBsAg positive at study baseline, but overall, only two subjects (both in the TDF group) experienced HBsAg loss, one of whom experienced both HBsAg loss and seroconversion to anti-HBs at Weeks 64 and 72.

Various composite endpoints of HBV DNA < 400 copies/mL and normal or normalised ALT with/without HBeAg loss or HBeAg seroconversion all yielded statistically significant difference between TDF and placebo, in favour of TDF. The results of the composite endpoints were largely driven by that of the component of HBV DNA < 400 copies/mL.

Genotypic analysis showed that virologic response to TDF of the 6 subjects in the TDF group who had lamivudine (LAM) resistance–associated mutations at baseline was comparable to that of the remaining 46 subjects in the TDF group without these mutations. In addition, the majority (4 out of the 6) of these TDF-treated subjects with baseline LAM resistance-associated mutations achieved HBV DNA < 400 copies/mL at Week 48 and maintained this through Week 72, while an additional 1 subject achieved HBV DNA < 400 copies/mL at Week 72.

The majority of subjects (5 out of 6 subjects) that qualified for genotypic analysis at Week 48 (that is, had HBV DNA > 400 copies/mL) had not experienced virologic breakthrough.

At Week 72, 3 out of the 5 subjects that qualified for genotypic analysis had confirmed virologic breakthrough and 1 subject had unconfirmed virologic breakthrough However, all 4 instances of viral breakthrough were associated with probable non-adherence to study drug (TDF) as determined by tenofovir plasma levels below the limit of quantification. Phenotypic analyses of 1 subject that qualified for phenotypic testing at Week 48 and 3 subjects that qualified for phenotypic testing at Week 72 showed that no resistance to tenofovir had developed among these subjects.

Pharmacokinetics (PK) evaluations showed that PK parameters of tenofovir in the adolescent CHB subjects in this study receiving TDF 300 mg daily were generally comparable with historical PK data from HIV-infected adolescents and adults.

Safety

Studies providing evaluable safety data

Evaluable safety data was provided in the pivotal efficacy study (Study GS-US-174-0115).

Patient exposure

All subjects completed at least 24 weeks of treatment. The mean duration of treatment was 497.3 days in the TDF group and 489.7 days in the placebo group. The percentage of subjects with 72 weeks of study drug exposure was 98.1% in the TDF group and 92.6% in the placebo group.

The evaluator considered that, overall, the study drug exposure is adequate to assess if the safety profile is consistent with that reported in the PI.

Post-marketing experience

The sponsor had stated that a cumulative assessment of paediatric safety data for TDF in HBV mono-infected patients from the Gilead Drug Safety and Public Health database up to 31 December 2011 had been performed, and that after excluding reports of serious adverse events (SAEs) from Study GS-US-174-0115, no cases involving HBV mono-infected paediatric patients < 18 years old had been identified. The sponsor had stated that a search of the literature had also been performed up to 31 December 2011, and did not identify any literature articles of clinical studies conducted to evaluate TDF in the treatment of HBV mono-infected paediatric subjects. Hence, no changes to the prescribing information relating to post-marketing adverse drug reactions are being proposed as a consequence of the data included in this submission.

Evaluator's overall conclusions on clinical safety

Overall, the incidences of all-causality adverse events (AEs) and of treatment-related AEs were comparable between the 2 treatment groups in Study GS-US-174-0115. The incidences of grade 3 or 4 all-causality AEs, grade 3 or 4 treatment-related AEs, all-causality SAEs and treatment-related SAEs were lower in the TDF group compared to the placebo group. The safety results of the study were consistent with the known adverse effects of TDF.

The AEs elicited in this pivotal study are known adverse effects of TDF stated in the currently-approved Australian PI for TDF. The incidence rate of any treatment-emergent grade 3 or 4 laboratory abnormalities was lower in the TDF group compared to the placebo group (26.9% versus 50.0%). The most frequently reported grade 3 or 4 laboratory abnormality in the TDF group involved ALT. This is a known adverse effect associated with TDF as stated in the currently-approved Australian PI for TDF. In addition,

the incidence of grade 3 or 4 ALT abnormalities was lower in the TDF group compared to the placebo group (11.5% versus 40.7%).

Safety analyses with regards to potential liver, renal and bone toxicities yielded results consistent with known effects of TDF and did not raise significant safety concerns. However, safety evaluations with regards to effect on growth raised some concerns which were not fully addressed in the CSR. This is described later in this section.

With regards to potential liver toxicity, study results showed that the proportion of subjects with on-treatment hepatic flares based on clinical laboratory criteria was lower in the TDF group compared to the placebo group (3.8% versus 18.5%). The proportion of subjects with hepatic flares reported as grade 3 or 4 AEs was also lower in the TDF group compared to the placebo group (3.8% versus 22.2%). The incidence of hepatitis reported as an AE was lower in the TDF group compared to the placebo group (5.8% versus 13.0%), as was that of increased ALT reported as an AE (5.8% versus 22.2%). No subjects in the TDF group had prothrombin time, a test of liver function, above the upper limit normal.

With regards to potential renal toxicity, study results showed that no TDF-treated subjects had a grade 3 or 4 increase in serum creatinine or decrease in serum phosphorus, a confirmed increase from baseline in serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance rate of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. The mean changes in creatinine from baseline to Week 72 were similar between the TDF and placebo groups (0.1 mg/dL in both TDF and placebo groups). No subject in the TDF group had renal and urinary disorders AEs, compared with 3 subjects in the placebo group who had.

With regards to potential bone toxicity, study results showed that at Week 72, the mean changes from baseline in the bone biochemical markers for bone formation (serum osteocalcin and bone specific alkaline phosphatase (ALP)) and for bone reabsorption (N- and C-telopeptides), serum parathyroid hormone (PTH) and 25-hydroxy vitamin D levels were all comparable between the TDF and placebo groups. The incidence of bone AEs was comparable between treatment groups (5.8% in the TDF group and 3.7% in the placebo group). With regards to bone fractures, one subject in the TDF group reported a fracture but this was not considered related to study drug.

No TDF-treated subjects met the safety endpoints of a 6% decrease in lumbar spine bone mineral density (BMD) or a 6% decrease in whole body BMD. There was an increase in mean lumbar spine BMD and in mean whole body BMD from baseline through to Week 72 in both treatment groups, but the percent increase from baseline in the TDF-treated subjects was statistically significantly less than that in the placebo subjects at Week 24 (lumbar spine BMD: 1.87% versus 3.42%, p = 0.005; whole body BMD: 1.10% versus 2.52%, p<0.001), at Week 48 (lumbar spine BMD: 3.50% versus 5.58%, p = 0.046; whole body BMD: 2.05% versus 3.87%, p<0.001) and at Week 72 for whole body BMD (2.84% versus 5.37%, p = 0.013). The percent increase from baseline in lumbar spine BMD was also less in the TDF-treated subjects than that in the placebo subjects at Week 72, but this was not found to be statistically significant (4.95% versus 8.14%, p = 0.053). At Week 72, there was a decrease of 0.05 in mean lumbar spine BMD Z-scores from baseline in the TDF group compared to an increase of 0.07 from baseline in the placebo group, and a decrease of 0.15 in mean whole body BMD Z-scores[1] from baseline in the TDF group compared to an increase of 0.06 in the placebo group, although these differences were not analysed for statistical significance. At Week 72, only 2 subjects in the TDF group had lumbar spine

[1] Z-scores were used to express the deviation from a reference population for lumbar spine and whole body BMD. A Z-score of 0 indicates that a subject's BMD is typical of the population for their age and gender. A negative Z-score indicates that the subject's recorded BMD value is lower than typical for their age and gender. A positive Z-score indicates that the subject's recorded BMD value is higher than typical for their age and gender.

BMD Z-scores of less than -2 (compared to one subject in the placebo group), and the majority of the subjects (65.4% in the TDF group and 72.2% in the placebo group) had lumbar spine BMD Z-scores of above -1 at Week 72. Similar results were obtained for whole body BMD Z-scores, where at Week 72, only 2 subjects in the TDF group had whole body BMD Z-scores of less than -2 (compared to one subject in the placebo group), and the majority of the subjects (67.3% in the TDF group and 70.4% in the placebo group) had whole body BMD Z-scores of above -1 at Week 72.

Overall, the safety analyses results with regards to potential bone toxicity were comparable with those presented in the currently approved Australian PI in TDF-treated HIV-infected adolescents.

Evaluation of effect on growth was done by analysing the Z-scores for height, weight and body mass index (BMI). Results showed that the difference between treatment groups in mean change from baseline in height Z-scores from Week 4 through to Week 72 was not statistically significant across all visit timepoints. However, weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at all timepoints except at Weeks 40, 48, 56 and 72 for weight Z-scores, and Weeks 40 and 48 for BMI Z-scores. Results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. The maximum decrease from baseline in mean weight Z-score in the TDF group was 0.20 at Week 64 (versus a decrease of 0.06 in placebo group; p=0.029) and at Week 72 (versus a decrease of 0.05 in placebo group; p=0.063). The maximum decrease from baseline in mean BMI Z-score in the TDF group was 0.30 at Week 72 (versus a decrease of 0.10 in placebo group; p=0.046). It is noted that the maximum decreases from baseline in mean weight Z scores and mean BMI Z-scores in the TDF group were small. However, the proportions of subjects in the TDF and placebo groups, respectively, with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1, which would allow a better evaluation of the clinical relevance of the weight and BMI Z-scores, were not presented by the sponsor. This was raised as a clinical question (see below).

First round benefit-risk assessment

First round assessment of benefits

The benefit of TDF in the proposed usage is the treatment of CHB in paediatric patients 12 years of age and older.

The exact prevalence of CHB in adolescents in Australia is not well-documented, but the overall prevalence of CHB in Australia was estimated in year 2000 to be between 90000 and 160000 patients, representing a prevalence rate of 0.5% to 0.8%, with about 6000-8000 new notifications to the National Notifiable Diseases Surveillance System annually.[2] In Australia between 1990 and 2002, deaths from CHB doubled from 100 to nearly 200 per annum. Australians with CHB had a 40-90% increased risk of mortality compared to a matched population, and the risks of liver disease-related mortality and of liver cancer-related mortality were estimated to be 12 and 28 times higher respectively, than those for the background population.

The risk of an acute HBV infection becoming chronic varies inversely with age: chronic HBV infection occurs in about 90% of infants infected at birth, 20%–50% of children infected at 1–5 years of age, and about 1%–10% of persons infected as older children and

[2] Gastroenterological Society of Australia, Australian and New Zealand Chronic Hepatitis B (CHB) Recommendations. *Digestive Health Foundation,* 2009/10

adults.[3] There are currently only 2 drugs approved in Australia for the treatment of CHB in adolescents aged 12 years and older: lamivudine (age 2 years and older) and adefovir (age 12 years and older). Entecavir and telbivudine are approved in Australia for use only in adolescents aged age 16 years and older. There is hence potential benefit in having an additional oral drug option for the treatment of CHB in adolescents aged 12 years and older.

The clinical goal of CHB treatment is to prevent progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma, through achieving HBV DNA suppression (desired treatment outcome: HBV DNA <2000 IU/mL [approximately 10000 copies/mL]; optimal treatment outcome: undetectable by PCR [HBV DNA <60 IU/mL; approximately 350 copies/mL]), ALT normalisation, HBsAg loss and seroconversion, HBeAg loss and seroconversion, and/or histological improvement.[4]

Efficacy results in Study GS-US-174-0115 showed statistically significant virological and biochemical responses with TDF compared to placebo. Overall, 88.5% of subjects in the TDF group achieved HBV DNA suppression to < 400 copies/mL at Week 72 (compared to 0.0% in the placebo group, p<0.001), and 84.6% of subjects in the TDF group achieved HBV DNA below the LLoQ for the PCR assay of 169 copies/mL at Week 72 (compared to 0.0% in the placebo group, p<0.001). Biochemical improvement in terms of ALT levels showed that the proportion of subjects with normal ALT at Week 72 was statistically significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p<0.001). The virological and biochemical response rates in the TDF-treated adolescent CHB subjects in this study through Week 48 were generally comparable with those of TDF-treated adult CHB subjects in previous studies. However, efficacy results of serological responses showed that the incidence rates of HBeAg loss and of seroconversion to anti-HBe at Week 72 in the TDF-treated subjects were not statistically significantly different from that of the subjects on placebo (20.8% versus 14.6% in TDF and placebo groups, respectively; p = 0.41 for both endpoints). The incidence rates of HBsAg loss and of seroconversion to anti-HBs at Week 72 were low in both treatment groups, and there was no statistically significant difference between treatment groups (1.9%% versus 0.0% in TDF and placebo groups, respectively; p = 0.32 for both endpoints).

Although treatment objectives of CHB include HBV DNA suppression, ALT normalisation, HBsAg loss and seroconversion, HBeAg loss and seroconversion, and/or histological improvement, evidence showed that the serum level of HBV DNA is the major clinical feature related to liver disease progression, and is predictive of the risk of disease progression.[5, 6] Prolonged ALT level elevation indicates liver injury and disease progression, and hence ALT within normal range with treatment is indicative of reduced liver inflammation and injury. The efficacy results of Study GS-US-174-0115 showed that the use of TDF in the treatment of CHB in adolescents aged 12 years and above led to statistically significant results in these 2 major outcomes of HBV DNA suppression and ALT within normal range, compared to placebo.

Although loss of HBsAg and seroconversion to anti-HBs is considered a complete response, it has been found to be uncommon after therapy with currently available

[3] Australian government department of health and ageing. Vaccine Preventable Disease in Australia, 2005-2007. *Communicable Disease Intelligence*, Volume 34, supplement Dec 2010.
[4] European Association for The Study Of The Liver, EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatology*, 50 (2):227-42, 2009
[5] Gastroenterological Society of Australia, Australian and New Zealand Chronic Hepatitis B (CHB) Recommendations. *Digestive Health Foundation,* 2009/10
[6] Chen C., Yang H, Iloeje U.H. Hepatitis B Virus DNA Levels and Outcomes in Chronic Hepatitis B. *Hepatology*, Vol. 49, No. 5, Suppl., 2009

treatment regimen, occurring in 3-8% of patients receiving interferon and <5% of patients receiving nucleoside/nucleotide analogue therapy. The low rate of HBsAg loss and of seroconversion to anti-HBs in study GS-US-174-0115 was consistent with this.

Loss of HBeAg and seroconversion to anti-HBe has been found to be associated with decreased viral replication and improved liver histology. The rate of HBeAg seroconversion has been reported in 10-30% of patients following interferon therapy. The Australian PI for lamivudine reported an HBeAg seroconversion rate of 16% to 18% in CHB adult patients on lamivudine 100 mg daily after 52 weeks, but that in children and adolescents was not presented. The Australian PI for TDF reported an HBeAg seroconversion rate of 12% in HBeAg positive CHB adult patients on TDF 300 mg daily after 48 weeks (study 0103). The rate of HBeAg seroconversion found in Study GS-US-174-0115 (20.8%) was generally comparable to these reported rates. The Australian PI for lamivudine reported an HBeAg seroconversion rate of 4% in CHB adult Asian patients on placebo (Study NUCB3009). This is in contrast to a higher rate of spontaneous HBeAg seroconversion found in the placebo group (14.6%) in Study GS-US-174-0115. A literature search showed that the rate of spontaneous HBeAg seroconversion in children varies according to geographic region and initial mode of acquisition of HBV infection, but the TGA-adopted EMA guidelines on the clinical evaluation of medicinal products intended for treatment of hepatitis B reported that the annual spontaneous HBeAg seroconversion rate in Caucasian children is up to 14-18%, that about 40% of children clear HBeAg within one year after the detection of elevated aminotransferase, and that long-term follow-up studies in Caucasian children have shown that more than 80% seroconvert from HBeAg to anti-HBe before reaching adulthood. These data suggest that there appeared to be a higher rate of spontaneous HBeAg seroconversion in children and adolescents with CHB (versus that in adult CHB patients), and that while the rate of HBeAg seroconversion in the TDF-treated adolescent CHB patients in Study GS-US-174-0115 appeared to be generally comparable with that in adult CHB patients treated with TDF or lamivudine, it was not statistically significantly higher than the spontaneous HBeAg seroconversion rate in adolescents with CHB. However, overall, study evaluation of the combined response (that is, composite endpoint) of HBV DNA < 400 copies/mL, normalised ALT and HBeAg loss or seroconversion among those who were HBeAg positive with abnormal ALT at study baseline, showed that a statistically significantly higher proportion of subjects in the TDF group (21.2%) achieved this composite endpoint at Week 72, than in the placebo group (0.0%, p=0.002).

Resistance analyses lent support to the potential benefit of TDF as an additional oral drug option for the treatment of CHB in adolescents, showing that the majority (5 out of the 6) of TDF-treated subjects with LAM resistance-associated mutations at baseline went on to have HBV DNA suppression < 400 copies/mL at Week 72. In addition, subgroup analyses showed that within the subgroup of subjects who had prior oral HBV medications, a much higher proportion of TDF-treated subjects than placebo-treated subjects achieved HBV DNA < 400 copies/mL (84.4% versus 0.0%) and HBV DNA < 169 copies/mL (78.2% versus 0.0%).

First round assessment of risks

The risks of TDF in the proposed usage are:

Potential liver toxicity: Study results showed that the incidence of on-treatment hepatic flares based on clinical laboratory criteria was lower in the TDF group compared to that in the placebo group (3.8% versus 18.5%), as was the incidence of hepatic flares reported as grade 3 or 4 AEs (3.8% versus 22.2%), the incidence of hepatitis reported as an AE (5.8% versus 13.0%), and the incidence of increased ALT reported as an AE (5.8% versus 22.2%). In addition, no subjects in the TDF group had prothrombin time, a test of liver function, above the upper limit normal.

Potential renal toxicity: Study results showed that no TDF-treated subjects had a grade 3 or 4 increases in serum creatinine or decrease in serum phosphorus, a confirmed increase from baseline in serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance rate of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. The mean change in creatinine from baseline to Week 72 was small and similar between the TDF and placebo groups (0.1 mg/dL in both TDF and placebo groups), and no subject in the TDF group had renal and urinary disorders AEs (compared with 3 subjects in the placebo group who had).

Potential bone toxicity: Study results showed that there was no statistically significant difference between TDF and placebo in mean change from baseline for the biochemical markers of bone formation (serum osteocalcin and bone specific ALP) and bone reabsorption (N- and C-telopeptides), as well as for serum PTH and 25-hydroxy vitamin D levels. There was also no statistically significant difference between TDF and placebo in the incidence of bone AEs in Study GS-US-174-0115. The percent increase from baseline of mean lumbar spine BMD whole body BMD and in the TDF-treated subjects was statistically significantly less than that in the placebo subjects at Weeks 24, 48, 72 (whole body BMD only at Week 72). In addition, there was a decrease of 0.05 in mean lumbar spine BMD Z-scores from baseline in the TDF group at Week 72 compared to an increase of 0.07 from baseline in the placebo group, and a decrease of 0.15 in mean whole body BMD Z-scores from baseline in the TDF group at Week 72 compared to an increase of 0.06 in the placebo group. However, these mean decreases from baseline in the lumbar spine and whole body BMD Z-scores in the TDF group were small, and results showed that at Week 72, only 2 subjects in the TDF group had lumbar spine BMD Z-scores or whole body BMD Z-scores of < -2, and the majority of the subjects (approximately 66%) had lumbar spine BMD Z-scores or whole body BMD Z-scores of above -1 at Week 72.

Potential effects on growth (height, weight, BMI): Weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at a majority of timepoints. At Week 72, BMI Z-score was statistically significantly more decreased from baseline in the TDF group compared to the placebo group. In addition, results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. It is noted that in the TDF group, from baseline through to Week 72, the maximum decrease from baseline in mean weight Z scores (0.20) and in mean BMI Z-scores (0.30) were small and not likely to be clinically significant. However, the respective proportions of subjects in the TDF and placebo groups with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1 at Week 72 would allow a better evaluation of the clinical relevance of the weight and BMI Z-scores, and these were not presented by the sponsor. This was raised as a clinical question (see below).

Overall, the safety results of the Study GS-US-174-0115 were consistent with the known adverse effects of TDF. Safety analyses with regards to potential liver, renal and bone toxicities also yielded results consistent with known effects of TDF, and did not raise significant safety concerns, although safety analyses with regards to effect on growth were not fully addressed in the CSR.

First round assessment of benefit-risk balance

The benefit-risk balance of TDF, given the proposed usage, is favourable.

The risk of an acute HBV infection becoming chronic varies inversely with age. CHB is associated with progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma. There are currently only 2 drugs approved in Australia for use in adolescents aged 12 and older with CHB.

Efficacy results in Study GS-US-174-0115 showed statistically significant virological and biochemical responses with TDF compared to placebo, with 88.5% of subjects in the TDF group achieving HBV DNA suppression to < 400 copies/mL at Week 72 (compared to 0.0% in the placebo group; p<0.001), and 84.6% achieving HBV DNA below the LLoQ for the PCR assay of169 copies/mL at Week 72 (compared to 0.0% in the placebo group; p<0.001). The proportion of subjects with normal ALT at Week 72 was statistically significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p<0.001). The incidence rates of HBsAg loss and of seroconversion to anti-HBs at Week 72 were low in both treatment groups with no statistically significant difference (1.9%% versus 0.0% in TDF and placebo groups, respectively; p = 0.32 for both endpoints), but this is comparable with the low rate of HBsAg seroconversion in CHB patients treated with interferon (3-8%) or nucleoside/ nucleotide analogue therapy (<5%). The rate of HBeAg seroconversion in the TDF-treated adolescent CHB patients in Study GS-US-174-0115 appeared to be generally comparable with that in adult CHB patients treated with TDF or lamivudine, although it was not statistically significantly higher than the spontaneous HBeAg seroconversion rate in adolescents with CHB. Overall study evaluation of the combined response (that is, composite endpoint) of HBV DNA < 400 copies/mL, normalised ALT and HBeAg loss or seroconversion among those who were HBeAg positive with abnormal ALT at study baseline, showed that a statistically significantly higher proportion of subjects in the TDF group (21.2%) achieved this composite endpoint at Week 72, than in the placebo group (0.0%, p=0.002)

Overall, the safety results of the Study GS-US-174-0115 were consistent with the known adverse effects of TDF. Safety analyses with regards to potential liver, renal and bone toxicities also yielded results consistent with known effects of TDF, and did not raise significant safety concerns.

First round recommendation regarding authorisation

It is recommended that the application for extension of indication of TDF for *'treatment of CHB in paediatric patients 12 years of age and older'* be approved.

This is subject to a satisfactory response to the clinical questions.

Clinical questions and second round evaluation of clinical data submitted in response to questions

This section provides summaries of the TGA requests for further clinical information and the sponsor's responses. See Attachment 2 of this AusPAR for full details.

Efficacy

- *Question 1. Please clarify the approved indication for orphan drug designation by the TGA*

Response from the sponsor

Gilead advises the orphan drug indication is '*for the treatment of chronic hepatitis B in adults and paediatric patients 12 years of age and older*'.

TGA comment: Response noted and accepted.

- *Question 2. Please provide rationale for the administration of TDF in study GS-US-174-0115 without regard to food.*

Response from the sponsor

The recommendation in the currently approved Australia PI is for Viread be taken with food, however Gilead does not consider that food has an adverse effect on the safety and efficacy of TDF and this is reflected in the approved US label for Viread. Since the GS-US-174-115 study was conducted in both the US and Europe, the study protocol was designed with this rationale in mind. Therefore patients in this study took Viread without consideration of food representing worse case scenario and efficacy was still shown.

TGA comment: Response acceptable

- *Question 3. Please review and verify the data presented in Table 8-3 of the CSR*

Response from the sponsor:

Gilead confirms that the revised table which TGA produced [see Attachment 2] is correct.

TGA comment: Response noted and accepted.

- *Question 4. Please provide details on the degree of deviation from the pre-specified inclusion criteria involving ALT levels at screening…*

Response from the sponsor:

Gilead provided full details as requested.

TGA comment: Response noted and accepted.

Safety

- *Question 1. Please provide analysis results on the proportions of subjects in the TDF and placebo groups, respectively, with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1.*

  Safety results showed that weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at all timepoints except at Weeks 40, 48, 56 and 72 for weight Z-scores, and Weeks 40 and 48 for BMI Z-scores. Results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. It is noted that in the TDF group, the maximum decrease from baseline in mean weight Z scores (0.20) and mean BMI Z-scores (0.30) were small and not likely to be clinically significant. However, the proportions of subjects in the TDF and placebo groups, respectively, with weight Z-scores and BMI Z-scores of < -2, between -2 and -1 and > -1 would allow a better evaluation of the clinical relevance of the weight and BMI Z-scores, and these were not presented by the sponsor.

Response from the sponsor:

Weight Z-scores and BMI Z-scores of <-2 between -2 and -1 and >-1 are provided. Please note no statistical differences in either BMI Z-score or Weight Z-score were observed between TDF and placebo groups considering the 3 categories analysed.

TGA comment: Response noted and accepted.

Second round benefit-risk assessment

There is no change to the first round benefit risk assessment following the responses to the clinical questions. The benefit-risk balance of TDF for treatment of CHB in paediatric patients 12 years of age and older is considered favourable.

Second round recommendation regarding authorisation

The sponsor's responses to the clinical questions are considered satisfactory. Registration approval is recommended for the extension of indications of TDF to include *'treatment of CHB in paediatric patients 12 years of age and older'*.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan, AU-RMP identified as Version 2.0, dated 10 May 2012, which was reviewed by the TGA's Office of Product Review (OPR). This was an updated version of the Viread RMP (Version 0.1 dated 19 October 2010) evaluated previously by the OPR.

Safety specification

Subject to the evaluation of the clinical aspects of the safety specifications by the TGA's Office of Medicines Authorisation, the summary of the Ongoing Safety Concerns as specified by the sponsor is as shown in Table 3.

Table 3. Summary of Ongoing Safety Concerns

Important Identified Risks	Renal toxicity
	Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients
	Interaction with didanosine
	Pancreatitis
	Lactic acidosis and severe hepatomegaly with steatosis
	Lipodystrophy
Important Potential Risks	Development of resistance during long-term exposure in HBV infected patients
	Tenofovir DF monotherapy in HIV/HBV coinfected patients
Important Missing Information	Safety in children
	Safety in elderly patients
	Safety in pregnancy
	Safety in lactation
	Safety in black HBV infected patients
	Safety of long-term exposure in HBV infected adults with compensated or decompensated liver disease
	Safety in HBV infected patients with decompensated liver disease and CPT score > 9
	Safety in patients with renal impairment
	Safety in liver transplant recipients infected with HBV

The above ongoing safety concerns are the same as those previously accepted for Viread. This is acceptable.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities, including targeted follow-up questionnaires for renal and bone events, to monitor all the specified ongoing safety concerns. Additional pharmacovigilance activities are also proposed for the important identified risk: 'Renal toxicity'; the important potential risk: 'Development of resistance during long-term exposure in HBV infected patients'; and the important missing

information: 'Safety in children', 'Safety in pregnancy', 'Safety in patients with renal impairment', 'Safety of long-term exposure in HBV infected adults with compensated or decompensated liver disease', 'Safety in HBV infected patients with decompensated liver disease and Child-Pugh-Turcotte (CPT[7]) classification score > 9' and 'Safety in liver transplant recipients infected with HBV'.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important identified risk: 'Renal toxicity' for which an additional risk minimisation activity is also proposed; and the important missing information: 'Safety in HBV infected patients with decompensated liver disease and CPT score > 9' for which no routine risk minimisation is proposed. The sponsor has stated: "No changes were made to the current risk minimisation activities", which were previously accepted for Viread.

In regard to the risk minimisation plan, the sponsor states: "The risk minimisation activities have been updated to include information of educational events and clinical audits throughout 2010. The educational programme "HIV and the Body" was also held in 2011. No changes were made to the current risk minimisation activities."

In addition the sponsor states that if this application is approved, the HBV renal risk minimisation activities will be updated to include information on HBV infected adolescents, as appropriate.

Summary of recommendations

A summary of the OPR recommendations following the first round evaluation is as follows:

- The sponsor should provide copies of the targeted follow-up questionnaires for renal and bone events and include these as an annex to the AU-RMP when this document is next updated.
- The sponsor should state when the protocol for the planned clinical study in HBV infected paediatric patients (GS-US-174-0144) is anticipated to be available. The sponsor should provide an assurance that once available this protocol will be sent to the TGA.
- The sponsor has stated that the planned clinical study (GS-US-174-0127) in HBV infected patients with moderate to severe renal impairment (creatinine clearance 20-60 mL/min), which was referred to in the previously accepted AU-RMP and is intended to provide information on the safety profile of TDF in patients with renal impairment, still does not have a protocol available. Consequently the sponsor should state when the protocol for this planned clinical study is anticipated to be available. The sponsor should provide an assurance that once available this protocol will be sent to the TGA.
- When the AU-RMP previously accepted for Viread was evaluated, the sponsor was requested to provide a copy of the printed educational materials. No such documentation has been provided in the updated AU-RMP. Consequently the sponsor should provide a copy of the printed educational materials and include these as an annex to the AU-RMP when this document is next updated.

[7] The Child-Pugh or Child-Pugh-Turcotte score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

- In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.
- In regard to the proposed routine risk minimisation activities, the draft Consumer Medicine Information (CMI) is considered satisfactory.

The sponsor adequately addressed all OPR recommendations, except as follows:

A previous application for this product to extend the treatment of HIV to include paediatric patients 12 years of age and older was approved as of 15 September 2011. An AU-RMP was evaluated in support of that application and the sponsor was requested to indicate how they would incorporate paediatricians as potential new prescribers in the education of physicians regarding renal toxicity, and if there would be any modification of the material to include the new indication. The sponsor's correspondence dated 14 June 2011 stated:

The Orphan Drug status of Viread in this subset of HIV infected patients reflects that the number of HIV infected adolescent patients and corresponding number of paediatricians treating HIV infected individuals is very low. Any paediatricians known to be treating HIV infected individuals will be invited to attend the ongoing educational programs conducted by Gilead as deemed appropriate. Gilead will conduct relevant in-service medical education sessions at key institutions in which paediatric patients aged 12 years and older who are infected with HIV are known to be treated. Further, Gilead has also prepared standard response documents that provide a summary of key data regarding safety and efficacy of Viread when used in the paediatric population. Such documents are available to health professionals upon request

Upon approval of this Category 1 Application all versions of the Product Information (full PI, abridged PI and minimum PI) will be updated to reflect the new indication as per TGA and Medicines Australia requirements. Copies of the abridged PI, minimum PI, and/or full PI documents are available during discussions with the Gilead sales team. Any other educational materials will be modified as deemed appropriate.

The current application submitted to the TGA included an updated AU-RMP which stated no changes were made to the current risk minimisation activities. In addition it stated that if this application was approved, the HBV renal risk minimisation activities would be updated to include information on HBV infected adolescents, as appropriate.

The sponsor was asked to provide a copy of the current printed educational materials associated with HIV renal risk minimisation activities. In response the sponsor's correspondence dated 18 December 2012 stated:

Due to the very small number of patients involved with both the approved VIREAD HIV paediatric indication and proposed VIREAD HBV paediatric indication, most of whom will not be suitable for treatment, Gilead will not be promoting these indications. Therefore no educational materials will be generated by Gilead for either paediatric indication.

This response would appear to be inconsistent with the previously accepted risk minimisation plan proposed for the HIV paediatric indication. It is considered that printed material would be essential for any such medical educational program or sessions to be conducted.

Consequently the sponsor should update the AU-RMP with details of the previously accepted risk minimisation plan proposed for the HIV paediatric indication, as provided in the sponsor's correspondence dated 14 June 2011. Copies of the printed educational materials associated with these additional risk minimisation activities should also be included in the revised AU-RMP as an annex. The sponsor must definitively state whether similar additional risk minimisation activities will be proposed for the HBV paediatric indication and provide an assurance that copies of the associated printed educational

materials will be provided to the TGA when available or provide compelling justification as to why such activity is not required. The sponsor should address this matter to the TGA's satisfaction preferably before this application is approved.

The sponsor subsequently provided a revised RMP, version 2.0, dated 02 September 2013. This version did not fully address previous undertakings in relation to the above issues. Consequently, the RMP evaluator recommended to the Delegate that:

- if this application is approved the following specific conditions of registration should be applied:
  - The Risk Management Plan for Australia identified as Version: 2.0, dated 2 September 2013, to be revised as specified in the sponsor's correspondence dated 14 June 2011 and 18 December 2012, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Viread (TDF) 300 mg tablet is currently registered in Australia for the following indications:

> *"Viread in combination with other antiretroviral agents is indicated for the treatment of HIV infected adults and paediatric patients 12 years of age and older.*
>
> *Viread is indicated for the treatment of chronic hepatitis B in adults."*

In the current application, the sponsor seeks the extension of indication to include the treatment of CHB in paediatric patients 12 years of age and older.

The proposed dose regimen for the treatment of paediatric CHB patients (≥12 years) is 300 mg (one tablet) once daily, which is the same as the currently registered dose regimen for the treatment of HIV-infected adults and paediatric patients ≥ 12 years of age.

The extension of indication to include the treatment of paediatric CHB patients (≥12 years) had been submitted to the EMA in 2011and to the FDA in 2012, respectively. Both applications were still under evaluation at the time of TGA submission. The FDA has since approved the extension of indication to include the treatment of chronic hepatitis B in paediatric patients 12 years of age and older. In the EU, Viread 245 mg film-coated tablets were approved *for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with: Compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and / or fibrosis.*

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

One pivotal study with Week 72 virology report (Study GS-US-174-0115) is submitted to support this application. The study is ongoing with an open-label phase for up to a total of 4 years.

Study GS-US-174-0115 (Study 0115)

Study 0115 was a randomised, double-blind, placebo-controlled, multi-centre study. The primary objective of the study was to compare the efficacy and safety of TDF 300 mg once daily (OD) versus placebo OD in adolescents with CHB infection. The secondary objectives were to evaluate the biochemical and serological responses to TDF versus placebo and to evaluate the incidence of drug resistance mutations.

The subjects enrolled in this study were adolescent (12-17 years of age) with HBeAg-positive, or HBeAg-negative chronic HBV infection, weighing ≥ 35 kg, with HBV DNA ≥ 100000 copies/mL, with creatinine clearance ≥ 80 mL/min/1.73 m^2, and either ALT ≥ 2 × upper limit normal (ULN) at screening or any history of ALT ≥ 2 × ULN over the past 24 months.

Subjects had to be naïve to TDF, but could have received interferon or any other non-TDF containing oral anti-HBV nucleoside or nucleotide therapy. Subjects receiving interferon had to have discontinued interferon ≥ 6 months prior to screening, while subjects on anti-HBV nucleoside or nucleotide therapy had to have discontinued therapy ≥ 16 weeks prior to screening, in order to avoid hepatitis flare if they were randomised to the placebo group. Subjects had to have been without serological evidence of co-infection with HIV, hepatitis C virus, or hepatitis D virus. Subjects with a history of significant bone or renal disease, de-compensated liver disease, or evidence of hepatocellular carcinoma (or α-fetoprotein> 50 ng/mL), and pregnant or breast-feeding females were not eligible for the study.

The primary efficacy endpoint was HBV DNA < 400 copies/mL at Week 72. Secondary endpoints were evaluated for Weeks 48 and 72 and are listed in the clinical evaluation report (CER; see AusPAR Attachment 2).

Subjects were randomised in a 1:1 ratio to TDF 300 mg OD or matching placebo OD. After 72 weeks of blinded randomised treatment, subjects could switch to open-label TDF for an additional 2.5 years (120 weeks). The clinical study report (CSR) submitted for this application presents only the results for the 72 week double-blind phase.

Pharmacokinetics analysis

Pharmacokinetics evaluations of this study showed that the PK parameters of tenofovir in the adolescent subjects receiving TDF 300 mg daily were generally comparable with the historical PK data from the HIV-infected adolescents and adults.

Efficacy analysis

Out of 149 subjects screened, 106 subjects were randomised and treated (52 and 54 subjects in the TDF and placebo groups, respectively). A total of 101 subjects (51 in the TDF group and 50 in the placebo group) completed the double-blind period through Week 72. Efficacy analyses were performed on the Full Analysis Set (FAS), which included all randomised subjects who had received at least 1 dose of study drug (that is, TDF 300 mg or matching placebo). The baseline demographic and disease characteristics of the study population were comparable between the two treatment groups.

- Hepatitis B virus DNA
  - The primary efficacy endpoint was the proportion of subjects with HBV DNA < 400 copies/mL at the end of double-blind treatment (Week 72). At Week 72, the

proportion of subjects with HBV DNA < 400 copies/mL was significantly higher in the TDF group (88.5%, 46/52) compared to the placebo group (0%, 0/54; p<0.001).

- The proportion of subjects with HBV DNA below the LLoQ for the PCR assay of 169 copies/mL at Week 72 was also higher in the TDF group (84.6% versus 0.0%; p < 0.001). The mean change from baseline in HBV DNA levels at Week 72 was -5.36 log_{10} copies/mL in the TDF group compared with -0.92 log_{10} copies/mL in the placebo group. The proportions of TDF-treated subjects with HBV DNA < 400 copies/mL and < 169 copies/mL increased from baseline to Week 48 and then was maintained through to Week 72. The mean change from baseline in HBV DNA levels in the TDF group also showed the same trend over time from baseline to Week 72.
- The virological response rates in this study through Week 48 were generally comparable with the observed virological response rates in the adult CHB subjects in the [previously evaluated] Phase III studies (Studies GS-US-174-0102 and GS-US-174-0103).

· Alanine transaminase levels

- The proportion of subjects with normal ALT at Week 72 was significantly higher in the TDF group compared to the placebo group (76.9% versus 38.9%; p<0.001), as was the proportion of subjects with abnormal ALT at baseline and whose ALT normalised at Week 72 (74.3% versus 31.0%; p < 0.001). Mean ALT change from baseline at Week 72 was -58 U/L in the TDF group and -13 U/L in the placebo group. The proportion of TDF- treated subjects with normal ALT and with normalised ALT increased from baseline to Week 16 and then was maintained through to Week 72. The mean change from baseline in ALT levels in the TDF group also showed the same trend over time from baseline to Week 72. Results for the proportion of subjects with normal ALT at Week 72 were consistent across the age subgroups (80.0% in the age subgroup of 12 to 14 years versus 76.2% in the age subgroup of 15 to 17 years). However, the proportion of subjects with normalised ALT at Week 72 was numerically higher in the age subgroup of 12 to 14 years (85.7%; 6/7) than in the age subgroup of 15 to 17 years (71.4%; 20/28).
- The biochemical response rates through Week 48 in this study were generally comparable with those of the adult CHB subjects treated with TDF in two Phase III studies (Studies GS-US-174-0102 and GS-US-174-0103).

· Serological responses (Hepatitis B early antigen loss or seroconversion; Hepatitis B surface antigen loss or seroconversion)

- The difference between the TDF and the placebo groups in the proportion of subjects who were HBeAg positive at baseline and who then experienced HBeAg loss or seroconversion to anti-HBe by Week 72 was not statistically significant. All subjects were HBsAg positive at baseline, but overall, only two subjects (both in the TDF group) experienced HBsAg loss, one of whom experienced both HBsAg loss and seroconversion to anti-HBs at Weeks 64 and 72.

· Composite endpoints

- Various composite endpoints of HBV DNA < 400 copies/mL and normal or normalised ALT with/without HBeAg loss or HBeAg seroconversion all yielded statistically significant difference between the TDF and the placebo group, in favour of the TDF group. The results of the composite endpoints were largely driven by that of the component of HBV DNA < 400 copies/mL.

Efficacy in subgroups

Subgroup analyses of the endpoints of HBV DNA < 400 copies/mL, HBV DNA < 169 copies/mL, normalised ALT (in subjects with abnormal ALT at study baseline), and HBsAg loss and seroconversion were performed on subpopulations of interest (12 to 14 years old versus 15 to 17 years old, subjects with normal versus those with abnormal baseline ALT, subjects with positive baseline HBeAg versus those with negative baseline HBeAg, and treatment-experienced with oral HBV medications versus treatment-naive). However, the event rates of the efficacy endpoint of HBsAg loss and seroconversion were too small for any subgroup analyses to be meaningful. In addition, the subgroup of subjects with baseline HBeAg negative was too small (n = 4 in TDF group, n = 6 in placebo group) for meaningful interpretation.

Analyses of the specified endpoints in the age subgroups showed that the proportions of subjects with HBV DNA < 400 copies/mL, and HBV DNA < 169 copies/mL were similar between the two age subgroups within the TDF group. At Week 72 the proportions of subjects with HBV DNA < 400 copies/mL were 90.0% (9/10) in the 12 to 14 years old and 88.1% (37/42) in the 15 to 17 years old, while the proportions of subjects with HBV DNA < 169 copies/mL were 90.0% (9/10) and 83.3% (35/42), respectively. At Week 72 the proportions of subjects with normalised ALT were numerically higher in the 12 to 14 years (85.7%; 6/7) than in the 15 to 17 years (71.4%; 20/28. No statistical analyses were applied to these results. Interpretation of these results is limited by the small number of subjects included in these analyses, with only 10 subjects in the 12 to 14 years.

The percentages of TDF-treated subjects with HBV DNA < 400 copies/mL and with HBV DNA < 169 copies/mL at Week 72 were greater in subjects with baseline abnormal ALT compared to those with baseline normal ALT (HBV DNA < 400 copies/mL:97.1% versus 70.6%, HBV DNA < 169 copies/mL: 94.3% versus 64.7%). The percentages of TDF-treated subjects with HBV DNA < 400 copies/mL and with HBV DNA < 169 copies/mL at Week 72 were also greater in subjects without prior oral HBV medications compared to those with prior oral HBV medications (HBV DNA < 400 copies/mL: 95.0% versus 84.4%, HBV DNA < 169 copies/mL: 95.0% versus 78.2%).

Genotypic analysis

Genotypic analysis showed that virologic response to TDF of the 6 subjects in the TDF group who had LAM resistance–associated mutations at baseline was comparable to that of the remaining 46 subjects in the TDF group without these mutations. In addition, the majority (4 out of the 6) of these TDF-treated subjects with baseline LAM resistance-associated mutations achieved HBV DNA < 400 copies/mL at Week 48 and maintained this through Week 72, while an additional 1 subject achieved HBV DNA < 400 copies/mL at Week 72.

The majority of subjects (5 out of 6 subjects) that qualified for genotypic analysis at Week 48 (that is, had HBV DNA > 400 copies/mL) had not experienced virologic breakthrough. At Week 72, 3 out of the 5 subjects that qualified for genotypic analysis had confirmed virologic breakthrough and 1 subject had unconfirmed virologic breakthrough. However, all 4 instances of viral breakthrough were associated with probable non-adherence to study drug (TDF) as determined by tenofovir plasma levels below the limit of quantification. Phenotypic analyses of 1 subject that qualified for phenotypic testing at Week 48 and 3 subjects that qualified for phenotypic testing at Week 72 showed that no resistance to tenofovir had developed among these subjects.

Overall, no patients had TDF resistance-associated mutation through week 72 in this study. TDF showed a high genetic barrier to resistance development in children as it was observed for adults.

Safety analysis

From Study GS-US-174-0115, the incidences of all-causality AEs and of treatment-related AEs were comparable between the two treatment groups. The incidences of grade 3 or 4 all-causality AEs, grade 3 or 4 treatment-related AEs, all-causality SAEs and treatment-related SAEs were lower in the TDF group compared to the placebo group. The safety results of the study were consistent with the known adverse effects of TDF.

Potential liver toxicity: the incidence of on-treatment hepatic flares based on clinical laboratory criteria was lower in the TDF group compared to that in the placebo group (3.8% versus 18.5%), as was the incidence of hepatic flares reported as grade 3 or 4 AEs (3.8% versus 22.2%), the incidence of hepatitis reported as an AE (5.8% versus 13.0%), and the incidence of increased ALT reported as an AE (5.8% versus 22.2%). In addition, no subjects in the TDF group had prothrombin time, a test of liver function, above the upper limit normal.

Potential renal toxicity: no TDF-treated subjects had a grade 3 or 4 increases in serum creatinine or decrease in serum phosphorus, a confirmed increase from baseline in serum creatinine concentration of at least 0.5 mg/dL, a confirmed creatinine clearance rate of < 50 mL/min, or a confirmed serum phosphorus concentration < 2 mg/dL. The mean change in creatinine from baseline to Week 72 was small and similar between the TDF and placebo groups (0.1 mg/dL in both TDF and placebo groups), and no subject in the TDF group had renal and urinary disorders AEs (compared with 3 subjects in the placebo group who had).

Potential bone toxicity: there was no statistically significant difference between TDF and placebo in mean change from baseline for the biochemical markers of bone formation (serum osteocalcin and bone specific ALP) and bone reabsorption (N- and C-telopeptides), as well as for serum PTH and 25-hydroxy vitamin D levels. There was also no statistically significant difference between TDF and placebo in the incidence of bone AEs in Study GS-US-174-0115. The percent increase from baseline of mean lumbar spine BMD whole body BMD and in the TDF-treated subjects was statistically significantly less than that in the placebo subjects at Weeks 24, 48, 72 (whole body BMD only at Week 72). In addition, there was a decrease of 0.05 in mean lumbar spine BMD Z-scores from baseline in the TDF group at Week 72 compared to an increase of 0.07 from baseline in the placebo group, and a decrease of 0.15 in mean whole body BMD Z-scores from baseline in the TDF group at Week 72 compared to an increase of 0.06 in the placebo group. However, these mean decreases from baseline in the lumbar spine and whole body BMD Z-scores in the TDF group were small, and results showed that at Week 72, only 2 subjects in the TDF group had lumbar spine BMD Z-scores or whole body BMD Z-scores of < -2, and the majority of the subjects (approximately 66%) had lumbar spine BMD Z-scores or whole body BMD Z-scores of above -1 at Week 72.

Potential effects on growth (height, weight, BMI): Weight and BMI Z-scores were statistically significantly more decreased from baseline in the TDF group compared to the placebo group at a majority of timepoints. At Week 72, BMI Z-score was statistically significantly more decreased from baseline in the TDF group compared to the placebo group. In addition, results also showed that there appeared to be a trend of decreasing mean weight and BMI Z-scores with time from baseline through to Week 72 in the TDF-treated subjects. It is noted that in the TDF group, from baseline through to Week 72, the maximum decrease from baseline in mean weight Z scores (0.20) and in mean BMI Z-scores (0.30) were small and not likely to be clinically significant. It is noted that the maximum decreases from baseline in mean weight Z scores and mean BMI Z-scores in the TDF group were small. Weight Z-scores and BMI Z-scores of <-2 between -2 and -1 and >-1 are provided in response to section 31 and no statistical differences in either BMI Z-score or Weight Z-score were observed between TDF and placebo groups considering the 3 categories analysed.

Clinical evaluator's recommendation

The clinical evaluator is of the view that the benefit-risk balance of TDF, given the proposed usage, is favourable. The clinical evaluator recommends the registration approval for the extension of indication to include *'treatment of CHB in paediatric patients 12 years of age and older'*.

Risk management plan

The RMP Version 2.0 dated 10 May 2012 has been evaluated by the OPR evaluator. The evaluator has made five recommendations. The one outstanding issue stated in the RMP evaluation report is reiterated below:

"The sponsor should update the AU-RMP with details of the previously accepted risk minimisation plan proposed for the HIV paediatric indication, as provided in the sponsor's correspondence dated 14 June 2011. Copies of the printed educational materials associated with these additional risk minimisation activities should also be included in the revised AU-RMP as an annex. The sponsor must definitively state whether similar additional risk minimisation activities will be proposed for the HBV paediatric indication and provide an assurance that copies of the associated printed educational materials will be provided to the TGA when available or provide compelling justification as to why such activity is not required. The sponsor should address this matter to the TGA's satisfaction preferably before this application is approved."

Risk-benefit analysis

Delegate considerations

The efficacy of TDF has been established in adult CHB patients. In the submitted paediatric study (GS-US-174-0115), the primary and secondary endpoints allowed evaluation of virological response, biochemical response, serological response, and combined responses of virological, biochemical and serological responses. Study 0115 demonstrated the superiority of TDF over placebo on the proportion of patients who achieved HBV DNA <400 copies/mL and the proportion of patients who achieved HBV DNA <169 copies/mL. The benefit of TDF over placebo was also demonstrated for many of the secondary endpoints. However, no statistically significant differences were observed between the two groups in the incidences of HBeAg loss or seroconversion, and of HBsAg loss or seroconversion.

It is noted that no liver biopsy was performed before the subjects were included in this study. The ALT criterion for inclusion was not considered stringent, as it allowed inclusion of patients with ALT ≥ 2 × ULN at screening or any history of ALT ≥ 2 × ULN over the past ≤ 24 months. The EMA's Committee for Medicinal Products for Human Use (CHMP) raised doubts about the study population. The sponsor addressed these concerns and provided an *ad hoc* analysis based on the ALT level at baseline. Two subgroups were identified: an Immune Active (IA) subgroup (baseline ALT > 1.5 × ULN) and an Immune Tolerant (IT) subgroup (baseline ALT ≤ 1.5 × ULN). In the IA and IT subgroups that were treated with TDF, viral suppression was demonstrated at Week 72 in comparison to placebo group (96.4% TDF IA versus 0% in Placebo IA, and 79.2% TDF IT versus 0% in Placebo IT group, $p < 0.001$). The IA subjects treated with TDF had a significantly greater biochemical (75% with normal ALT) response in comparison to the Placebo IA group at Week 72. In the IT subgroups, there was a suggestion of a treatment effect on ALT levels. In the TDF IA subgroup, 8/26 (30.8%) subjects experienced HBeAg loss at Week 72 compared with 4/32 (12.5%) subjects in the Placebo IA subgroup ($p = 0.11$). In contrast, in the IT subgroups, 2/22 (9.1%) subjects in the TDF IT subgroup and 3/16 (18.8%) subjects in the Placebo IT

subgroup experienced HBeAg loss at Week 72 (p = 0.63). In the TDF groups, the stringent composite endpoint of HBV DNA < 400 copies/mL, normal ALT and HBeAg loss was achieved in 23% (n = 6) of patients with IA disease versus 4.5% (n=1) in IT patients, which further highlights that the IA population is the population that can most benefit from the treatment.

The safety results of this study are consistent with the known safety profile of TDF. Safety analyses with regards to the potential liver, renal and bone toxicities also yielded results consistent with the known effects of TDF. The results at Week 72 showed a lower increase of total mean lumbar spine BMD and total BMD in the TDF group compared to the placebo group. The decreases in total body BMD Z-scores observed following TDF therapy do not appear to be associated with an increased fracture rate (1 pathological fracture/103 patients treated with TDF).

Compared to the adults, the CHB infection in paediatric patients has a more benign course and a relatively higher annual rate of spontaneous seroconversion. There is therefore a particular need to obtain the robust evidence on the benefit of the treatment and to have reassurance on the safety of the treatment proposed for paediatric CHB patients. The renal and bone toxicity are the special concerns for the long-term use of TDF in paediatric patients who are in evolving bone modelling process. There are currently insufficient information on the long-term effect of TDF on bone modelling and the potential reversibility of bone toxicity. It is acknowledged that there is lack of correlation between BMD and clinical events. Due to the lack of long-term safety data and the difficulties in assessing the clinical relevance of BMD decrease in children, bone toxicity related to TDF remains a particular concern for the use of TDF in paediatric patients.

In this context, the Delegate proposed to include in the *Precautions* section of the PI[8] the following statement:

There are uncertainties associated with the long term effects of bone and renal toxicity in paediatric population. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment.

Proposed action

The Delegate agreed that there is a benefit of TDF treatment for CHB infection in paediatric patients 12 years of age and older with compensated liver disease. In view of the renal and bone toxicity, the Delegate proposed to make a final decision on this application following advice from the Advisory Committee on Prescription Medicines (ACPM) on the issues raised below.

Any approval would be subject to amendments of the Viread PI to the satisfaction of the TGA; and to the implementation of the RMP and its subsequent updates as agreed with the TGA.

Request for ACPM advice

The Delegate sought general advice on this application from the ACPM, and requested the following issues be addressed in particular:

1. The ACPM was asked to comment on the clinical significance of "no difference between TDF and placebo group on the serological endpoints" observed in the submitted study;

[8] Other revisions to product literature proposed by the Delegate are beyond the scope of the AusPAR.

2. Since CHB infection in paediatric patients has a more benign course and a relatively higher annual rate of spontaneous seroconversion, the ACPM was asked to comment on the benefit of starting TDF treatment in paediatric CHB patients;
3. The ACPM was asked to advise on whether TDF treatment should be limited to the subgroup of paediatric CHB patients who are in the immune active status of the disease;
4. The ACPM was asked to advise on whether the benefit of TDF on virological suppression outweighs the risk of renal and bone effects in paediatric CHB patients.

Response from sponsor

Summary

The majority of paediatric patients with HBV do not require treatment; however there are instances where treatment is very beneficial to reduce the risk of chronic liver disease and the decision to treat CHB patients during adolescence must take into account the potential risks as well as the benefits of therapy. Similarly as in adults, the primary treatment objective is to suppress the HBV DNA replication to undetectable limits for as long as possible and reduce liver inflammation. Most paediatric patients remain until late childhood in the IT phase, characterised by high levels of serum HBV DNA, normal or mildly elevated ALT and aspartate aminotransferase (AST), and mild to moderate histological changes seen on biopsy. The IT phase is followed by the immune clearance phase, characterised by fluctuating ALT and HBV DNA levels.

Given the prolonged period of time in the IA phase is associated with an increased risk of cirrhosis and hepatocellular carcinoma, paediatric patients who are in the IA status of the disease benefit the most from treatment. However, the selection of patients that would benefit from this orphan indication should be left to specialist prescribers who are well versed in CHB therapy instead of limiting the patient group to only those in the IA phase. For instance, there will be times when paediatric patients in the IT phase of HBV infection will require treatment to reduce the risk of reactivation of the virus as their immune system is compromised due to other treatments such as chemotherapy.

Based on data from Study GS-US-174-0115, TDF is safe and effective for the treatment of chronic HBV in an adolescent population (12 to 17 years old). Gilead supports the proposed recommendation of the clinical evaluator for registration and appreciates the concerns of the Delegate surrounding bone and renal effects in a paediatric patient group. With regard to renal effects the safety results of the study were consistent with the known safety profile of TDF.

The issue of bone effects in a paediatric group was considered by Gilead during the initial protocol development. Gilead addressed this concern by the inclusion of a primary safety endpoint which compared BMD of the spine between the TDF and placebo groups. The results demonstrated adequate bone safety. Gilead believes that the overall risk can be adequately managed by suitable guidance provided to prescribers in the label and as such accepts the inclusion of a statement in the *Precaution* section of the PI, given below, to further highlight to prescribers the long term effects of bone and renal effects in paediatric population (sponsor-proposed amendments shown as struck-through and normal text).

~~There are uncertainties associated with the~~ clinical relevance of the *long term effects of* tenofovir disoproxil fumarate treatment on BMD are unknown, and at present*~~, bone and renal toxicity in paediatric population. Moreover,~~ the* data on the *reversibility of renal ~~toxicity~~* effects is limited *~~cannot be fully ascertained~~. Therefore, a multidisciplinary approach is recommended to ~~adequately~~* consider *~~weigh on a case by case basis~~ the benefit/risk balance of treatment.*

The remainder of this response is separated into 4 sections to address the Delegates comments under *Request for ACPM advice.*

Discussion of Delegate's comments

(1) The ACPM was asked to comment on the clinical significance of "no difference between TDF and placebo group on the serological endpoints" observed in the submitted study.

The pivotal study (Study GS-US-174-0115) in this orphan population was small and not powered to be able to demonstrate a significant difference in the serological endpoints of HBeAg or HBsAg loss or seroconversion. The European *Guideline on the clinical evaluation of medicinal products intended for treatment of hepatitis B* (CHMP/EWP/6172/03), also adopted in Australia, states that due to the nature of nucleot(s)ide analogues, the use of HBeAg seroconversion to judge clinical efficacy is untenable and other measures should be used. These guidelines also state that the HBeAg conversion rates in paediatrics can be very variable.

At Week 72, 10/48 (20.8%) subjects treated with TDF experienced HBeAg loss compared with 7/48 (14.6%) placebo subjects (p = 0.41; DBEE analysis).

When evaluated by IA status, differences were observed between TDF and placebo. In the TDF IA subgroup, 8/26 (30.8%) subjects experienced HBeAg loss at Week 72 compared with 4/32 (12.5%) subjects in the placebo IA subgroup (p = 0.11). In contrast, in the IT subgroups, 2/22 (9.1%) subjects in the TDF IT subgroup and 3/16 (18.8%) subjects in the placebo IT subgroup experienced HBeAg loss at Week 72 (p = 0.63). Identical results were observed when the IA and IT subgroups were evaluated for HBeAg seroconversion to anti-HBe.

Although only a trend toward statistical significance was demonstrated, the rate of HBeAg loss with TDF (30.8%) is higher than previously reported rates in paediatric/adolescent HBV subjects treated with lamivudine (26.0%,) and adefovir dipivoxil (16.8%), indicating a treatment effect with TDF in IA subjects. Gilead does not believe there is any clinical significance between the observed lack of difference between TDF and placebo for serological response as the natural history of CHB infection in children is variable and spontaneous seroconversion can occur in many during the first two decades of life.

(2) Since Chronic Hepatitis B infection in paediatric patients has a more benign course and relatively higher annual rate of spontaneous seroconversion, the ACPM was asked to comment on the benefit of starting TDF treatment in paediatric patients.

The decision to treat CHB patients during early childhood or adolescence must take into account the potential risks as well as the benefits of therapy.

Most HBeAg-positive children with CHB are "immune tolerant," that is, HBV DNA levels > 20,000 IU/mL (> 10^5 copies/mL) and normal ALT levels. In contrast, HBeAg-positive paediatric patients who are immune active with elevated HBV DNA levels and marked elevations in ALT indicative of ongoing necroinflammation in the liver could benefit from treatment.

The 2006 CHMP guideline on the *Clinical Evaluation of Medicinal Products Intended for Treatment of Hepatitis B* recognise the importance of treating paediatric patients in the IA phase. More recently, an expert panel of paediatric liver specialists convened and has addressed treatment-related questions.[9] The recommendation of the panel, based on published data from prospective, randomised, placebo-controlled trials in paediatric patients with CHB treated with first generation antiviral agents (interferon, lamivudine

[9] Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, *et al*. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. *Hepatology* 2010;52(6):2192-205.

and adefovir) is to treat those who are in the IA phase and who have elevated levels of HBV DNA and ALT values >1.5 times the ULN.

Based on the panel's recommendation, Gilead has further analysed the data by subgroups categorised as immune active (IA: baseline ALT > 1.5 × ULN), and immune tolerant (IT: baseline ALT ≤ 1.5 × ULN). When biochemical responses were evaluated by IA status, a clear treatment effect with TDF on the percentage of subjects with normal ALT levels was demonstrated. Furthermore, when serological response (HBeAg loss and seroconversion) was evaluated in the IA subgroup, the impact of TDF on HBeAg loss (and seroconversion) is more clearly delineated relative to placebo.

Given that paediatric patients with HBV are clearly at risk of progressive liver disease, Gilead strongly believes there is benefit to starting TDF treatment in clinically selected paediatric patients to minimise any risk for end stage liver disease as cirrhosis and hepatocellular carcinoma. There is an unmet medical need for new therapies for CHB for children in Australia to maintain chronic suppression of viral replication whilst at the same time having a high genetic barrier to the development of resistance, and Viread could fill this medical need for adolescents with active CHB. The selection of patients that are appropriate for treatment with this efficacious treatment option should be left in the hands of prescribers versed in assessing the need for treatment in HBV infected patients.

(3) The ACPM was asked to advise on whether TDF treatment should be limited to the subgroup of paediatric CHB patients who are in the immune active status of the disease.

Specialists prescribing Section 100 (s100[10]) medications are currently well versed in when CHB therapy should be initiated in patients with HBV infection. Gilead appreciates that those paediatric (and adult) patients who are in the IA status of the disease will benefit the greatest from the use of anti-HBV treatment. However there will be instances in IT patients where treatment is clearly warranted. For example, paediatric patients having chemotherapy treatment who are currently in the IT phase would appropriately be prescribed Viread as a prophylaxis to prevent reactivation of the virus during their treatment. Accordingly, Gilead does not believe that TDF treatment should be limited to only those paediatric CHB patients who are in the IA status of the disease. Gilead does not advise limiting an indicated patient population in such a specialist area of treatment as it may have unintended consequences of denying on-label treatment to patients that would likely benefit and in whom safety and efficacy have been appropriately demonstrated.

(4) The ACPM was asked to advise on whether the benefit of TDF on virological suppression outweighs the risk of renal and bone effects in paediatric CHB patients.

- Renal effects

Rare events of renal dysfunction, specifically renal tubular dysfunction, and one of the manifestations of solute loss, hypophosphatemia, have been reported in adult patients receiving TDF in clinical practice. Through 72 weeks, no subjects randomised to TDF had a confirmed decrease in serum phosphate < 2.0 mg/dL and no TDF-treated subjects had evidence of proximal tubulopathy.

Changes in serum creatinine from the baseline at Week 72 were also evaluated for both treatment groups and no clear differences were observed. Over 72 weeks, no subjects in either treatment group had a confirmed (upon re-test) increase of ≥ 0.5 mg/dL in serum creatinine above the baseline value.

[10] The Australian Government provides funding for certain specialised medications under the Highly Specialised Drugs Program (Section 100 program). 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 through public and private hospitals having access to appropriate specialist facilities.

No subject in either group had a confirmed decrease in glomerular filtration rate as estimated by creatinine clearance below 80 mL/min/1.73 m^2.

In summary, through 72 weeks of treatment, there was no clear signal to suggest clinically relevant renal toxicity with TDF in adolescent subjects with CHB.

· Bone effects

Given that adolescents are actively growing and have not yet reached peak bone mass, change in BMD results (g/cm^2) or % change in BMD results are difficult to interpret in terms of clinical relevance in this patient population. While the T-score [for BMD] is a validated measure in older adults for predicting risk of osteoporosis, the T-score is not optimal in this population as it compares individual patient BMD results to a young, healthy adult who has achieved peak bone mass. Thus, Z-scores were used for assessing bone changes in adolescent HBV subjects over time since this methodology is age and sex matched and has validated references in adolescents. The Z-score is also considered the optimal comparative measure in paediatric patients by the International Society for Clinical Densitometry (ISCD). In general, a Z-score of ≤ -2 is considered by the ISCD to be an indication of low BMD. For purposes of data analyses, however, a conservative cut-off of -1.5 was used to identify the subjects with the lowest Z-scores to compare TDF data to placebo.

Overall, the distribution of individual Z-scores is similar between TDF and placebo subjects with the majority of subjects having Z-scores above -1.5 at Week 72. There were a small number of subjects (2 placebo and 3 TDF) who had Z-scores ≤ -1.5 at both baseline and Week 72, and a small number of subjects (2 placebo and 1 TDF) who had baseline Z-scores above -1.5 and who then shifted to a Z score ≤ -1.5 at Week 72. In summary, at Week 72 there were equal numbers of subjects in each treatment group (4 placebo and 4 TDF) who had Z scores ≤ -1.5.

One bone fracture was reported in the study during the double-blind phase. A Subject (age group 12 to 14 years) in the TDF group had a grade 3 fracture of the left hand forefinger sustained in an altercation on Day 406. The event was reported as a serious AE because it required fracture reduction and osteosynthesis, but was not considered related to study drug, and was resolved by Day 448. The subject was accruing BMD and BMD Z-scores were increased from baseline (spine BMD Z-scores were -1.15 at baseline and -0.97 on Day 337; total body BMD Z-scores were -0.79 at baseline, -0.52 on Day 337, and -0.03 on Day 390). The subject remained in the study with no interruption to study drug administration.

In summary, these data do not clearly demonstrate an obvious signal of a deleterious effect of TDF on BMD or gross skeletal growth in adolescent subjects with CHB who are treated for 72 weeks. Long-term follow up of these subjects is planned until Week 192.

In conclusion results of GS-US-174-0115 were consistent with the known safety profile of Viread and did not raise any new safety concerns. The renal and bone toxicity effects of tenofovir are well documented within the approved Viread PI. Gilead accepts the inclusion of a statement given below in the *Precautions* section of the PI to further educate prescribers, who are well versed on when to initiate CHB therapy and, on the long term effects of bone and renal effects in paediatric population:

~~There are uncertainties associated with the~~ clinical relevance of the *long term effects of* tenofovir disoproxil fumarate treatment on BMD are unknown, and at present*~~, bone and renal toxicity in paediatric population. Moreover,~~ the* data on the *reversibility of renal ~~toxicity~~* effects is limited *~~cannot be fully ascertained~~. Therefore, a multidisciplinary approach is recommended to ~~adequately~~* consider *~~weigh on a case by case basis~~ the benefit/risk balance of treatment.*

Gilead strongly believes that the benefit of TDF on virological suppression for paediatric patients outweighs any risk of renal and bone effects, as the safety results shown were consistent with the known safety profile of TDF and no new safety concerns were raised during this study.

Conclusion

Viread has been available since 2008 for use in CHB infected adults. The Phase III study provided in this application demonstrated efficacy and safety in adolescent patients (aged 12 to 17), whilst the ongoing widespread use of TDF in adults provides supportive safety and virological evidence. There is a clear need for alternative therapies for paediatric patients with HBV infection.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy and safety, agreed with the delegate and considered Viread (containing tenofovir disoproxil fumarate) to have an overall positive benefit–risk profile for the indication;

> *Viread is indicated for the treatment of chronic hepatitis B in adults and in paediatric patients 12 years of age and older with compensated liver disease and with evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels or evidence of active inflammation*

The ACPM agreed with the Delegate that there is a benefit from Viread treatment for CHB infection in paediatric patients 12 years of age and older with compensated liver disease. The ACPM shared the Delegate's concern for paediatric and adolescent patient populations in view of their particular vulnerability to renal and bone toxicity. The ACPM advised lack of long term safety data on the effects of tenofovir disoproxil fumarate treatment alters the benefit-risk balance for long term use to negative for this population.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Implementation of the RMP as agreed with the TGA and its subsequent updates.
- Amendments of the Product Information to the satisfaction of the TGA.

Proposed PI/CMI amendments

The ACPM advised that the amendments to the PI and CMI should include the following:

- A statement in the PI and relevant sections of the CMI suitably stressing the importance of clinical monitoring for active disease.
- Statements in the *Clinical Trials* section of the PI and relevant sections of the CMI to reflect the duration of treatment tested and immune states of the study population.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Viread containing tenofovir disoproxil fumarate 300 mg tablet for the new indication:

VIREAD is indicated for the treatment of chronic hepatitis B in paediatric patients 12 years of age and older with compensated liver disease and with evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels or evidence of active inflammation.

The full indications are now:

VIREAD in combination with other antiretroviral agents is indicated for the treatment of HIV-infected adult and paediatric patients 12 years of age and older.

VIREAD is indicated for the treatment of chronic hepatitis B in adults (see CLINICAL TRIALS).

VIREAD is indicated for the treatment of chronic hepatitis B in paediatric patients 12 years of age and older with compensated liver disease and with evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels or evidence of active inflammation.

Specific conditions applying to this therapeutic good

The Viread (tenofovir disoproxil fumarate) 300 mg Risk Management Plan (RMP), version 2.0, dated 02 September 2013 and to be revised as specified in the correspondence dated 14 June 2011 and 18 December 2012, included with submission PM-2012-01178-3-2, and any subsequent revisions, as agreed with the TGA must be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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