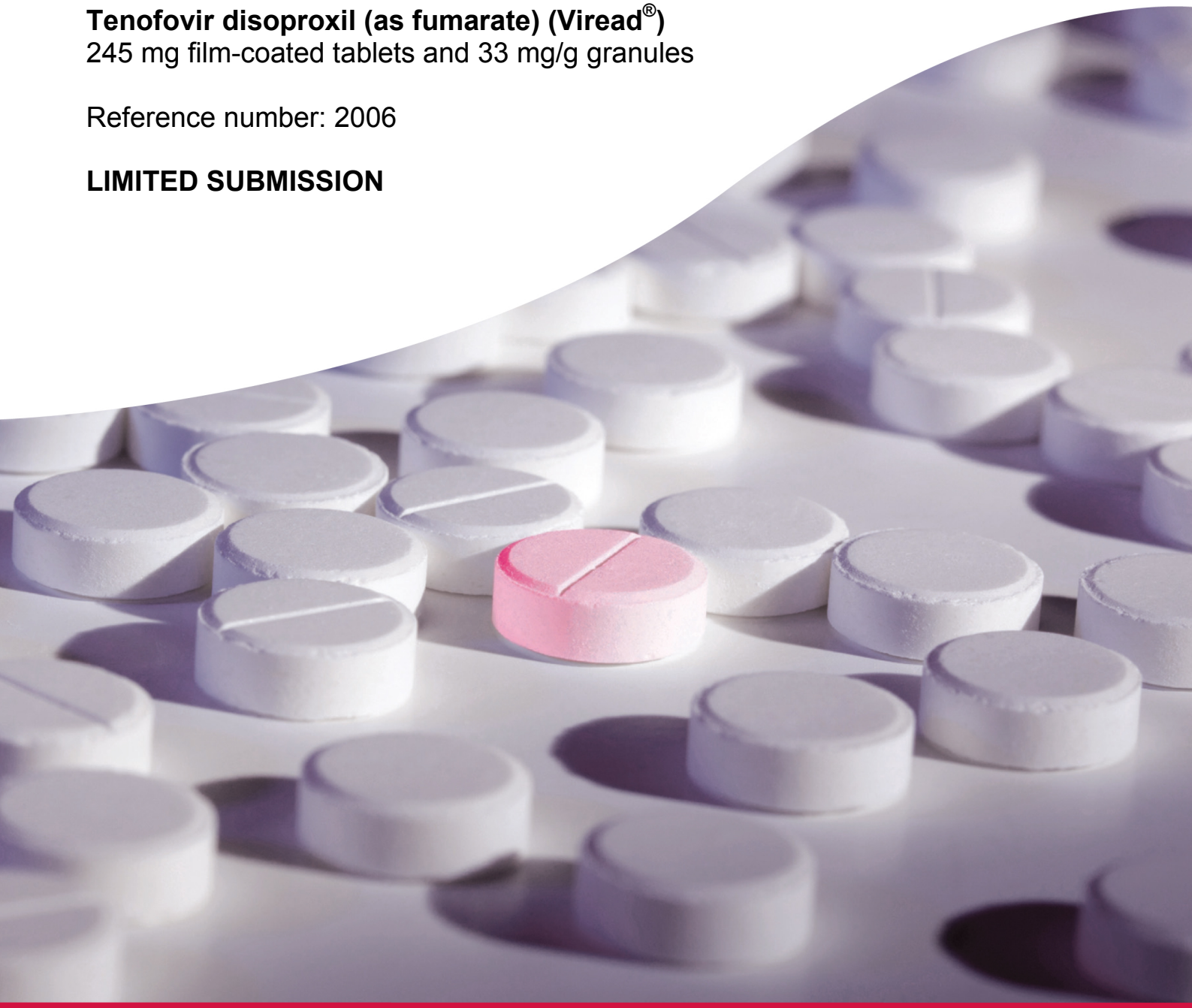
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 2006

LIMITED SUBMISSION



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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 27 September 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 adults with evidence of lamivudine-resistant hepatitis B virus. Refer to the Summaries of Product Characteristics (SPCs) for tablets[2] and granules[3] for further details.
Marketing authorisation date	29 April 2013 (tenofovir disoproxil 245 mg tablets were originally licensed for treatment of chronic hepatitis B in adults on 23 April 2008)[4].
Comparators	The applicant company did not highlight a comparator in their submission.
Limited submission details	Tenofovir disoproxil for the above indication met the following criteria for eligibility for a limited submission: • 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

In their submission, the company included details of one pivotal trial, GS-US-174-0121, which compared tenofovir disoproxil (as fumarate) versus emtricitabine/tenofovir disoproxil fixed dose therapy in adult patients with chronic hepatitis B who were resistant to lamivudine. The company also included information on an additional five trials, which were conducted in patients with chronic hepatitis B; however, the results of these trials will not be discussed, as they do not specifically reflect the indication under consideration. Evidence of bioequivalence for the granule formulation was also provided as part of the company submission[1].

2.1 Clinical evidence

GS-US-174-0121 was a randomised, multicentre, double-blind, double-dummy, phase IIIb trial, which investigated the efficacy, safety and tolerability of tenofovir disoproxil monotherapy versus emtricitabine/tenofovir disoproxil fixed dose therapy in adult patients with chronic hepatitis B (hepatitis B early antigen [HBeAg] positive or negative status), who were receiving lamivudine, had genotypic evidence of lamivudine resistance and hepatitis B virus DNA level ≥ 3 $\log_{10}$ IU/ml at screening. Patients (n = 280) were randomised to receive either tenofovir disoproxil 245 mg plus placebo once daily (n = 141), or emtricitabine/tenofovir disoproxil (200 mg/300 mg) plus placebo once daily (n = 139). The primary endpoint, the percentage of patients with HBV DNA < 400 copies/ml at week 96, was met in 89.4% of patients treated with tenofovir disoproxil and 86.3% of patients treated with emtricitabine/tenofovir disoproxil[5]. Based on the resistance surveillance and genotypic analysis data, no subjects showed

genotypic resistance to tenofovir disoproxil through week 96. Proportion of viral breakthrough was low and no clear pattern of mutations to tenofovir disoproxil was found[5].

No new adverse events were identified in lamivudine-resistant patients receiving tenofovir disoproxil; the safety profile was consistent with the known safety profile of tenofovir disoproxil and no major liver, renal and bone toxicities were reported. However, the Committee for Medicinal Products for Human Use (CHMP) noted that an unexpected pattern of decrease in hip bone mineral density (BMD) was observed, with gradual decrease not reaching plateau at week 96[5].

2.2 Evidence of bioequivalence

In their submission, the applicant company included a bioequivalence study (GS-US-104-0312), which compared the granules formulation with the 245 mg tablet in adult healthy volunteers. CHMP concluded the bioequivalence criteria were met for the area under the curve of plasma concentration versus time[6].

2.3 Points to note

- 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 five years)[7]. In addition, National Institute for Health and Care Excellence (NICE) Clinical Guideline 165 suggests the use of tenofovir disoproxil in adults with chronic hepatitis B who have a history of lamivudine resistance[8].
- CHMP concluded that, overall, a clear benefit of tenofovir disoproxil monotherapy in patients with lamivudine resistance has been demonstrated. It was noted that tenofovir disoproxil should be indicated in patients with lamivudine resistance regardless of whether they have compensated or decompensated chronic hepatitis B. Although there is limited experience in patients with both lamivudine-resistant chronic hepatitis B and decompensated liver disease, CHMP considers tenofovir disoproxil's high potency and genetic barrier, and the lack of cross-resistance between tenofovir disoproxil and lamivudine, make the extrapolation from compensated disease adequate[5].
- In their submission, the company stated that entecavir would not be an appropriate comparator, as patients with pre-existing lamivudine resistance are associated with an increased risk of developing entecavir resistance[1,9]. In addition, adefovir was considered to be an inappropriate comparator as it is not licensed for use in the population under consideration[1,10].
- Although the mean decrease from baseline in hip BMD observed in study GS-US-174-0121 remained small, CHMP noted that it would need to be closely monitored in future safety reports[5].
- Efficacy and safety data are provided for up to 96 weeks; however, a total of 240 weeks of blinded treatment are planned for study GS-US-174-0121[5].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company estimates that, based on Welsh Experts' opinion, less than five patients per annum will be eligible for treatment. The 33 mg/g oral granules are priced at parity on a per mg basis with the currently available 245 mg film-coated tablets[1].

3.2 AWTTC critique of the budget impact analysis

- The number of eligible patients reported by the company is based on the opinion of experts from South Wales. This may be subject to uncertainty.

- 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.

3.3 Comparative unit costs

Table 1. Examples of acquisition costs for formulations of tenofovir disoproxil and entecavir

Treatment	Example daily dose	Example annual cost of treatment per patient
Tenofovir disoproxil (as fumarate) (Viread®) 245 mg film-coated tablets	245 mg daily with food	£2,926
Tenofovir disoproxil (as fumarate) (Viread®) 33 mg/g oral granules	245 mg (7.5 scoops) daily	£2,926
Entecavir (Baraclude®) 1 mg film-coated tablets	1 mg once daily	£4,420
Entecavir (Baraclude®) 0.05 mg/ml oral solution	1 mg (20 ml) once daily	£14,732
Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of October 2013[11]. See the Summaries of Product Characteristics (SPCs) for licensed indications and full dosing details[2,3,9].		

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, tenofovir disoproxil (as fumarate) (Viread®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that tenofovir disoproxil (as fumarate) (Viread®) may be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 9 September 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®). 2013.

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

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

4 European Medicines Agency. Viread®. Procedural steps taken and scientific information after the authorisation. 2013. 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 Sep 2013.

5 European Medicines Agency. Assessment Report for Viread®. Procedure No.: EMEA/H/C/000419/II/0120. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000419/WC500148673.pdf. Accessed Sep 2013.

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

7 European Medicines Agency. Assessment Report for Viread®. Procedure No.: EMEA/H/C/000419/II/0115. Sep 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000419/WC500136222.pdf. Accessed Oct 2013.

8 National Institute for Health and Care Excellence. Clinical Guideline 165. Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults. 2013. Available at: http://guidance.nice.org.uk/CG164. Accessed Oct 2013.

9 Bristol-Myers Squibb Pharmaceutical Ltd. Baraclude®. Summary of Product Characteristics. Nov 2012. Available at: http://www.medicines.org.uk/emc/medicine/18377/SPC/Baraclude++0.5+mg+and+1.0+mg+film+coated+tablets+and+Baraclude+0.05mg+ml+oral+solution/. Accessed Oct 2013.

10 Gilead Sciences Ltd. Hepsera®. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/12438/SPC/Hepsera+10+mg+tablets/. Accessed Sep 2013.

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