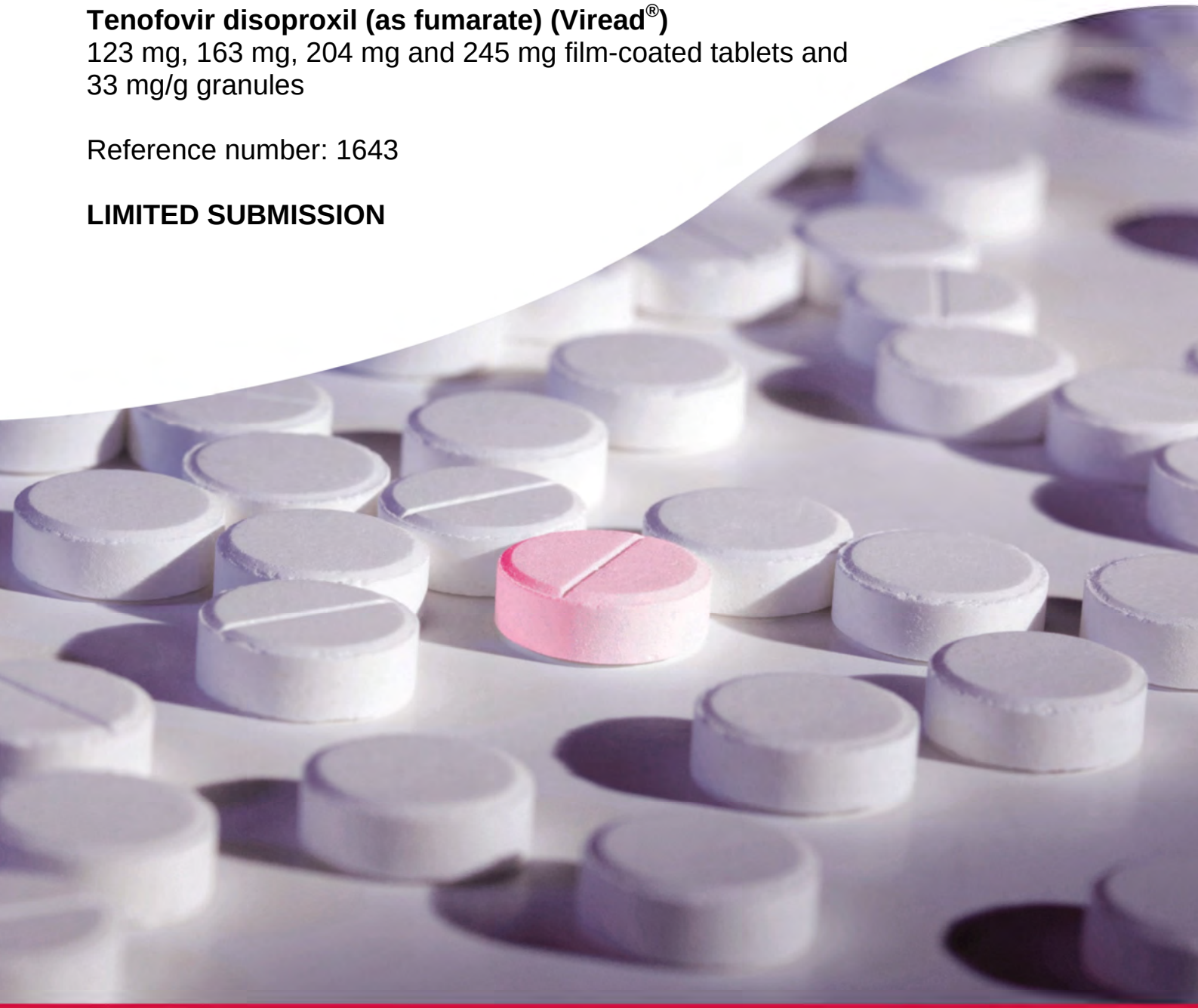
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Tenofovir disoproxil (as fumarate) (Viread®)
123 mg, 163 mg, 204 mg and 245 mg film-coated tablets and 33 mg/g granules

Reference number: 1643

LIMITED SUBMISSION



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

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AWMSG Secretariat Assessment Report
Tenofovir disoproxil (as fumarate) (Viread®) 123 mg, 163 mg, 204 mg and 245 mg film-coated tablets and 33 mg/g granules

This assessment report is based on evidence from two limited submissions (one for tablets[1] and one for granules[2]) by Gilead Sciences Ltd on 22 March 2013.

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Tenofovir disoproxil (as fumarate) film-coated tablets in combination with other antiretroviral medicinal products for the treatment of HIV-1-infected adolescent and paediatric patients, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years (245 mg tablets) and aged 6 to < 12 years who weigh from 17 kg to less than 22 kg (123 mg tablets), 22 kg to less than 28 kg (163 mg tablets) and 28 kg to less than 35 kg (204 mg tablets). Tenofovir disoproxil (as fumarate) 33 mg/g granules in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected paediatric patients, with NRTI resistance or toxicities precluding the use of first line agents, from 2 to < 6 years of age, and above 6 years of age for whom a solid dosage form is not appropriate. The choice of tenofovir disoproxil to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients. Refer to the Summaries of Product Characteristics (SPCs) of tablets[3–6] and granules[7] for further details.
Marketing authorisation date	22 November 2012[8] (tenofovir disoproxil 245 mg tablets were originally licensed for the treatment of HIV-1 in adults on 5 February 2002)[9].
Comparators	The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were abacavir (Ziagen®) and zidovudine.
Limited submission details	Tenofovir disoproxil tablets and granules 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 submissions include pharmacokinetic data for the 33 mg/g granule and 245 mg tablet formulations in children and adolescents, together with clinical trials of tenofovir disoproxil for the treatment of HIV-1 in children (GS-US-104-352) and in adolescents (GS-US-104-321)[1,2]. The Summaries of Product Characteristics (SPCs) note that tenofovir disoproxil exposure in 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[3–7]. In support of the granules, the Committee for Medicinal Products for Human Use (CHMP) notes that in a bioequivalence study between 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[9].

2.1 Clinical evidence

Study GS-US-104-352 was an open-label, 48 week phase III trial to compare safety and efficacy in 97 patients aged 2 to < 12 years. Patients with stabilised virologic suppression were pre-treated for ≥ 12 weeks with either stavudine or zidovudine containing regimens[1,9]. Subjects were randomised to either replace stavudine or zidovudine with tenofovir disoproxil (n = 48) or continue on their original regimen (n = 49). The primary endpoint was the number and percentage of subjects with HIV-1 RNA concentrations < 400 copies/ml at week 48. During the trial patients continued with their pre-existing highly active antiretroviral therapy. Forty children weighing ≤ 37 kg received tenofovir disoproxil granules and of eight children weighing > 37 kg, five received tenofovir disoproxil 245 mg tablets and three received both tenofovir disoproxil granules and tablets. At week 48, 83% of the patients in the tenofovir disoproxil arm and 92% of patients in the stavudine/zidovudine arm had HIV-1 RNA concentrations < 400 copies/ml and the pre-defined criteria for non-inferiority was not met. The CHMP notes that the difference in the proportion of patients who maintained < 400 copies/ml at week 48 was mainly influenced by the higher number of discontinuations (due to withdrawal of consent and poor adherence) in the tenofovir disoproxil treatment group.

An extension study of GS-US-104-352 in which all subjects (n = 89) were treated with tenofovir disoproxil was used to generate further efficacy and safety data. Four patients discontinued the extension study due to adverse events arising from proximal renal tubulopathy. There was a statistically significant difference in the total body bone mineral density (BMD) change from baseline between tenofovir disoproxil (1.22%) versus stavudine/zidovudine (2.68%), p = 0.043 in the main study at week 48. At 48 weeks there was a modest reduction in total body BMD Z-score in the tenofovir disoproxil group compared to no change in the stavudine/zidovudine group and the median total body BMD Z-score was observed to decrease further for the all tenofovir disoproxil group in the extension phase from week 48 to week 144[9].

Study GS-US-104-321 was a double-blind, phase III, randomised, placebo-controlled 48 week study to assess the efficacy and safety of tenofovir disoproxil plus optimised background therapy (OBR) in the treatment of HIV-1 infected adolescents, who were failing to respond to their current antiretroviral treatment and had HIV-1 RNA levels ≥ 1000 copies/ml[1,10]. Patients, naïve to tenofovir disoproxil received either tenofovir disoproxil 245 mg tablets (n = 44) or placebo (n = 41). The primary endpoint was the time-weighted average change in plasma HIV-1 RNA from baseline at week 24. At 24 weeks there was no statistically significantly difference in plasma HIV-1 RNA for tenofovir disoproxil treated adolescents compared to placebo-treated patients. CHMP reported that poor efficacy of tenofovir disoproxil in the trial was likely to be due to worse baseline viral susceptibility to OBR and increased tenofovir disoproxil resistance in the tenofovir disoproxil arm. There was a trend for lower increase of total BMD and increased occurrence of osteopenia in the tenofovir disoproxil group compared to the placebo group[11].

2.2 Points to note

- CHMP states that tenofovir disoproxil is a widely used backbone regimen in adult patients, due to its virological efficacy and high genetic barrier. The limitations of current backbone treatments (hypersensitivity, anaemia and lipodystrophy) and its once daily regimen support the use of tenofovir disoproxil in children as an additional therapeutic option[9].
- CHMP note that renal and bone toxicity are of concern for long term usage of tenofovir disoproxil in both adults and for paediatric patients[9]. The SPCs were revised to alert physicians to uncertainties in the long term effects of bone and renal toxicities for paediatric patients and that the reversibility of renal toxicity cannot be fully ascertained[3–7]. CHMP observes that given the lack of correlation between BMD decrease and clinical events, the long term effects of bone and renal toxicity remain theoretical, whereas there are established benefits in a population of paediatric patients in need of treatment[9].
- The company felt that the most appropriate comparator was tenofovir disoproxil 245 mg film-coated tablets[1,2]. The company note in their submissions that the Paediatric Network for Treatment of AIDS (PENTA) guidelines recommend the dual use of two NRTIs as the backbone for any treatment and that abacavir and lamivudine are the preferred combination[12]. The company believe tenofovir disoproxil would complement the use of the other recommended NRTIs and therefore would be used in conjunction; as such the company state that these would not be appropriate comparators. The company also cite the lack of trials of abacavir versus tenofovir disoproxil for the treatment of HIV-1 in paediatric patients[1,2].
- Since limited clinical data are available for the 6.5 mg/kg dose of the granules, the SPC and risk management plan both advise close monitoring of efficacy and safety[7,9].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

In the company's submissions, it is estimated that less than 5 patients per annum will be eligible for treatment with the granules and less than 10 patients per annum will be eligible for treatment with the different strengths of the tablets[1,2]. This is based on Welsh experts' opinion. The company reports that the granules and the lower strength tablets (123 mg, 163 mg and 204 mg) are all priced at parity with the currently available 245 mg tablets. Based on dosage equivalence for the adults and adolescents with body weight > 35 kg, the company estimates that using the oral granules would cost the same as the 245 mg tablets with an annual cost per patient estimated to be £2925.60. The company estimates that the use of the lower strength tablets (123 mg, 163 mg and 204 mg) in the eligible patient population will result in annual costs per patient of £1468.64, £1946.42 and £2436.01 respectively. The company's submission also includes a license extension for the 245 mg oral tablets to be used in adolescents with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to <18 years at an annual cost of £2925.60 per patient.

3.2 AWTTC critique of the budget impact analysis

The company reported that using tenofovir disoproxil formulations in the indications covered by this submission will have minimal budget impact compared to any relevant comparators given the small number of eligible patients. Based on the company's submission, tenofovir disoproxil 33 mg/g granules are priced at parity, on a per mg basis, with the 245 mg tablets, which represents the maximum recommended daily dose in the target patient group. Hence, patients with body weights < 35 kg will require a lower daily dose, resulting in a lower annual cost per patient than that estimated by the company.

Due to limitations of the available trial data in the paediatric and adolescent populations, efficacy in these populations is assumed based on extrapolation of data from adult populations and comparative pharmacokinetic data. The number of eligible patients is reported to be based on expert opinion and as no further details were provided these numbers could not be verified.

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	Over 2 years, 6.5 mg/kg once daily with food. Max 245 mg (7.5 scoops) daily.	£780.13 - £2925.60
Tenofovir disoproxil (Viread®) film-coated tablets 123 mg, 163 mg, 204 mg and 245 mg	Under 6 years: use granules. Children 6—18 years 17—22 kg: 123 mg 22—28 kg: 163 mg 28—35 kg: 204 mg. >35 kg: 245 mg. Adults: 245 mg All once daily with food	£1468.64 - £2925.60
Doses need to be individually tailored based on patient body weight. *Costs are based on MIMS list prices[13] as of 11/04/2013 and average body weight range of 11 kg (average body weight for 2 year-old female) to 68 kg (average body weight for an adult male)[14].* *See the Summaries of Product Characteristics for licensed indications and full dosing details[3–7].*		

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

REFERENCES

1 Gilead Sciences Ltd. Form C: Limited appraisal submission. Tenofovir disoproxil fumarate (Viread®). (HIV Tablets for paediatrics and adolescents). Mar 2013.

2 Gilead Sciences Ltd. Form C: Limited appraisal submission. Tenofovir disoproxil fumarate (Viread®). (HIV Granules). Mar 2013.

3 Gilead Sciences Ltd. Viread® 204 mg film-coated tablets. Summary of Product Characteristics. Dec 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27280/SPC/Viread+204+mg+film-coated+tablets/. Accessed Mar 2013.

4 Gilead Sciences Ltd. Viread® 163 mg film-coated tablets. Summary of Product Characteristics. Dec 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27281/SPC/Viread+163+mg+film-coated+tablets/. Accessed Mar 2013.

5 Gilead Sciences Ltd. Viread® 123 mg film-coated tablets. Summary of Product Characteristics. Dec 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27258/SPC/Viread+123+mg+film-coated+tablets/. Accessed Mar 2013.

6 Gilead Sciences Ltd. Viread® 245 mg film-coated tablets. Summary of Product Characteristics. Dec 2012. Available at: http://www.medicines.org.uk/EMC/medicine/9008/SPC/Viread+245+mg+film-coated+tablets/. Accessed Mar 2013.

7 Gilead Sciences Ltd. Viread® 33 mg/g granules. Summary of Product Characteristics. Dec 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27282/SPC/Viread+33+mg+g+granules/. Accessed Mar 2013.

8 European Medicines Agency. (Viread®). Procedural steps taken and scientific information after the authorisation. Dec 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000419/WC500051736.pdf. Accessed Apr 2013.

9 European Medicines Agency. Assessment Report for Viread®. Procedure No.: EMEA/H/C/000419/X/0105/G (HIV paediatrics). Sep 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000419/WC500136224.pdf. Accessed Mar 2013.

10 Della Negra M, de Carvalho AP, de Aquino MZ et al. A randomised study of tenofovir disoproxil fumarate in treatment-experienced HIV-1 infected adolescents. *Pediatr Infect Dis* 2012; 31 (5): 469-73.

11 European Medicines Agency. Assessment Report for Viread®. Procedure No.: EMEA/H/C/000419/II/0119 (HIV adolescents). Sep 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000419/WC500136223.pdf. Accessed Mar 2013.

12 British HIV Association. PENTA guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine* 2009; 10: 591-613.

13 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Apr 2013. Available at: http://www.mims.co.uk/. Accessed Apr 2013.

14 Royal College of Paediatrics and Child Health. UK-WHO growth charts. 2013. Available at: http://www.rcpch.ac.uk/child-health/research-projects/uk-who-growth-charts/uk-who-growth-chart-resources/uk-who-growth-ch-0. Accessed Apr 2013.