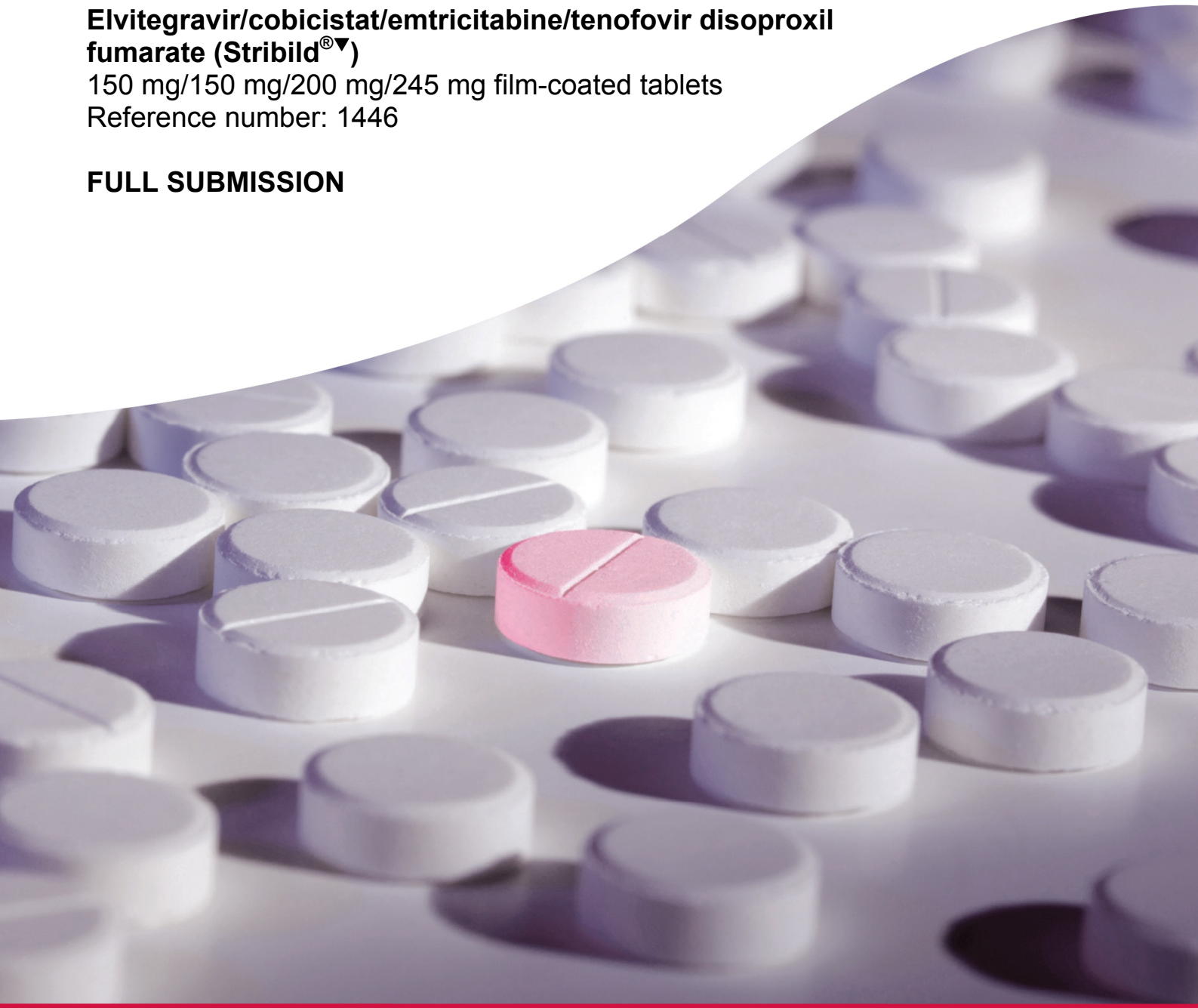
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®▼)
150 mg/150 mg/200 mg/245 mg film-coated tablets
Reference number: 1446

FULL 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.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®▼) 150 mg/150 mg/200 mg/245 mg film-coated tablets. Reference number: 1446. September 2013.

AWMSG Secretariat Assessment Report
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®▼) 150 mg/150 mg/200 mg/245 mg film-coated tablets

This assessment report is based on evidence submitted by Gilead Sciences Ltd on 22 May 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®▼) for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral-treatment-naive or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild®▼[2].
Dosing	The recommended dose of Stribild®▼ is one tablet, taken orally, once daily. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	24 May 2013[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]. Two forms of the virus, HIV-1 and HIV-2 are known, of which HIV-1 is the more virulent and responsible for the current pandemic. While there is no cure for HIV, the various enzymes in the viral life cycle are useful targets for arresting its spread, and thus reducing the morbidity and mortality of infected patients[5].

Current guidelines recommend that the antiretroviral therapy in treatment-naive HIV-1 patients consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in addition to a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor or an integrase inhibitor[6]. NRTIs and NNRTIs hamper the formation of the DNA transcript[5]. Protease inhibitors interfere with the cleavage of synthesised polypeptides into active viral proteins that are essential for the HIV replication cycle, thus reducing infectivity[5]. Integrase inhibitors reduce the ability of the retroviral DNA to become incorporated into the host genome[7]. Atripla® and Eviplera®▼ are both single tablet regimens containing an NNRTI (efavirenz [EFV] and rilpivirine [RPV], respectively) in combination with two NRTIs (tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC])[8,9]. Stribild®▼ contains the same combination of NRTIs together with elvitegravir (EVG; an integrase inhibitor) and cobicistat (COBI), within a single tablet, provided as a once daily dose[2]. COBI, though not itself an antiretroviral, boosts the concentration of EVG by inhibiting the liver enzyme, CYP3A, a metaboliser of EVG[10] (refer to the list of abbreviations regarding treatment names).

By the end of December 2012, there were 2,173 diagnoses of HIV in Wales, from which there were 377 associated deaths resulting in a patient population of 1,796[11]. The company estimates, using Health Protection Agency data, that there will be 160

newly diagnosed Welsh patients each year. Data to the end of December 2012 indicated that HIV patients in Wales were 74% male and 63% white[11]. The company estimates that Stribild®▼, which is indicated for treatment-naive patients only, would be used in nine patients in year one, rising to 68 patients in year five[1].

2.2 Comparators

The comparators included in the company submission were:

- Efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®)
- Atazanavir/ritonavir plus emtricitabine/tenofovir disoproxil fumarate (ATV/RTVFTC/TDF)

In their submission, the company included Atripla® and ATV/RTV/FTC/TDF as comparators, as the company consider them to be standards of care within Wales. However, it should be noted that Atripla® is not indicated for use in antiretroviral treatment-naive patients[8]. The company have not included Eviplera®▼ or raltegravir (RAL) as comparators; they state that these medicines do not currently represent usual Welsh standard of care[1].

2.3 Guidance and related advice

- British HIV Association (BHIVA) guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy (2012)[6].
- European AIDS Clinical Society. European guidelines for the treatment of HIV-infected adults in Europe. Version 6.1. (2012)[12].
- British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1 infected individuals (2011)[13].

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

- Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®▼) is recommended as an option for use within NHS Wales 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 (2012)[14].
- 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)[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes evidence from two phase III trials in HIV-1 infected, antiretroviral treatment-naive patients[1]. GS-US-236-0102 compared the relative efficacy and safety of two single tablet regimens, Stribild®▼ and Atripla®, and GS-US-236-0103 compared the relative efficacy and safety of Stribild®▼ with the combination ATV/RTV/FTC/TDF. A phase II study (GS-US-236-0104) in which 71 patients received either Stribild®▼ or Atripla® for the initial treatment of HIV infection was included in the submission but was not powered to compare efficacy of the treatments[16]. The company additionally submitted a comparison of the efficacy and safety of Stribild®▼, Atripla® and ATV/RTV/FTC/TDF using an integrated analysis of the combined data from the GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104 trials. In addition, the company has submitted evidence from GS-US-236-0123, a phase III, open-labelled study which evaluated the efficacy and safety aspects of switching from a combined raltegravir/emtricitabine/tenofovir disoproxil fumarate (RAL/FTC/TDF) regimen to

Stribild®▼ in 48 virologically suppressed HIV-1 infected patients. The results of this study are briefly discussed in section 3.4[1].

3.1 Clinical evidence comparing Stribild®▼ with Atripla®

GS-US-236-0102 was a randomised, double-blind, multicentre, noninferiority study, which evaluated the efficacy and safety of Stribild®▼ versus Atripla® (EFV 600 mg/FTC 200 mg/TDF 300 mg) in antiretroviral-naive HIV-1 infected adults[1,17]. Patients (n = 700), who were 89% male and 63% white, with a plasma HIV RNA concentration of ≥ 5,000 copies per ml and susceptibility to EFV, FTC and TDF, received a regimen of either a once daily tablet of Stribild®▼ (n = 348) or Atripla® (n = 352). The primary endpoint was the proportion of patients achieving viral suppression (maintaining HIV-1 RNA concentration < 50 copies/ml) at week 48 according to snapshot analysis as defined by the US Food and Drug Administration (FDA). Secondary endpoints included the proportion of patients achieving and maintaining HIV-1 RNA < 50 copies/ml through week 96, and the change from baseline in $CD4^+$ cell count at weeks 48 and 96. Stribild®▼ was noninferior to Atripla® for the primary endpoint; viral suppression was achieved in 305 patients (87.6%) in the Stribild®▼ arm compared with 296 patients (84.1%) in the Atripla® arm (difference 3.6%, 95% confidence interval [CI]: −1.6%, 8.8%). Secondary endpoints for Stribild®▼ versus Atripla® are presented in Table 1. In the Stribild®▼ arm, after 48 weeks, eight patients developed NRTI resistance mutations, of which, seven patients also had integrase resistance mutations. In the Atripla® arm, at 48 weeks, eight patients had NNRTI resistance, of which, two patients also had NRTI resistance[1,17].

Table 1. Secondary endpoints for Stribild®▼ versus Atripla® (study GS-US-236-0102)[17,18]

Secondary endpoint	Stribild®▼	Atripla®	p value	Difference in LSM (95% CI)
Mean increase from baseline in $CD4^+$ cell count at week 48	239 cells/microlitre	206 cells/microlitre	0.009	–
Mean (SD) increase from baseline in $CD4^+$ cell count at week 96	295 (213.3) cells/microlitre	273 (189.7) cells/microlitre	–	22 (−10, 54)
Proportion of patients with HIV RNA concentration < 50 copies/ml at week 96	293/348 (84.2%)	287/352 (81.5%)	0.35 (NS)	–
SD: standard deviation; LSM: least-squares mean; CI: confidence interval; NS: non-significant				

GS-US-236-0104 was a phase II, 48-week, randomised, double-blind, double-dummy, multicentre study, which investigated the efficacy and safety of Stribild®▼ versus Atripla® in antiretroviral-naive HIV-1 infected adults. Patients (n = 71) received either Stribild®▼ (n = 48) or Atripla® (n = 23). Viral suppression was achieved in 43/48 (90%) patients in the Stribild®▼ arm and in 19/23 (83%) patients in the Atripla® arm[16]. In a pre-planned integrated analysis of studies, GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104, virological success at week 48 was achieved in 659/749 (89%) patients receiving Stribild®▼ versus 315/375 (84%) patients receiving Atripla®. The results were statistically significant in favour of Stribild®▼ (treatment difference 5.1%, CI: 0.7%, 9.4% [p = 0.016])[1].

3.2 Clinical evidence comparing Stribild®▼ with ATV/RTV/FTC/TDF

GS-US-236-0103 was a randomised, double-blind, multicentre, noninferiority study, which was designed to assess the efficacy and safety of Stribild®▼ versus a combination of ATV 300 mg/RTV 100 mg/FTC 200 mg/TDF 300 mg in antiretroviral-naive HIV-1 infected adults[1,19]. Patients (n = 708), who were 90% male and 74% white, with a plasma HIV RNA concentration of ≥ 5,000 copies per ml and susceptibility to ATV, FTC and TDF, received a regimen of either Stribild®▼ (n = 353) or ATV/RTV/FTC/TDF (n = 355). To achieve blinding, each patient received four tablets daily: Stribild®▼ (active or placebo), ATV (active or placebo), RTV (active or placebo) and combined FTC/TDF (active or placebo). The primary endpoint was the proportion of patients achieving viral suppression (maintaining HIV-1 RNA concentration < 50 copies/ml) at week 48 according to FDA snapshot analysis. Secondary endpoints included the proportion of patients achieving and maintaining HIV-1 RNA < 50 copies/ml through week 96 and the change from baseline in $CD4^+$ cell count at weeks 48 and 96. Stribild®▼ was noninferior to ATV/RTV/FTC/TDF for the primary endpoint; viral suppression was achieved in 316 (89.5%) patients in the Stribild®▼ arm compared with 308 (86.8%) patients in the ATV/RTV/FTC/TDF arm (adjusted difference 3.0%, 95% CI: −1.9%, 7.8%). Secondary endpoint results are presented in Table 2. Resistance mutations developed in five patients in the Stribild®▼ arm: four patients had resistance to EVG and cross-resistance to RAL, and three patients developed resistance to FTC. No patients in the ATV/RTV/FTC/TDF arm developed resistance mutations[1,19].

Table 2. Secondary endpoints for Stribild®▼ versus ATV/RTV/FTC/TDF (study GS-US-236-0103)[18,19]

Secondary endpoint	Stribild®▼	ATV/RTV/FTC/TDF	p value	Difference in LSM (95% CI)
Mean (SD) $CD4^+$ cell count at week 48	207 (164) cells/microlitre	211 (160) cells/microlitre	–	–
Mean (SD) increase from baseline in $CD4^+$ cell count at week 96	256 (167) cells/microlitre	261 (188) cells/microlitre	–	−8 (−35,19)
Proportion of patients with HIV RNA concentration < 50 copies/ml at week 96	294/353 (83.3%)	292/355 (82.3%)	0.70 (NS)	-
SD: standard deviation; LSM: least-squares mean; CI: confidence interval; NS: non-significant				

3.3 Comparative safety

3.3.1 Comparative safety of Stribild®▼ and Atripla®

In GS-US-236-0102, five patients treated with Stribild®▼ had renal adverse events (AEs) leading to treatment discontinuation; four of these patients developed signs of tubular toxicity[1,17]. Renal laboratory test results or serum creatinine concentration either improved or returned to baseline after patients stopped the study medication. In the Atripla® arm, the treatment-emergent AE (TEAE) causing the largest number of patient discontinuations was rash events, occurring in 1.1% of participants. Nausea was significantly more common in the Stribild®▼ arm than in the Atripla® arm, occurring in 21% versus 14% of patients, respectively (p = 0.016). The proportions of patients with central nervous system effects were significantly lower in the Stribild®▼ arm compared to the Atripla® arm for abnormal dreams (15% versus 27%, p < 0.001), insomnia (9% versus 14%, p = 0.031) and dizziness (7% versus 24%, p < 0.001[1,17,20]). In line with previous studies using COBI, serum creatinine concentration increased for Stribild®▼-treated patients leading to a statistically significant difference (p < 0.001) in the decrease in the median estimated glomerular filtration rate (eGFR) between patients in the Stribild®▼ arm and patients in the Atripla® arm. Median increases in the fasting cholesterol concentration, the low density lipoprotein (LDL) cholesterol

concentration and the high density lipoprotein (HDL) cholesterol concentration were all significantly larger for Atripla®-treated patients than for Stribild®▼-treated patients[1,17]. Bone fractures occurred in six patients in each treatment arm, all of which were related to trauma; none were considered pathological or osteoporotic. The phase II study, GS-US-236-0104, did not raise any additional safety concerns[1,16].

3.3.2 Comparative safety of Stribild®▼ and ATV/RTV/FTC/TDF

In GS-US-236-0103, severe and life-threatening laboratory abnormalities occurred in 47 (16.2%) patients in the Stribild®▼ arm and in 239 (67.9%) patients in the ATV/RTV/FTC/TDF arm, with the difference resulting mainly from the number of patients with bilirubin abnormalities (2 [0.6%] in the Stribild®▼ arm versus 205 [58.2%] in the ATV/RTV/FTC/TDF arm)[1,19]. Both treatments resulted in decreases in eGFR; this decrease was statistically larger for Stribild®▼-treated patients (−12.7 [CI: −21.8 to −4.3] versus −9.5 [CI: −17.9 to 0.2]; $p < 0.001$). The median change in the fasting concentration of triglycerides was lower in the Stribild®▼ arm than in the ATV/RTV/FTC/TDF arm. Ocular icterus was significantly more prevalent in the ATV/RTV/FTC/TDF arm compared to the Stribild®▼ arm. In both arms, the TEAE leading to the largest number of patient discontinuations was gastrointestinal disorders which occurred in four patients [1.1%] receiving Stribild®▼ and five patients [1.4%] receiving ATV/RTV/FTC/TDF[19]. Mean decreases in bone mineral density were comparable between treatments, bone fractures occurred in three patients in the Stribild®▼ group versus six patients in the ATV/RTV/FTC/TDF group and were mostly due to traumatic injury[1,19].

3.4 AWTTC critique

- Stribild®▼ is the first integrase inhibitor/NRTI treatment available as a single tablet in a once daily regimen[1].
- The company estimates that 10% of patients, treatable within the licensed indication for Stribild®▼, would be ineligible due to a creatinine clearance < 70 ml/min[1].
- Since COBI inhibits the CYP3A enzyme, co-administration of Stribild®▼ with treatments that are primarily metabolised by CYP3A may result in increased plasma concentrations of these products; therefore, certain medicines are contraindicated for use in conjunction with Stribild®▼. Similarly, co-administration of Stribild®▼ and treatments which induce CYP3A may result in decreased levels of COBI and EVG. Refer to the Summary of Product Characteristics (SPC) for specific instructions regarding Stribild®▼ co-administration[2].
- Although Atripla® is licensed for the treatment of HIV-1 infection in adults, it is not indicated for use in treatment-naive patients[8]. Eviplera®▼, available as a single tablet to be taken once daily for use in treatment-naive HIV-1 infected patients, was not included as a comparator in the company submission[9]. The company points out that Eviplera®▼ is licensed to treat antiretroviral-naive patients with viral loads < 100,000 copies/ml, whilst Stribild®▼ use is not restricted by viral load[9].
- The company did not provide a comparison of the efficacy of RAL/FTC/TDF and Stribild®▼. However, the GS-US-236-0123 study found that switching from RAL/FTC/TDF to Stribild®▼ was well tolerated with no discontinuations after 12 weeks. The primary endpoint, the proportion of patients achieving HIV-1 RNA < 50 copies/ml at week 12, was met for all 48 participants; however, the study was not powered to provide clinical comparison between these treatments[1].
- In study GS-US-236-0102, Stribild®▼ and Atripla® achieved statistically equivalent viral suppression; however, when data from this trial were integrated with results from the GS-US-236-0103 trial and the phase II trial, GS-US-236-0104, Stribild®▼ achieved statistically superior clinical efficacy versus Atripla®[1].

- The company have provided no evidence on whether the use of a combined, once-daily treatment impacts patients' adherence to treatment.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company has submitted a cost-utility analysis comparing Stribild®▼ to two alternative combinations of treatments for the first-line therapy of treatment-naive HIV patients:

- EFV/FTC/TDF (EFV plus Truvada®)
- ATV/RTV/FTC/TDF(ATV, RTV plus Truvada®)

The comparators are stated in the submission to be those used in Welsh clinical practice, with the EFV/FTC/TDF regimen representing the primary treatment used. A comparison was not made with the individual treatment combination of emtricitabine and tenofovir (FTC/TDF), or ATV/RTV/FTC/TDF. These have slightly lower treatment acquisition costs but may not represent standard practice.

A Markov Model with one year cycles and a lifetime horizon of analysis (70 years maximum) was conducted from the perspective of the NHS and personal social services in Wales. Patients could be in a state of unsuppressed viral load (i.e. HIV RNA ≥ 50 copies/ml), or suppressed (i.e. HIV RNA < 50 copies/ml). At the start of the model, and in any one cycle, patients could also be in any one of six immunological health states according to $CD4^+$ cell count, ranging from ≤ 50 cells/microlitre to > 500 cells/microlitre. Patients experiencing no initial virologic response or a loss of virologic response (failure to achieve HIV RNA < 50 copies/ml), or AEs, switched to second or third-line treatments with the probability of switching based on median treatment time on each therapy line from a UK retrospective database study conducted between 1996–2002[21]. The treatments assumed to be used in second and third line were based on clinical expert opinion.

Data on virological response and transition among $CD4^+$ cell count groups were from two comparative clinical trials[17,19]. Both were 48 week studies; hence, in order to extrapolate outcomes beyond this time point, an exponential curve was fitted to data on virologic response at 96 and 144 weeks from the EFV plus TDF/FTC arm of an alternative published clinical trial[22–24]. $CD4^+$ cell count was also extrapolated from 48 weeks to 96 and 144 weeks using the same data source.

The expected annual cost for Stribild®▼ is £12,589, [Commercial in confidence data removed]. Costs for switching treatment were included, involving consultant visits and laboratory tests. Hospital costs by $CD4^+$ cell count group for the clinical management of HIV was based on resource use and costs from a previously published study[25]. Utility values were also estimated by $CD4^+$ cell count group, based on SF-6D values for symptomatic and asymptomatic HIV states from a published study[26]. Costs and outcomes beyond one year were discounted at 3.5%.

One way sensitivity analyses varied efficacy, discontinuation by 95% CI, and cost parameters by ±25%. In the base case it was assumed that $CD4^+$ cell count increased by 50% after year three compared to the previous year. As this assumption was based on limited data, the increase was varied from 0–100% in sensitivity analysis. The analysis was performed for each comparator regimen with and without the WPAS applied.

4.1.2 Results

The incremental cost-effectiveness ratio (ICER) for Stribild®▼ at list price versus EFV/FTC/TDF and Atripla® was estimated to be £1.192 and £1.168 million per quality-adjusted life-year (QALY) gained, respectively. With the WPAS applied, Stribild®▼ was estimated to result [Commercial in confidence data removed]. Refer to Table 3. The ICER at list price for Stribild®▼ versus ATV/RTV/FTC/TDF was estimated to be £2.361 million per QALY gained. With WPAS applied, Stribild®▼ was estimated to result [Commercial in confidence data removed].

Table 3. Results of the base case analysis (versus EFV/FTC/TDF, Atripla® and ATV/RTV/FTC/TDF)

	Stribild®▼	EFV/FTC/TDF	Difference	Atripla®	Difference	ATV/RTV/FTC/TDF	Difference*
Treatment costs (Stribild®▼ list price)	£237,461	£206,296	**£31,165**	£206,920	**£30,541**	£211,914	**£22,518**
Clinical management + switching costs	£122,010	£122,554	−£544	£122,554	−£544	£121,420	−£154
Total costs at Stribild®▼ list price	£359,471	£328,850	**£30,621**	£329,474	**£29,997**	£333,334	**£22,364**
Treatment costs (Stribild®▼ with WPAS)	CIC	206,296	CIC	£206,920	CIC	£211,914	CIC
Total costs with WPAS	CIC	£328,850		£329,474	CIC	£333,334	CIC
Total life-years	17.30	17.29	**0.01**	17.29	**0.01**	17.139	**0.008**
Total QALYs	16.07	16.04	**0.03**	16.04	**0.03**	15.903	**0.009**
ICER (£/QALY gained) without WPAS			**£1,192,402**		**£1,168,105**		**£2,361,003**
ICER (£/QALY gained) with WPAS			**CIC**		**CIC**		**CIC**

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
*Results for Stribild®▼ in the comparison with ATV/RTV/FTC/TDF are marginally different from the figures presented in the Stribild®▼ column of this table.
For the analysis vs. ATV/RTV/FTC/TDF the cost of Stribild®▼ has been estimated at [Commercial in confidence data removed] . This difference is due to the different clinical data source used for this comparison

The most influential variable on cost-effectiveness in univariate analysis for each of the comparisons was the estimated virological response rate. Commercial in confidence data removed].

Scenario analysis was performed using Welsh specific data for distribution of patients across $CD4^+$ cell count groups rather than using trial based data, and a scenario removing withdrawals due to AEs (to avoid the risk these patients have been counted as part of the virological response rates in the model). Based on the list price the ICERs were > £1.5 million per QALY gained for each of the comparisons across these scenarios. [Commercial in confidence data removed].

The results of the most influential variables in sensitivity analysis and the two scenario analyses performed are summarised in Table 4, with WPAS applied.

Table 4. Results of selected sensitivity and scenario analyses (with WPAS)

Sensitivity Analyses	ICER versus EFV/FTC/TDF	ICER versus Atripla®	ICER versus ATV/RTV/FTC/TDF	Plausibility
Virological response for Stribild®▼ Lower 95% CI Upper 95% CI	CIC	CIC	CIC	Use of extreme ranges of the 95% confidence intervals are less plausible than the mean, but illustrates potential sensitivity of the ICER to possible, albeit improbable, values
Virological response for comparator Lower 95% CI Upper 95% CI	CIC	CIC	CIC	
Annual change in $CD4^+$ cell count after year 3 (50% in base case) 0% 100%	CIC	CIC	CIC	
Scenario 1: Wales specific $CD4^+$ cell count data used in model	CIC	CIC	CIC	Could be considered as plausible as the base case, but not necessarily more plausible –using trial based data directly corresponds to treatment outcomes in the model whereas using Welsh distributions has direct relevance for Wales
Scenario 2: Effect of setting withdrawals due to AEs to zero	CIC	CIC	CIC	Not more plausible than the base case – it reduces risk of double counting withdrawals, but setting to zero maybe too extreme to be considered more plausible than base case
*ICER for ATV versus Stribild®▼				

The probabilistic sensitivity analysis indicated that there was a 0% probability of the ICER for Stribild®▼ (at list price) falling below £30,000 per QALY gained for each of the comparisons against EFV/FTC/TDF, Atripla® or ATV/RTV/FTC/TDF. , [Commercial in confidence data removed].

4.1.3 AWTTC critique

At its list price, Stribild®▼ is associated with high ICERs versus the combination regimens of EFV/FTC/TDF or ATV/RTV/FTC/TDF that are currently being used in Welsh clinical practice for the first-line treatment of patients with HIV. The high ICERs are driven by the additional treatment cost associated with Stribild®▼, and QALY benefits relative to the comparators that are negligible, based on small differences in virologic response at 48 weeks and extrapolated estimates at 96 and 144 weeks. [Commercial in confidence data removed].

Strengths of the economic evaluation include:

- Availability of comparative data for Stribild®▼ versus the primary comparators for the treatment of antiretroviral naive HIV patients of EFV/FTC/TDF, and ATV/RTV/FTC/TDF for use in the economic model.
- The model had a recognised and appropriate structure consistent with previous models used in health technology assessments in the UK for the economic evaluation of HIV treatments.
- The model reflects clinical practice by incorporating three active treatment lines.

Limitations of the economic evaluation include:

- Although EFV/FTC/TDF and ATV/RTV/FTC/TDF represent the current standard of care, not all potential first line comparators in antiretroviral-naive patients have been considered in the economic evaluation, in particular Eviplera®▼ (which has a similar cost as EFV/FTC/TDF and Atripla®). Raltegravir tends not to be used as a first-line treatment in clinical practice; therefore, it may not be as relevant a comparator.
- The data for improved virological response with Stribild®▼ comes from studies concluding noninferiority in this outcome. Hence, Stribild®▼, at list price is more costly than the comparators considered, with no strong evidence of additional clinical (and hence QALY) benefit. [Commercial in confidence data removed] In an AWTTC run scenario using the model with WPAS applied but assuming no difference in virologic response or $CD4^+$ cell outcomes,[Commercial in confidence data removed]
- Extrapolation of virologic response and $CD4^+$ cell counts beyond 48 weeks from the pivotal trials to 144 weeks is based on data from a published clinical study not including Stribild®▼. There is no rationale provided in the submission for using these specific data apart from that they extend to 144 weeks, and so their reliability as a basis for extrapolation is uncertain. The choice of exponential function for extrapolating these data is also not justified, and alternative functions were not explored.
- Costs of AEs were not directly included in the evaluation, so it is uncertain what impact their consideration could have [Commercial in confidence data removed] for Stribild®▼ versus the comparators with WPAS applied.
- No case was made, nor evidence provided, on the impact of any differential rates of adherence among treatment regimens.

4.2 Review of published evidence on cost-effectiveness

There were no published studies of the cost-effectiveness of Stribild®▼ identified in literature searches conducted.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company have estimated the number of new HIV antiretroviral treatment-naive patients as 160 per year, for years one to five, based on new diagnosis data derived from the Health Protection Agency Wales report from 2011[1]. A proportion of these patients are assumed to be eligible for Stribild®▼ according to the licence, and assumed to be 75% of the new diagnosis patient population with a further 10% ineligible due to having a creatinine clearance < 70 ml/min. The company has assumed that 9% of patients eligible for Stribild®▼ would be prescribed the treatment in year one, equating to nine patients. In years two to five, it is assumed that uptake from annual newly diagnosed patients will rise by 2% each year to 17% by year five. Hence, in year two with 11% uptake, there will be 21 patients treated (12 new patients from year two, and the nine patients from year one). By year five there is an estimated 68 patients treated with Stribild®▼.

The company has estimated the budget impact of Stribild®▼ at its list price, and with the WPAS applied. [Commercial in confidence data removed]. Net treatment budget impact costs have been calculated by assuming a 40% reduction in the use of EFV/FTC/TDF and Atripla® regimens, and a 20% reduction in use of the ATV/RTV/FTC/TDF regimen.

5.1.2 Results

The estimated annual acquisition cost of Stribild®▼ at list price is estimated to be £12,589. Based on these proportions, the average weighted annual cost of the displaced comparators is £7,866. Based on list price, the net treatment budget impact after the assumed displacement of the comparator first line regimens is estimated to be £44,211 in year one rising to £319,301 in year five (see Table 5). [Commercial in confidence data removed].

Table 5. Company-reported costs associated with use of Stribild®▼ for the treatment of antiretroviral naive HIV

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Number of eligible patients (Indication covered in this submission)	108	108	108	108	108
Uptake (%)	9%	11%	13%	15%	17%
Treated patients	9	21	34	50	68
Net costs					
Annual cost of Stribild®▼ (list price)	**£12,589**	**£12,589**	**£12,589**	**£12,589**	**£12,589**
Annual cost of Stribild®▼ (WPAS)	**CIC**	**CIC**	**CIC**	**CIC**	**CIC**
Annual cost of displaced medications	**£7,866**	**£7,866**	**£7,866**	**£7,866**	**£7,866**
Overall net cost (list price)	**£44,211**	**£98,246**	**£162,106**	**£235,791**	**£319,301**
Overall net cost (WPAS)	**CIC**	**CIC**	**CIC**	**CIC**	**CIC**

5.1.3 AWTTC critique

The data for new diagnoses of treatment-naive HIV patients is from a reliable source; hence the total number of patients is likely to be accurate. However, there are a number of limitations and so uncertainty in the estimates of numbers of patients treated. These are:

- Whether there is likely to be an increase (or decrease) in the numbers of new diagnoses over the next five years has not been accounted for.
- No sources or rationale are provided for the Stribild®▼ uptake estimates or expected proportions for the displacement of the comparator regimens.
- Account has not been taken for expected time on treatment with Stribild®▼. It appears that it is assumed that newly diagnosed patients will stay on treatment for the full five years.
- No sensitivity analyses have been performed around the budget impact estimates, especially around the uptake rates and proportions of each comparator regimen displaced.

Overall, the level of uncertainty in the budget impact estimates is limited by reliable estimates of newly diagnosed patients, but within this there is uncertainty over the actual number of patients who may be treated with Stribild®▼ in Wales. The final numbers treated estimates appear quite low.

5.2 Comparative unit costs

The comparators considered by the company were EFV/FTC/TDF, Atripla®, and ATV/RTV/FTC/TDF. There are other combination products with indications that enable them to be used in treatment-naive HIV patients. The annual costs of these are included in Table 6.

Table 6. Examples of medicine acquisition costs

Regimens*	Example doses	Approximate costs per patient per year§
EVG/COBI/FTC/TDF (Stribild®▼)	One tablet once daily consisting of 150 mg EVG, 150 mg COBI, 200 mg FTC, 300 mg tenofovir disoproxil fumurate†	£12,589
EFV + FTC/TDF (Truvada®)	Once daily EFV 600 mg + one tablet of Truvada® consisting of 200 mg FTC, 245 mg TDF	£7,528
EFV/FTC/TDF (Atripla®)	One tablet of Atripla® once daily consisting of 600 mg EFV , 200 mg FTC , 245 mg TDF	£7,627
ATV/RTV + FTC/TDF (Truvada®)	Once daily 300 mg ATV + 100 mg ritonavir + one tablet of Truvada® consisting of 200 mg FTC, 245 mg TDF	£9,019
EFV + FTC + TDF	Once daily EFV 600 mg + 200 mg FTC + 245 mg TDF	£7,351
ATV/RTV + FTC + TDF	Once daily 300 mg ATV + 100 mg ritonavir + 200 mg FTC + 245 mg TDF	£8,842
FTC + RPV + TDF (Eviplera®▼)	One tablet once daily consisting of 200mg FTC, 25 mg rilpivirine, 245 mg TDF	£7,528
RAL + FTC/TDF (Truvada®)	Twice daily raltegravir 400 mg + one tablet of Truvada® consisting of 200 mg FTC, 245 mg TDF	£11,465
RAL+ FTC+TDF	Twice daily raltegravir 400 mg + 200 mg FTC + 245 mg TDF	£11,288

ATV: atazanavir; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; RPV: rilpivirine; RTV: ritonavir; TDF: tenofovir disproxil fumarate

*Not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details.
†300 mg of tenofovir disoproxil fumurate is equivalent to 245 mg of tenofovir disproxil
§Costs are based on BNF list prices as of July 2013[27], except Stribild®▼ for which the cost was based on Monthly Index of Medical Specialities (MIMS) July 2013[28].
Costs of administration are not included, but assumed zero due to oral administration.
This table does not imply therapeutic equivalence of treatments or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, EVG/COBI/FTC/TDF (Stribild®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that EVG/COBI/FTC/TDF (Stribild®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission has not highlighted any ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

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

ABBREVIATIONS

ATV: atazanavir
COBI: cobicistat
EFV: efavirenz
EVG: elvitegravir
FTC: emtricitabine
RAL: raltegravir
RPV: rilpivirine
RTV: ritonavir
TDF: tenofovir disoproxil fumarate

REFERENCES

1 Gilead Sciences Ltd. Form B: Detailed appraisal submission. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (Stribild®▼). May 2013.
2 Gilead Sciences Ltd. Stribild®▼. Summary of Product Characteristics. Jun 2013. Available at: http://www.medicines.org.uk/emc/medicine/27810/SPC/. Accessed Jun 2013.
3 Kwong PD, Wyatt R, Robinson J et al. Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a netralizing human antibody. *Nature* 1998; 303 (6686): 648-59.
4 Public Health Wales Health Protection Division. HIV. General information. Dec 2012. Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgId=457&pid=26424. Accessed Jun 2013.
5 Anderson J. Infectious disease, tropical medicine and sexually transmitted infection. In: Kumar P and Clark M, editor. *Kumar and Clark's Clinical Medicine*. 7 ed. Saunders; 2009.
6 Anderson J, Boffito M, Churchill D et al. British HIV Association Guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012. *HIV Med* 2012; 13 (2): 1-85.
7 Semenova E, Marchand C, Pommier Y. HIV-1 Integrase Inhibitors: Updates and Perspectives. 2013. Available at: http://discover.nci.nih.gov/pommier/IntegraseBookFull.pdf. Accessed Jun 2013.
8 Gilead Sciences Ltd. Atripla®. Summary of Product Characteristics. Feb 2013. Available at: http://www.medicines.org.uk/emc/medicine/20505/SPC/Atripla+600+mg+200+mg+245+mg+film+coated+tablets/. Accessed Jun 2013.
9 Gilead Sciences Ltd. Eviplera®▼. Summary of Product Characteristics. Apr 2013. Available at: http://www.medicines.org.uk/emc/medicine/25518/SPC/Eviplera+200+mg+25+mg+245+mg+film+coated+tablets/. Accessed Jun 2013.
10 Shah BM, Schafer JJ, Priano J et al. Cobicistat. A New Boost for the Treatment of Human Immunodeficiency Virus Infection. *Pharmacotherapy* 2013; Published electronically ahead of printing.
11 Public Health England. Wales New HIV diagnoses to end of December 2012. Jan 2013. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1237970256309. Accessed Jun 2013.
12 European AIDS Clinical Society. European guidelines for the treatment of HIV-infected adults in Europe. version 6.1. Nov 2012. Available at: http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41. Accessed Jun 2013.
13 Asboe D, Aitken C, Boffito M et al. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012; 13 (1): 1-44.
14 All Wales Medicines Strategy Group. Final Appraisal Recommendation. Advice no. 1412. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®▼). Jul 2012. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/880. Accessed Jun 2013.
15 All Wales Medicines Strategy Group. Final Appraisal Recommendation. Advice no. 0209. Efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®). Feb 2009. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/119. Accessed Jun 2013.
16 Cohen C, Elion R, Ruane P et al. Randomised, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtrcitabine/tenofovir disoproxil fumarate

versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. *AIDS* 2011; 25 (6): F7-F12.
17 Sax PE, Dejesus E, Mills A et al. Co-formulated elvitegravir, cobicistat, emtricitabine and tenofovir versus co-formulated efavirenz, emtricitabine and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet* 2012; 379 (9835): 2439-48.
18 European Medicines Agency. Assessment Report for Stribild. Procedure No.: EMEA/H/C/002574. Mar 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002574/WC500144274.pdf. Accessed Jun 2013.
19 Dejesus E, Rockstroh JK, Henry K et al. Co-formulated elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet* 2012; 379 (9835): 2429-38.
20 Wills T, Vega V. Elvitegravir: A once-daily inhibitor of HIV-1 integrase. *Expert Opinion on Investigational Drugs* 2012; 21 (3): 395-401.
21 Beck EJ, Mandalia S, Youle M et al. Treatment outcome and cost-effectiveness of different highly active antiretroviral therapy regimens in the UK (1996-2000). *Int J STD AIDS* 2008; 19 (5): 297-304.
22 Arribas JR, Pozniak AL, Gallant JE et al. Tenofovir disoproxil fumarate, emtricitabine and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144 week analysis. *JAIDS* 2008; 47 (1): 74-8.
23 Gallant JE, Dejesus E, Arribas JR et al. Tenofovir DF, emtricitabine and efavirenz versus zidovudine, lamivudine and efavirenz for HIV. *NEJM* 2006; 354 (3): 251-60.
24 Pozniak AL, Gallant JE, Dejesus E et al. Tenofovir disoproxil fumarate, emtricitabine and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic and morphologic changes - A 96 week analysis. *JAIDS* 2006; 43 (5): 535-40.
25 Mandalia S, Mandalia R, Lo G et al. Rising Population Cost for Treating People Living with HIV in the UK, 1997-2013. . 2010;5(12). *PLoS ONE* 2013; 5 (12): e15677R.
26 Schackman BR, Goldie SJ, Freedberg KA et al. Comparison of Health State Utilities Using Community and Patient Preference Weights Derived from a Survey of Patients with HIV/AIDS. *Medical Decision Making* 2002; 22 (1): 27-38.
27 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary. No. 65.* 2013.
28 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2013. Available at: http://www.mims.co.uk/. Accessed Aug 2013.