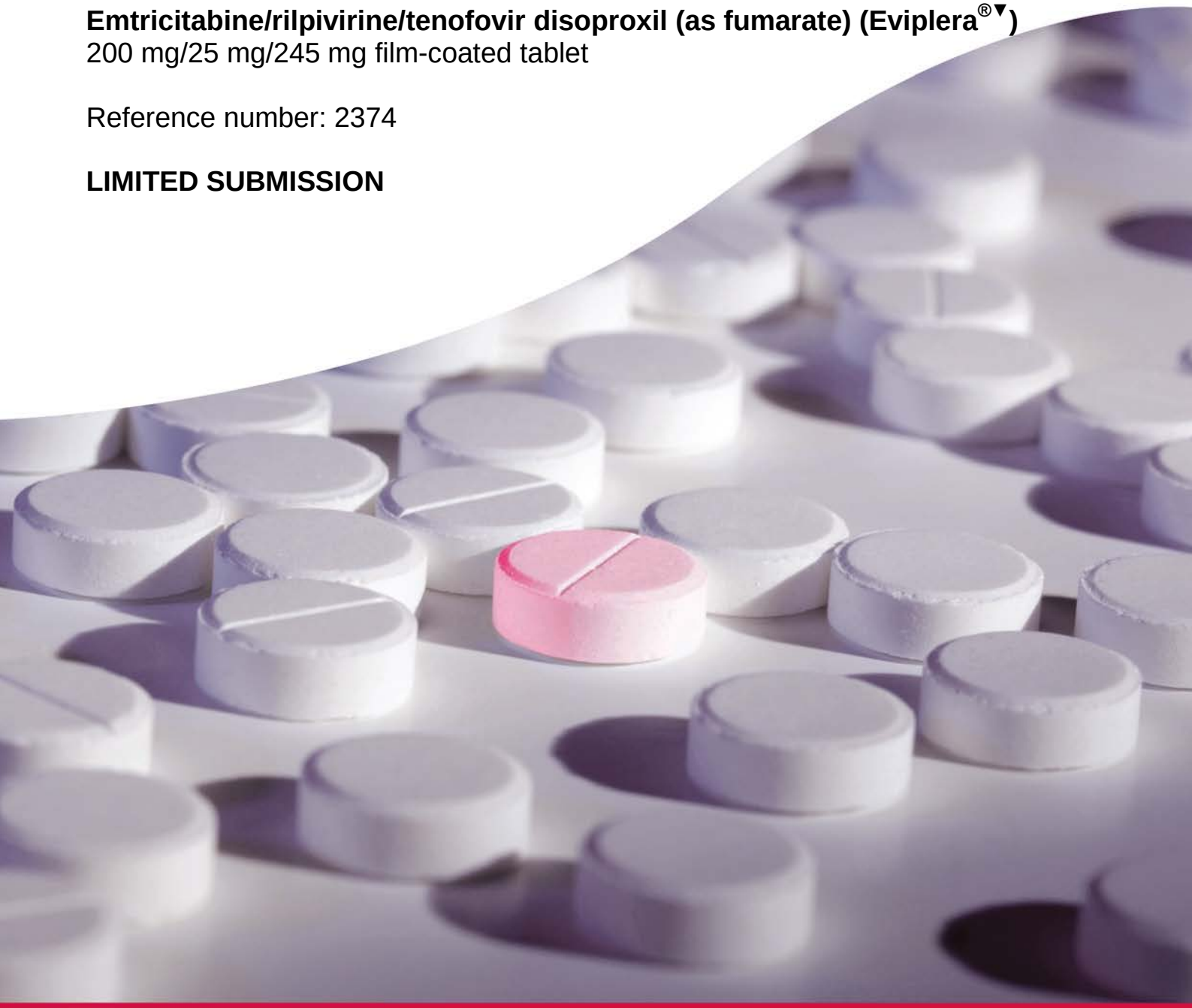
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Emtricitabine/rilpivirine/tenofovir disoproxil (as fumarate) (Eviplera®▼)
200 mg/25 mg/245 mg film-coated tablet

Reference number: 2374

LIMITED SUBMISSION



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AWMSG Secretariat Assessment Report
Emtricitabine/rilpivirine/tenofovir disoproxil (as fumarate) (Eviplera®▼)
200 mg/25 mg/245 mg film-coated tablet

This assessment report is based on evidence from a limited submission by Gilead Sciences Ltd. on 31 January 2014[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Emtricitabine/rilpivirine/tenofovir disoproxil (as fumarate) (Eviplera®▼) is indicated for the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/ml. As with other antiretroviral medicinal products, genotypic resistance testing and/or historical resistance data should guide the use of Eviplera®▼[2]. The indication under consideration is the licence extension for antiretroviral treatment-experienced adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/ml.
Dosing	The recommended dose of Eviplera®▼ is one tablet, taken orally, once daily. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	29 November 2013 (originally licensed for antiretroviral treatment-naive patients on 28 November 2011)[3].
Comparators	The comparators included in the company submission were: • Efavirenz/emtricitabine/tenofovir disoproxil (Atripla®) • Emtricitabine/tenofovir disoproxil (Truvada®) + atazanavir (Reyataz®) + ritonavir (Norvir®) (booster for Reyataz®) • Emtricitabine/tenofovir disoproxil (Truvada®) + darunavir (Prezista®) + ritonavir (Norvir®) (booster for Prezista®)[1]
Limited submission details	Emtricitabine/rilpivirine/tenofovir disoproxil (Eviplera®▼) for the above indication met the following criteria for eligibility for a limited submission: • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparators.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The indication under consideration is the licence extension for antiretroviral treatment-experienced adults with HIV-1 without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load (VL) of ≤ 100,000 HIV-1 RNA copies/ml. The All Wales Medicines Strategy Group (AWMSG) has previously recommended emtricitabine/rilpivirine/tenofovir disoproxil (Eviplera®▼) as an option for use within NHS

Wales for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients with VL ≤ 100,000 HIV-1 RNA copies/ml[4].

In support of the licence extension under consideration, the applicant company has provided data from several clinical studies on switching from alternative antiretroviral therapy (ART) to Eviplera®▼ in HIV-1 positive patients[1]. The most relevant clinical evidence was from virologically suppressed patients in the phase III trial GS-US-264-0106 (SPIRIT) and the phase II trial GS-US-264-0111[5,6]. Supplementary data from conference abstracts and posters supported the findings of the main trials[1].

2.1 Study GS-US-264-0106 (SPIRIT)

This was a phase III, multicentre, international (including UK), randomised, open-label, 48-week switching study[1,5]. The objective of the study was to investigate noninferiority of the single tablet regimen (STR) Eviplera®▼ relative to a ritonavir-boosted protease inhibitor (rPI) based regimen. Virologically suppressed (HIV-1 RNA < 50 copies/ml) patients (n = 476) receiving a rPI and two nucleoside reverse transcriptase inhibitors (2NRTIs) for a minimum of six months were randomised (2:1); the first group (n = 317) was switched to Eviplera®▼ on day one (immediate switch group) and the second group (n = 159) remained on the rPI + 2NRTIs for 24 weeks and switched to Eviplera®▼ from week 24 to week 48 (delayed switch group)[5]. The majority of patients (88%) had enrolled in the study with a desire to simplify their current ART regimen[7]. The primary endpoint was the proportion of patients maintaining HIV-1 RNA < 50 copies/ml at week 24 using snapshot analysis[5].

Eviplera®▼ was found to be virologically noninferior (12% predefined margin) to rPI + 2NRTIs at 24 weeks. In the immediate switch group, virologic suppression was maintained in 93.7% of patients compared to 89.9% of the rPI + 2NRTIs group (3.8% difference, 95% confidence interval −1.6 to 9.1%; p = 0.15)[5]. Consistent with this, 92.1% of subjects in the delayed switch group had HIV-1 RNA < 50 copies/ml at week 48 after 24 weeks of treatment with Eviplera®▼[5,7].

The percentage of adverse events (AEs) considered to be related to Eviplera®▼ were similar in the immediate switch group (24.9%) and the delayed switch group (23.0%) during 48 and 24 weeks of Eviplera®▼ treatment, respectively. This percentage was lower among the patients remaining on their current ART regimen for the first 24 weeks of the study (2.5% in the rPI + 2NRTIs group). The most frequently reported study drug related AEs were nausea, diarrhoea and fatigue. Serious AEs (SAEs) thought by the investigator to be related to the study drug were reported in three patients (toxic nephropathy due to tenofovir without treatment interruption, renal impairment and dyspnoea; the latter two resulted in permanent discontinuation)[5,7]. There were differences in the percentages of some disorders reported in the Eviplera®▼ group versus the rPI + 2NRTIs group prior to switch (psychiatric: 17.5% vs 6.3%; nervous system: 14.9% vs 9.4%; gastrointestinal: 27.5% vs 16.4%, respectively)[7]. In total, 13 patients permanently discontinued the study drug due to AEs; seven from the immediate switch group and six from the delayed switch group, after they had switched to Eviplera®▼. Three patients dropped out due to lack of efficacy; two in the immediate switch group and one in the delayed switch group after switching to Eviplera®▼. No patients in the delayed switch group discontinued due to a treatment-emergent AE in the first 24 weeks whilst continuing on established rPI regimens[5,7].

2.2 Study GS-US-264-0111

This was a phase II, multicentre (18 centres in the US), open-label, single-arm, 48-week switching study. The study evaluated the efficacy, safety and pharmacokinetics of switching from Atripla® STR to Eviplera®▼ STR. Virologically suppressed (HIV-1 RNA < 50 copies/ml) patients (n = 49) who had been on Atripla® for

≥ 3 months at screening, and who had decided they would like to change regimen due to efavirenz intolerance, were switched to Eviplera®▼ at baseline[1,6,7].

All 49 patients achieved the primary endpoint of VL < 50 copies/ml at week 12; and virologic suppression was maintained at week 24. At week 48, two patients (4.1%) experienced virologic failure; one patient had low level VLs and was switched back to prestudy regime; another patient had VLs of 330,000 copies/ml at week 48, this patient was noted to have poor study drug adherence prior to week 48. AEs considered by the investigator to be related to the study drug were reported in 12 patients (24.5%); the highest incidence was gastrointestinal disorders (seven patients [14.3%]). No participants discontinued the study drug due to AEs[6,7].

2.3 Points to note

- Study GS-US-264-0106 demonstrated that switching to Eviplera®▼ was noninferior to remaining on rPI + 2NRTIs at 24 weeks[5]. The Committee for Medicinal Products for Human Use (CHMP) noted that the introduction of Eviplera®▼ after switch from a protease inhibitor (PI) based regimen did not result in reductions of proportions of subjects with VL < 50 copies/ml at week 24 when Eviplera®▼ was compared with continuation of a PI based regimen. It was therefore concluded that efficacy was demonstrated in this study[7].
- In Study GS-US-264-0106, discontinuation of treatment due to AEs was higher in both groups after switch to Eviplera®▼. CHMP noted, however, that this is often the case in switch studies as the patient population has been selected to tolerate their preswitch regimen[5,7].
- The clinical trial data provided by the applicant company did not provide any evidence that the simplification of medication to a once daily STR improved adherence. CHMP acknowledge, however, that the reduction in pill burden compared to PI regimens, or improvement of neuropsychiatric disorders associated with efavirenz, can be considered benefits which may increase adherence[7]. Additionally, some studies have demonstrated that self-reported adherence was higher with STR regimens[8,9].
- The licensed indication for Eviplera®▼ is for patients with VL ≤ 100,000 copies/ml. However, the main clinical trial data are largely limited to patients with VL < 50 HIV-1 RNA copies/ml and there are no robust clinical trial data on patients with virologic failure whilst on other ART regimes switching to Eviplera®▼. During the window phase between screening and treatment initiation in study GS-US-264-0106, 25 subjects had increased viral loads, including 7 with loads > 400 copies/ml. A small number of participants (n = 80) in an observational cohort study provided as part of the company submission had VL > 50 copies/ml at switch to Eviplera®▼. The study concluded that viral suppression was less likely in this patient population[10].
- In both of the main clinical trials, CHMP noted that the VL prior to commencement of the very first ART regimen is not known and that it is therefore unknown whether cases that failed on Eviplera®▼ after switch were subjects with VL > 100,000 copies/ml at the initiation of ART[7].
- A secondary outcome reported in four of the studies provided reported a lipid lowering effect with observed reduction in total cholesterol, LDL cholesterol and triglycerides[5,6,11,12]. CHMP noted that study GS-US-264-0106 demonstrated limited benefit in the short term as discontinuation of statin therapy was only reported in < 2.8% of individuals[7]. Benefits associated with lipid lowering effects might become apparent in the longer term.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The applicant company included a cost-minimisation analysis and a budget impact analysis in their submission[1]. Eviplera®▼ for the indication under consideration met the criteria for a limited submission; in line with this process, evidence of budgetary impact in comparison to the existing comparators is considered in this report.

Public Health England reports that 1,307 patients in Wales were diagnosed with HIV infection and were receiving ART in 2012[1,13]. Based on a report on 2011 UK data from Health Protection England, the applicant company estimates that 86% of these patients have an undetectable VL[1,14] and have assumed that these patients would be considered stable and eligible for switch to Eviplera®▼ (n = 1,124). Using projected market share data, the company has estimated the percentage of patients in this group switching to Eviplera®▼ over a five year period [commercial in confidence data removed] and have calculated the total weighted average price of the comparators likely to be displaced by Eviplera®▼ (£8,244). The company calculated that the annual cost of Eviplera®▼ per patient was £7,534[1]. These data are summarised in Table 1.

Table 1. Estimated annual budget impact of Eviplera®▼ in Wales[1]

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients eligible for switch to Eviplera®▼	1,124	1,124	1,124	1,124	1,124
Estimated proportion treated with Eviplera®▼	†	†	†	†	†
Cumulative number of patients treated	†	†	†	†	†
Cost of Eviplera®▼ *	£7,534	£7,534	£7,534	£7,534	£7,534
Weighted average cost of displaced ART regimen*	£8,244	£8,244	£8,244	£8,244	£8,244
Difference in cost per patient	−£710	−£710	−£710	−£710	−£710
Total difference in cost	†	†	†	†	†

*Costs are based on 365.25 days per year.
†Commercial in confidence data removed.

3.2 AWTTC critique of the budget analysis

- The number of patients eligible for switch to Eviplera®▼ in Wales has been based on UK-wide data[13,14], which would appear reasonable. This assumes that figures have remained static since 2011 and will continue to remain so.
- The estimated proportion of eligible patients treated with Eviplera®▼ has been based on market research from an unpublished in-house company source and cannot be verified.

3.3 Comparative unit costs

Table 2 provides an example of comparative acquisition costs for Eviplera®▼ and potential comparators identified by clinical experts in NHS Wales.

Table 2. Example comparative annual medicine acquisition costs for ARTs in treatment-experienced HIV-1 infected adult patients with HIV-1 RNA virologic suppression

Example regimens	Dose*	Approximate Annual cost†
Triple combination products		
Emtricitabine/rilpivirine/tenofovir disoproxil (Eviplera®▼) 200 mg/25 mg/245 mg film-coated tablets	One tablet daily	£7,528
Efavirenz/emtricitabine/tenofovir disoproxil (Atripla®) 600 mg/200 mg/245 mg tablets	One tablet daily	£7,627
Individual constituents		
Emtricitabine/tenofovir disoproxil (Truvada®) 200 mg/245 mg + atazanavir (Reyataz®) + ritonavir (Norvir®)	Truvada® once daily + Reyataz® 300 mg once daily + Norvir® 100 mg once daily	£9,020
Emtricitabine/tenofovir disoproxil (Truvada®) 200 mg/245 mg + darunavir (Prezista®) + ritonavir (Norvir®)	Truvada® once daily + Prezista® 600 mg twice daily + Norvir® 100 mg twice daily	£11,000
Emtricitabine/tenofovir disoproxil (Truvada®) 200 mg/245 mg + darunavir (Prezista®) + ritonavir (Norvir®)	Truvada® once daily + Prezista® 800 mg once daily + Norvir® 100 mg once daily	£8,951
Abacavir/lamivudine (Kivexa®) 600 mg/300 mg + atazanavir (Reyataz®) + ritonavir (Norvir®)	Kivexa® once daily + Reyataz® 300 mg once daily + Norvir® 100 mg once daily	£7,571
Abacavir/lamivudine (Kivexa®) 600 mg/300 mg + darunavir (Prezista®) + ritonavir (Norvir®)	Kivexa® once daily + Prezista® 600 mg twice daily + Norvir® 100 mg twice daily	£9,551
Abacavir/lamivudine (Kivexa®) 600 mg/300 mg + darunavir (Prezista®) + ritonavir (Norvir®)	Kivexa® once daily + Prezista® 800 mg once daily + Norvir® 100 mg once daily	£7,502

*Based on MIMs and individual SPCs dosing instructions[2,15–20].
†Costs are based on 365 days per year and MIMS list prices as of 20 February 2014[19].
This table does not imply therapeutic equivalence of medicines or the stated doses.

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

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

The company anticipate that Eviplera®▼ 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: 7 February 2014
Date range of evidence search: No date limits were applied to database searches.

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Appendix: Previous AWMSG secretariat assessment report (published July 2012)

This report was published as part of a previous AWMSG appraisal of emtricitabine/rilpivirine/tenofovir (Eviplera®) (Advice number 1412). The advice from this appraisal has been superseded by advice number 1514. The original appraisal documentation is included here for completeness.

AWMSG Secretariat Assessment Report – Advice No. 1412
Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®▼)
200 mg/25 mg/245 mg film-coated tablets

This assessment report is based on evidence from a limited submission by Gilead Sciences Ltd on 14 October 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®▼) is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naive adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml. As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of Eviplera®▼[2].
Dosing	The recommended dose of Eviplera®▼ is one tablet, taken orally, once daily with a meal. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	28 November 2011[2].

2.0 DECISION CONTEXT

2.1 Background

Human immunodeficiency virus (HIV) is a retrovirus that infects cells in the human immune system, such as $CD4^+$ lymphocytes, causing their destruction, which results in the progressive suppression of the host immune system and the development of acquired immunodeficiency syndrome (AIDS)[3,4]. The number of Welsh patients receiving treatment for HIV or AIDS in 2009 was 1,193[5], and there were a further 161 new diagnoses of HIV infection reported in 2010[6].

Current guidelines recommend that the first-line highly active antiretroviral therapy (HAART) regimen in newly diagnosed HIV-1 patients consists of two nucleoside reverse transcriptase inhibitors (NRTIs), in addition to a non-nucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor[7]. Guidelines also recommend that HAART regimens are individualised for patients in order to improve potency, durability, adherence and tolerability, as well as minimise long term toxicities or possible drug interactions[7].

Eviplera®▼ is a combination tablet, composed of two NRTIs (emtricitabine and tenofovir disoproxil fumarate [TDF]) and an NNRTI (rilpivirine), licensed for the treatment of patients with plasma HIV levels (viral load) ≤ 100,000 RNA copies/ml and who have not previously received treatment for HIV[2].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership* were TDF/efavirenz/emtricitabine (Atripla®) or TDF/emtricitabine (Truvada®) plus efavirenz (Sustiva®).

2.3 Guidance and related advice

- British HIV Association (BHIVA) guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals (2011)[8].
- European AIDS Clinical Society. European guidelines for the clinical management and treatment of HIV-infected adults in Europe (2011)[9].
- British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy (2008)[7]. At the time of writing, these guidelines are under review.

The All Wales Medicines Strategy Group (AWMSG) has previously issued the following recommendation for the use of NNRTIs and NRTIs in adult patients:

- Efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in adults with virological suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiviral therapy for more than three months and in accordance with current BHIVA guidance (2009)[10].

AWMSG is also considering in June 2012:

- Rilpivirine (Edurant®▼) 25 mg tablets in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naive adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission provides evidence for the bioequivalence of Eviplera®▼ and the individual constituents (emtricitabine, rilpivirine and TDF) administered individually[1]. The submission also includes evidence for the clinical effectiveness of rilpivirine in combination with emtricitabine and TDF[1].

3.1 Evidence of bioequivalence

GS-US-264-0103 was a phase I, randomised, open-label single-centre, single-dose, three-way crossover study[1]. Healthy subjects (n = 36) were randomised to initial study treatment (Eviplera®▼ [combination tablet] or individual constituents), which was administered in the morning, under fed conditions, with a 14-day washout period before receiving the alternate treatments. Pharmacokinetic sampling assessed the maximum plasma concentration (C_{max}), the area under the concentration versus time curve from time zero to the last quantifiable concentration (AUC_{last}), and the area under the concentration versus time curve, extrapolated to infinite time (AUC_{inf}) for Eviplera®▼ versus the individual constituents[1].

For all three pharmacokinetic parameters, the 90% confidence interval for the geometric least-square means ratio of Eviplera®▼ versus each individual component fell within the accepted equivalence bounds of 80% to 125%[12], indicating that Eviplera®▼ is bioequivalent to concurrent administration of its individual constituents[1,13].

* In April 2012 the Welsh Medicines Partnership became a part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

3.2 Clinical effectiveness of emtricitabine, rilpivirine and TDF

The company submission provided data from the THRIVE and ECHO studies, which were randomised, double-blind, double-dummy, active-controlled phase III studies that compared chemotherapeutic regimens containing rilpivirine and efavirenz in treatment-naive patients over a 96-week period[1,1,14,15]. The background regimen administered to patients in the ECHO study (n = 690) was composed of TDF and emtricitabine[15]; 406 (60%) patients enrolled in the THRIVE study (n = 678) also received this NRTI combination[14], while others were treated with zidovudine with lamivudine (30%) or abacavir with lamivudine (10%). The studies included HIV-1 infected treatment-naïve patients with a viral load of > 5,000 RNA copies/ml.

The primary endpoint was the proportion of patients with confirmed virological response, defined as plasma viral load < 50 HIV-1 RNA copies/ml, at week 48[14,15]. This was achieved in 86% and 82% of patients that received rilpivirine and efavirenz, respectively, in the THRIVE study, and in 83% of patients in both groups of the ECHO study; non-inferiority of rilpivirine was demonstrated at both the 12% ($p < 0.0001$) and 10% (THRIVE $p < 0.0001$; ECHO $p = 0.0007$) predefined margins[14,15]. A pooled analysis of patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml from the two studies also demonstrated non-inferiority, although the studies were not powered for this analysis[13].

Results from the full analysis raised concerns regarding virological failure and development of resistance-associated mutations (RAMs) in rilpivirine-treated patients with viral load > 100,000 RNA copies/ml[16]. Therefore, the combination product Eviplera®▼ was granted a licence for use in patients with viral load ≤ 100,000 HIV-1 RNA copies/ml[2,17].

3.3 Evidence of comparative safety

At the time of licensing, the safety profiles of regimens containing rilpivirine was evaluated by the Committee for Medicinal Products for Human Use (CHMP) and it was concluded that rilpivirine-based regimens were generally safe and well tolerated[13]. The incidence of adverse events (AEs) considered related to treatment was 318/686 (46.4%) and 437/682 (64.1%) in patients treated with rilpivirine and efavirenz, respectively. AEs of grade 3 or more were observed in 13.3% of rilpivirine-treated patients and 18% of efavirenz-treated patients, while serious AEs were observed in 45/686 (6.6%) and 55/682 (8.1%), respectively. No deaths were considered related to the study medication. Discontinuation due to AEs occurred in 23 (3.4%) patients in the rilpivirine group and 52 (7.6%) efavirenz-treated patients; the most common AEs leading to discontinuation were psychiatric disorders in both groups (1.5% versus 2.2% in the rilpivirine and efavirenz groups, respectively)[1,13].

The most commonly observed treatment-related AEs in the rilpivirine treatment group were nausea (10.1% versus 11.3% in efavirenz-treated patients), dizziness (8.0% versus 26.2%), abnormal dreams (6.3% versus 9.4%) and headache (6.1% versus 6.2%)[1,13]. Among the AEs reported as at least grade 2 in severity, rash (2.2% versus 9.4%) and dizziness (0.7% versus 6.6%) were reported significantly more often in the efavirenz treatment group, while depression was slightly more frequent in rilpivirine-treated patients (3.5% versus 2.2%). Cardiac and hepatic AEs appeared comparable between the two groups[13].

3.4 AWTTC critique

- At the time of licensing, CHMP noted that bioequivalence has been demonstrated between the Eviplera®▼ combination tablet and the individual constituents and concluded that, since efficacy and safety have been established with these constituents, the results are considered applicable to the

combination product[13]. The clinical and cost-effectiveness of rilpivirine (Edurant®▼) for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml, in combination with other antiretroviral medicinal products, is being assessed by AWMSG as a separate appraisal[11].

- The full analysis of the clinical effectiveness studies demonstrated non-inferiority of rilpivirine to efavirenz in treatment-naive adults with HIV-1 infection, regardless of viral load[14,15]. The licensed indication of Eviplera®▼ is limited to a subpopulation of these studies with a baseline viral load ≤ 100,000 copies/ml[2]. Results for the primary endpoint in a pooled analysis of this subpopulation also demonstrated non-inferiority; however the studies were not powered for this analysis[13].
- While considering the use of Eviplera®▼ in this indication, CHMP stated that simple dosing regimens are one of the drivers of good adherence, leading to reduced risk of drug resistance development. It also noted that among regimens of comparable efficacy, physicians and HIV-1 infected patients rate pill burden and dosing frequency as obstacles to achieving adherence[13].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

Manufacturers are not required to submit evidence on cost-effectiveness for a limited submission, and literature searches by AWTTC identified no relevant studies.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company reports that 152 new HIV-1 diagnoses have been recorded in Wales in 2010, based on data from the Health Protection Agency[1,6]. The company estimates that of these new diagnoses, around 70% will have viral load < 100,000 HIV-1 RNA copies/ml and approximately 40% of these, equivalent to around 40 patients, will be deemed suitable for treatment with Eviplera®▼ fixed-dose combination tablet.

5.1.2 Results of the budget impact analysis

Based on an estimated 40 new patients being eligible for treatment with Eviplera®▼ in year 1, the company anticipates that the first year sales will be in the region of £0.1 million, and that the total cost to the NHS will be less than £1 million in each of the first five years.

The company anticipates that there will be net cost savings to the NHS from the use of Eviplera®▼, based on the assumption that patients being initiated on the main comparator would commence treatment with emtricitabine/TDF (Truvada®) plus efavirenz (Sustiva®) and then switch to the triple combination product of efavirenz/emtricitabine/TDF (Atripla®).

5.1.3 AWTTC critique of the budget impact analysis

- No details have been provided in relation to the use of the triple combination product Eviplera®▼ rather than the individual component medicines. The single agent rilpivirine (Edurant®▼) is currently undergoing appraisal by AWMSG.
- The company has limited its estimates of eligible patient numbers to incident cases of HIV-1. Around a fifth of patients that have received a HIV-1 diagnosis

are estimated to be treatment-naive and may constitute an additional eligible patient population[7,18].

- Irrespective of these limitations, there is no difference in costs between Eviplera®▼ and its individual constituents, or between Eviplera®▼ and efavirenz plus a fixed combination of two NRTIs (e.g. Truvada®). Furthermore, Eviplera®▼ is marginally less costly than the triple combination product of efavirenz/emtricitabine/TDF (Atripla®). The magnitude of any potential cost savings from the use of Eviplera®▼ rather than Atripla® will depend on the proportion of patients who would hypothetically be switched from efavirenz plus Truvada® to Atripla®.

5.2 Table of comparative unit costs

Treatment regimens need to be individually tailored to HIV-1 patients based on resistance profiling. There are many possible first-line treatment options. The table below provides example comparative costs for common NNRTI and NRTI combinations used as first-line treatment regimens.

Table 1. Examples of drug acquisition costs for licensed first-line HAART regimens.

Example regimens	Dose	Approximate Annual cost
Triple combination products		
Emtricitabine/rilpivirine/TDF (Eviplera®▼) 200 mg/25 mg/245 mg film-coated tablets	One tablet daily	£7,534
Efavirenz/TDF/emtricitabine (Atripla®) 600 mg/245 mg/200 mg tablets	One tablet daily	£7,633
Individual constituents		
Rilpivirine 25 mg (Edurant®▼)* tablets + TDF 245 mg/emtricitabine 200 mg (Truvada®)	Rilpivirine 25 mg once daily + Truvada® once daily	£7,533
Efavirenz 600 mg (Sustiva®) tablets + TDF 245 mg/emtricitabine 200 mg (Truvada®)	Efavirenz 600 mg once daily + Truvada® once daily	£7,533
Rilpivirine 25 mg (Edurant®▼) tablets + abacavir 600 mg/lamivudine 300 mg (Kivexa®)	Rilpivirine 25 mg once daily + Kivexa® once daily	£6,727
Efavirenz 600 mg (Sustiva®) tablets + abacavir 600 mg/lamivudine 300 mg (Kivexa®)	Efavirenz 600 mg once daily + Kivexa® once daily	£6,727
Rilpivirine 25 mg (Edurant®▼) tablets +zidovudine 300 mg/lamivudine 150 mg (Combivir®)	Rilpivirine 25 mg once daily + Combivir® once daily	£6,092
Efavirenz 600 mg (Sustiva®) tablets + zidovudine 300 mg/lamivudine 150 mg (Combivir®)	Efavirenz 600 mg once daily + Combivir® once daily	£6,092

* Edurant®▼ is currently undergoing appraisal by AWMSG.
Atripla® is not licensed for initiation of first-line treatment; patients who are stabilised on individual constituents may switch to Atripla® when sustained virological suppression is achieved[19].
Costs based on MIMS list prices as of 3 March 2012[20].
This table does not imply therapeutic equivalence of the stated drugs and doses.
See all relevant SPCs for full dosing details.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that Eviplera®▼ is appropriate for specialist only prescribing within NHS Wales.

6.2 Ongoing studies

The company submission highlighted ongoing studies:

- Study GS-US-264-0106 (NCT01252940): a phase III randomized, open-label study to evaluate switching from regimens consisting of a ritonavir-boosted protease inhibitor and two NRTIs to emtricitabine/rilpivirine/TDF fixed-dose regimen in virologically suppressed, HIV-1 infected patients[21].
- Study GS-US-264-0110 (NCT01309243): a phase IIIb, randomized, open-label study to evaluate the safety and efficacy of a single tablet regimen of emtricitabine/rilpivirine/TDF compared with a single tablet regimen of efavirenz/emtricitabine/TDF in HIV-1 infected, antiretroviral treatment-naive adults[22].
- Study GS-US-264-0111 (NCT01286740): a phase IIb open-label pilot study to evaluate switching from a regimen consisting of efavirenz/emtricitabine/TDF single tablet regimen to emtricitabine/rilpivirine/TDF in virologically suppressed, HIV-1 infected subjects[23].

6.3 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).

6.4 Evidence search

Date of evidence search: 23 January 2012
Date range of evidence search: No date limits were applied to database searches.

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