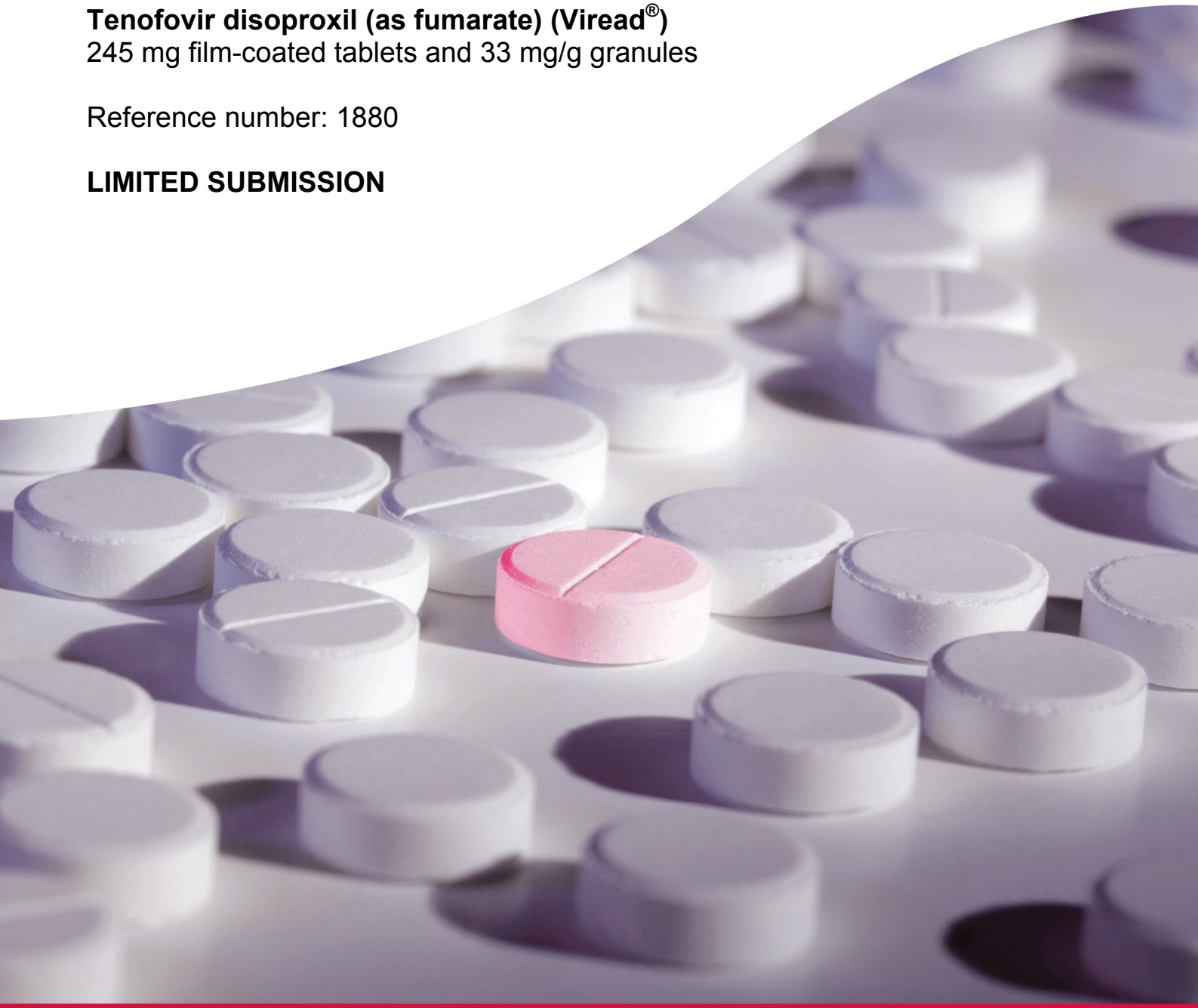
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Tenofovir disoproxil (as fumarate) (Viread®)
245 mg film-coated tablets and 33 mg/g granules

Reference number: 1880

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Tenofovir disoproxil (as fumarate) (Viread®)
245 mg film-coated tablets and 33 mg/g granules

This assessment report is based on evidence from a limited submission by Gilead Sciences Ltd on 3 April 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Tenofovir disoproxil (as fumarate) 245 mg film-coated tablets and 33 mg/g granules (when a solid dosage form is not appropriate) for the treatment of chronic hepatitis B in adolescents 12 to < 18 years with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and/or fibrosis. Refer to the Summaries of Product Characteristics (SPCs) for tablets[2] and granules[3] for further details.
Marketing authorisation date	22 November 2012[4] (tenofovir disoproxil 245 mg tablets were originally licensed for treatment of chronic hepatitis B in adults on 23 April 2008)[4].
Comparators	The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were adefovir (Hepsera®) and lamivudine (Zeffix®).
Limited submission details	Tenofovir disoproxil for the above indication met the following criteria for eligibility for a limited submission: • Significant new formulation which has a pro-rata or lower cost per treatment. • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes pharmacokinetic data for the 33 mg/g granule and 245 mg tablet formulations in HIV-1 infected children and adolescents and a clinical trial, GS-US-174-0115 of tenofovir disoproxil for the treatment of chronic hepatitis B in adolescents[1]. The SPCs note that tenofovir disoproxil exposure in HIV-1 infected adolescent and paediatric patients, receiving oral daily doses of 245 mg tablets or 6.5 mg/kg body weight as granules, was similar to the exposure achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg tablets[2,3]. Tenofovir disoproxil exposure in adolescents with chronic hepatitis B receiving a daily dose of 245 mg was similar to exposures achieved in adults receiving once-daily doses of 245 mg[2,3]. In support of the granules, the Committee for Medicinal Products for Human Use (CHMP) notes that in a bioequivalence study comparing the 245 mg tablet and the granules in healthy adults, the bioequivalence criteria were met for the area under the curve of plasma concentration versus time[5].

2.1 Clinical evidence

Study GS-US-174-0115 was a randomised, double-blind, placebo-controlled 72 week, phase III trial in 106 adolescents, aged 12–17 years, weighing ≥ 35 kg with chronic hepatitis B [6,7]. Patients received either tenofovir disoproxil 245 mg tablets once daily (n = 52) or placebo once daily (n = 54). The majority (85%) of patients had previously received at least one hepatitis B treatment and most patients were positive for both hepatitis B early antigen (HBeAg) and hepatitis B surface antigen. The primary endpoint, the proportion of patients with hepatitis B virus DNA < 400 copies/ml at week 72, was met in 46 patients (89%) treated with tenofovir disoproxil and zero patients (0%) treated with placebo (p<0.001). The mean whole body bone mineral density increase from baseline was 2.84% for patients in the tenofovir disoproxil arm versus 5.37% for patients in the placebo arm. The mean percentage increase from baseline in lumbar spine bone mineral density was 4.95% for patients receiving tenofovir disoproxil and 8.14% for patients receiving placebo at week 72.

2.2 Points to note

- The company stated that adefovir and lamivudine are not appropriate comparators as neither are licensed for the treatment of chronic hepatitis B in adolescents[8,9].
- In adults, tenofovir disoproxil (in addition to entecavir) has become a standard of care for the treatment of chronic hepatitis B, due to its potency and high genetic barrier (no emerging resistance at 5 years). It is expected to show similar efficacy in adolescents[6].
- In study GS-US-174-0115 CHMP observed that tenofovir disoproxil displayed striking superiority versus placebo in increasing the proportion of patients with hepatitis B DNA < 400 copies/ml; however this was not translated into a significant difference in HBeAg seroconversion rate, which illustrated the need for life long treatment for the vast majority of adolescents[6].
- Although renal and bone toxicity during long term use of tenofovir disoproxil is a concern in adults; it is of particular concern in adolescents given that they are in an evolving bone modelling process. The impact of bone toxicity remains a theoretical risk given the lack of correlation between reduced bone mineral density and clinical events[6]. The SPCs were revised to alert physicians to uncertainties in the long term effects of bone and renal toxicities and that the reversibility of renal toxicity cannot be fully ascertained[2,3]. Further studies are included in the risk management plan to help address concerns regarding long term efficacy and safety[6].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company estimates that less than five patients per annum will be eligible for treatment. This is based on Welsh experts' opinion. The company reports that the oral granules are priced at parity on a per mg basis with the currently available 245 mg film-coated tablets. Based on dosage equivalence for adults and adolescents with body weight ≥ 35 kg, the company estimates that using the oral granules would cost the same as the 245 mg film-coated tablets with annual cost per patient estimated to be £2,926[1].

3.2 AWTTC critique of the budget impact analysis

- Based on the company's submission, tenofovir disoproxil 33 mg/g oral granules are priced at parity with 245 mg tablets, which represents the maximum recommended daily dose in the target patient group[1].
- The number of eligible patients reported by the company is based on the opinion of two experts from South Wales[1].

3.3 Comparative unit costs

Table 1. Examples of acquisition costs for tenofovir disoproxil formulations

Treatment	Example daily dose	Example annual cost of treatment per patient
Tenofovir disoproxil (Viread®) oral granules 33 mg/g	Age 12 years and over (with difficulty swallowing oral tablets): max 245 mg (7.5 scoops) daily	£2,926
Tenofovir disoproxil (Viread®) film-coated tablets 245 mg	Adults: 245 mg daily with food	£2,926
Doses need to be individually tailored based on patient body weight. *Costs are based on MIMS list prices[10] as of 11/04/2013 and average body weight range of 39 kg to 46 kg for children and adolescents aged 12 years and over[11].* *See the Summaries of Product Characteristics for licensed indications and full dosing details[2,3].*		

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that if recommended for the indication under consideration, tenofovir disoproxil is appropriate for specialist only prescribing within NHS Wales.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 14 March 2013.
Date range of evidence search: No date limits were applied to database searches.

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