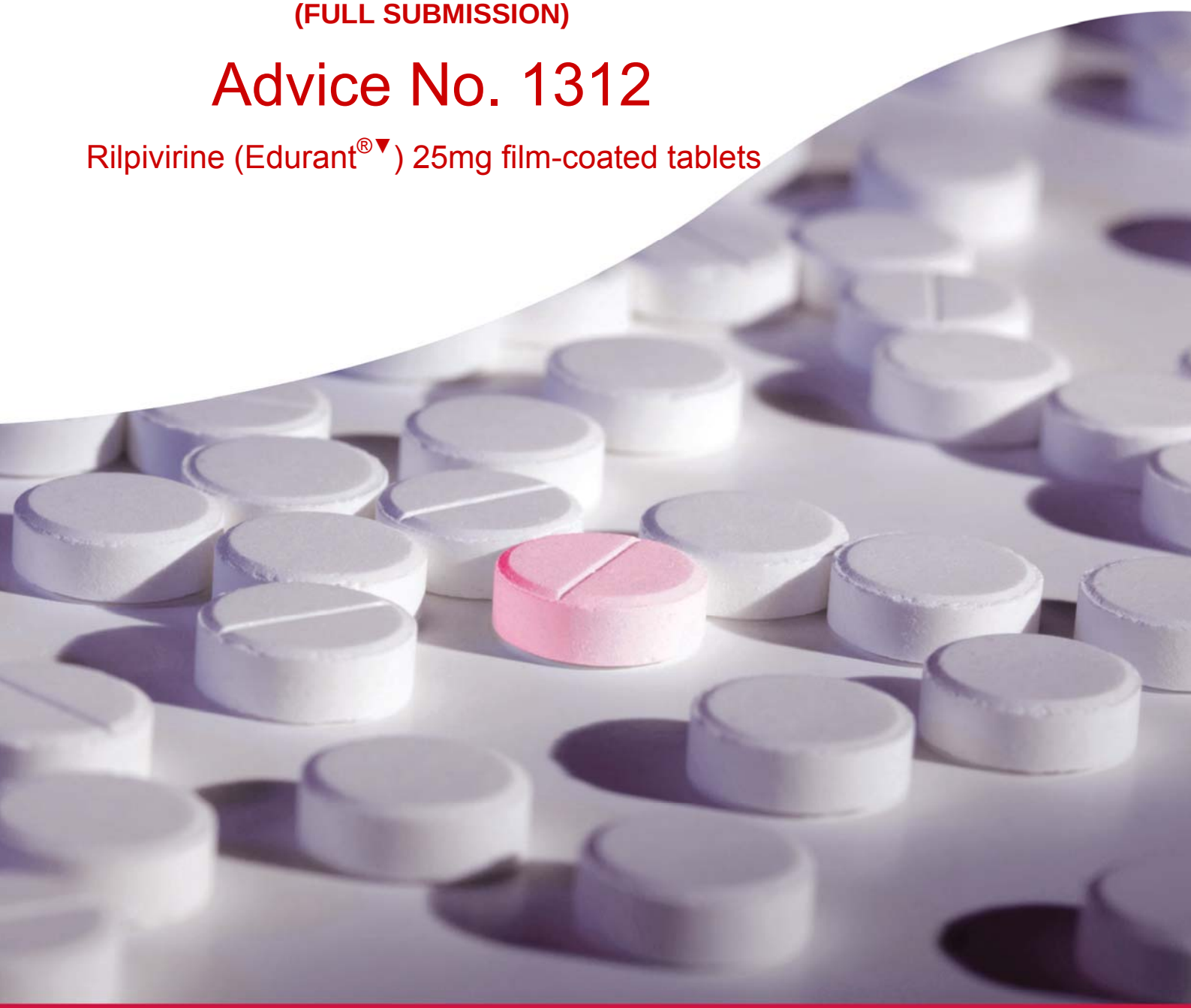
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 1312

Rilpivirine (Edurant®▼) 25mg film-coated tablets



AWMSG Secretariat Assessment Report – Advice No. 1312
Rilpivirine (Edurant®▼) 25 mg film-coated tablets

This assessment report is based on evidence submitted by Janssen-Cilag Ltd on 22 December 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Rilpivirine (Edurant®▼), in combination with other antiretroviral medicinal products, 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 rilpivirine[2].
Dosing	Rilpivirine must always be given in combination with other antiretroviral medicinal products. The recommended dose is one 25 mg tablet taken orally once daily with a meal[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, resulting 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].

Rilpivirine is an NNRTI that acts to inhibit the action of the HIV-1 reverse transcriptase. The licensed indication is for patients with viral load of ≤ 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 efavirenz and nevirapine (Viramune®). The company submission includes a comparison with efavirenz, which is suggested to be the most commonly prescribed NNRTI in the UK for this patient group and is recommended by current guidelines[1,7].

2.3 Guidance and related advice

- British HIV Association 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 recommendations 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 concurrently considering:

- Nevirapine (Viramune®) 400 mg prolonged release tablets in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults[11].
- Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®▼) 200 mg/ 25 mg/245 mg tablets 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[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes two pivotal studies that evaluated the safety and efficacy of rilpivirine in comparison to efavirenz in treatment-naive HIV-1 patients: ECHO and THRIVE. Marketing authorisation was originally sought to allow the use of rilpivirine for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients in combination with other antiretroviral medicinal products; as such, ECHO and THRIVE were designed to include all HIV-1 infected patients with a viral load of >5,000 copies/ml. However, results from the full analysis raised concerns regarding virological failure and development of resistance-associated mutations (RAMs) in patients with plasma HIV levels (viral load) > 100,000 RNA copies/ml. Therefore, rilpivirine was granted a licence for those with viral load ≤ 100,000 HIV-1 RNA copies/ml. As evidence of effectiveness in the licensed population, the applicant company supplied a pooled analysis of all treatment-naive HIV-1 patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml enrolled into the THRIVE and ECHO studies[1].

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

3.1 Overview of THRIVE and ECHO studies

Both THRIVE and ECHO were randomised, double-blind, double-dummy, active-controlled phase III studies that compared rilpivirine and efavirenz over a 96-week treatment period. Following screening, patients were stratified according to viral load (≤ 100,000 copies/ml, 100,001–500,000 copies/ml and > 500,000 copies/ml) and randomised 1:1 to receive a once-daily dose of either 25 mg rilpivirine (or matched placebo) with food or 600 mg efavirenz (or matched placebo) on an empty stomach[13,14]. Patients in the THRIVE study received a background NRTI regimen of tenofovir disoproxil fumarate and emtricitabine (60% of patients enrolled), zidovudine with lamivudine (30%) or abacavir with lamivudine (10%), dependent on investigator selection[13]; all patients in the ECHO study received tenofovir disoproxil fumarate and emtricitabine[14].

Subjects entering the study were HIV-1 infected treatment-naive patients with a plasma viral load of ≥ 5,000 copies/ml, who were susceptible to the selected background regimen at screening and did not have any NNRTI resistance associated mutations (RAMs) from a predefined list. Main exclusion criteria included life expectancy of less than six months, HIV-2 co-infection or the presence of an AIDS-defining illness except cutaneous Kaposi sarcoma and HIV wasting syndrome[13,14].

The primary endpoint of both studies was the proportion of patients with confirmed virological response, defined as plasma viral load < 50 HIV-1 RNA copies/ml, at week 48, at a predefined non-inferiority margin of 12%. The main secondary endpoints were non-inferiority at a 10% margin, superiority (if non-inferiority was demonstrated), change in $CD4^+$ cell count from baseline and assessment of the evolution of HIV genotypic and phenotypic characteristics (in virological failures)[13,14]. Additional secondary endpoints included patient-reported outcomes such as health-related quality of life (HRQoL) and adherence[1,13,14]. See Glossary for endpoint definitions and criteria.

3.1.1 Overview of endpoint data from THRIVE and ECHO studies

The primary endpoint 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 (see Appendix 1)[13,14]. The 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; however, superiority was not demonstrated. Both treatment groups also demonstrated an increased $CD4^+$ cell count[13,14] and showed similar improvements in patient-reported HRQoL endpoints[15,16]. Data obtained at 96 weeks showed that these responses were maintained over this period[1].

In rilpivirine-treated patients there was an increased incidence of virological failure over the efavirenz treatment group. There was also an increased emergence of NNRTI and NRTI RAMs in patients treated with rilpivirine[13,14]. However, this patient group included subjects with high viral load, which is not part of the licensed indication, and it was noted that the elevated failure rate was driven by this subgroup[17].

Further endpoint data for the intent-to-treat (ITT) population of these studies is provided in Appendix 1.

3.1.2 Pooled analysis of patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml from THRIVE and ECHO studies

In the population of patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml, the proportion with a virological response was 90.2% and 83.6% in patients receiving rilpivirine and efavirenz, respectively, demonstrating the non-inferiority at the 12% margin (see Table 1 and Appendix 1)[1,17]. Data submitted by the company shows that this efficacy was maintained up to 96 weeks[1].

Mean $CD4^+$ cell count increases were comparable between the treatment groups, although tended to be slightly higher in the rilpivirine-treated group (see Table 1). The rate of treatment discontinuation was also lower in rilpivirine-treated patients (9.8%) than in patients receiving efavirenz (14.3%). However, the incidence of virological failure and treatment-emergent RAMs was slightly higher in patients receiving rilpivirine than efavirenz.

Table 1. Summary of data from pooled analysis of patients with viral load ≤ 100,000 HIV-1 RNA copies/ml enrolled in THRIVE and ECHO studies[1,17].

Endpoint description	Rilpivirine (n = 368)	Efavirenz (n = 329)
Primary endpoint		
Proportion of virological responders at week 48	332 (90.2%)	276 (83.6%)
Between group difference (95% CI)	6.1% (1.6, 11.5)	
Secondary endpoints		
Proportion of virological responders at week 96	84%	79.9%
Between group difference (95% CI)	4% (-1.7, 9.7)	
Mean change in $CD4^+$ cell count from baseline at week 48	185 cells/mm^3 (week 96: 223 cells/mm^3)	160 cells/mm^3 (week 96: 206 cells/mm^3)
Virological failures at week 48 (efficacy endpoint)	14 (3.8%)	11 (3.3%)
Virological failures at week 96 (resistance analysis)	7.3%	5.1%
See glossary for endpoint definitions.		

3.2 Evidence of comparative safety

The company submission includes a comparison of the safety profiles of rilpivirine and efavirenz in treatment-naive patients with HIV-1 infection, which is a wider population than that described by the licensed indication[1].

At the time of licensing, rilpivirine was concluded to be generally safe and well tolerated[17]. 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 91/686 (13.3%) of rilpivirine-treated patients and 123/682 (18.0%) 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)[17].

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%). 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[17].

3.3 AWTTC critique

- At the time of licensing, The Committee for Medicinal Products for Human Use (CHMP) concluded that the superior tolerability profile of rilpivirine was clinically significant[17]. However, it also highlighted the high incidence of virological failure and emerging resistance observed in the rilpivirine-treated patient group in the clinical studies ECHO and THRIVE, which is suggested to have greater clinical consequences than improved tolerability. Virological failure and resistance in the rilpivirine group was found to be driven by patients with high baseline viral load (> 100,000 copies/ml); therefore this population was excluded from the licensed indication. However, the incidence within the licensed population (treatment-naive adults with viral load ≤ 100,000 HIV-1 copies/ml) was still higher in rilpivirine-treated patients than in those that received efavirenz (see Table 1 and Appendix 1)[17].
- The full analysis of the pivotal studies demonstrated non-inferiority of rilpivirine to efavirenz in treatment naive adults with HIV-1 infection regardless of viral load[13,14]. The licensed indication 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[1,17].
- Improved tolerability and safety have been acknowledged as important drivers of good patient adherence, which should be considered during the development of new antiretroviral therapies, especially for treatment-naive patients[17]. CHMP acknowledge the superior tolerability profile of rilpivirine[17] and the applicant company highlight the lower incidence of AEs more usually associated with efavirenz treatment, such as rash, dizziness and abnormal dreams, in rilpivirine-treated patients[1]; due to this, the company suggests that rilpivirine could provide more assurance of adherence in patients with disorders relating to these events. However, there is no evidence to support this conclusion (see Appendix 1). Furthermore, at the time of licensing, CHMP noted that reduced patient adherence was associated with worse outcomes in the rilpivirine treatment arm than in the efavirenz group[17]. However, as this analysis included patients with baseline viral load > 100,000 copies/ml, which is not part of the licensed indication, the effect of low adherence on the licensed population is unknown.
- The applicant company has noted that during the THRIVE and ECHO studies, treatment discontinuation was lower in rilpivirine-treated patients (9.8%) than in the efavirenz group (14.3%) for the licensed population[1,17].
- Low rilpivirine exposure resulting from concomitant non-HAART therapies or intake on an empty stomach could reduce efficacy and affect the development of resistance[17]. This is reflected in the Summary of Product Characteristics (SPC)[2].
- At the time of licensing, it was noted that low baseline $CD4^+$ cell count was associated with reduced efficacy in the pivotal trials; however, definite conclusions could not be drawn due to a limited numbers of patients enrolled with a $CD4^+$ count < 50 cells/microlitre[17]. Additionally, the trials included few patients over 60 years of age or with AIDS-defining or clinically significant co-existing illnesses, hindering the extrapolation of outcomes to these populations[17].
- Although the efficacy of rilpivirine has been demonstrated at 96 weeks, there is a lack of long-term effectiveness data at present, as noted by the company[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis of first-line rilpivirine in its licensed indication for HIV-1 infected adults with a baseline viral load ≤ 100,000 copies/ml who have not previously received treatment[1,2]. The comparator is efavirenz, and both are given in combination with two NRTI background agents (78% are suggested to receive emtricitabine plus tenofovir disoproxil fumarate). The analysis is based on a Markov model, similar to other HIV models in which treatment duration with each line of therapy is determined primarily by virological response or discontinuations due to AEs, and outcomes are determined by health states, defined by $CD4^+$ cell count. Up to four lines of treatment are modelled over a lifetime analytical time horizon.

First-line treatment efficacy is modelled using pooled direct comparative data from the subpopulation of the ECHO and THRIVE trials meeting the licensed indication. Efficacy of subsequent lines of therapy is reported to be derived from pooled analyses of pivotal trials of the respective agents. Non-drug costs are based on historical costs derived from a UK database study and have been inflated to 2010 prices. See Appendix 2 for further details.

4.1.2 Results

Table 2. Company-reported results of the base case analysis[1].

	Rilpivirine + BR	Efavirenz + BR	Difference
ART drug costs	£179,898	£182,248	-£2,350
Other drug costs	£22,405	£22,965	-£561
Inpatient costs	£5,318	£5,413	-£95
Outpatient costs	£7,248	£7,233	£14
Total costs	**£214,869**	**£217,860**	**-£2,991**
Total LYG	17.250	17.174	0.077
Total QALYs	13.650	13.582	0.068
ICER (£/QALY gained)	Rilpivirine dominates efavirenz*		

* Rilpivirine is both more effective and less costly than efavirenz
ART: antiretroviral therapy; BR: background regimen; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year gained

The company model estimates first-line rilpivirine to be both more effective (gain of 0.068 quality-adjusted life-years [QALYs]) and less costly (by around £3,000) than first-line efavirenz over a lifetime horizon. One way sensitivity analyses indicate that the model is most sensitive to the modelled rate of $CD4^+$ cell count changes and the costs of third- and fourth-line regimens; however, within the parameter values explored, all of the reported sensitivity and scenario analyses indicate that first-line rilpivirine is less costly and generates more QALYs than efavirenz. The impact of removing utility decrements associated with AEs and alternative sources of utility weights, including those derived from the THRIVE and ECHO trial participants, have been explored and suggest the model is relatively insensitive to the assumed utility values. A probabilistic

sensitivity analysis indicates that around 65% of modelled simulations fall below a threshold of £20,000–£30,000 per QALY gained. See Appendix 2 for further details.

4.1.3 AWTTC critique

It is not certain that the base case analysis would provide the most plausible estimate of the cost-effectiveness of rilpivirine in routine practice. Rilpivirine has been described as unforgiving in relation to patient adherence and clinical exposure[17], which may be reduced in clinical practice compared with that observed in the clinical trial setting; however, all analyses conducted by the company retain the small differences in virological and immunological responses observed in favour of rilpivirine in subgroup analyses of the trial data. It would seem plausible that costs and outcomes could be comparable over the lifetime horizon of analysis.

Strengths of the economic evidence include:

- Direct comparative data are used to model efficacy in the licensed population for rilpivirine and the comparator efavirenz.
- A pragmatic approach has been adopted to modelling the efficacy of second and subsequent lines of therapy using the key trials of these different agents.
- A wide range of sensitivity and scenario analyses have been conducted to explore the impact of key assumptions.

Limitations of the economic evidence include:

- The efficacy data for rilpivirine versus efavirenz are based on subgroup analyses, for which the ECHO and THRIVE trials were not powered. CHMP noted that based on the patient population from the THRIVE and ECHO studies, adherence must be high with rilpivirine and that it must be taken in strict accordance with the SPC to ensure maximum exposure to combat the risk of virological failure and development of resistance (see Section 3.3)[17]. It is therefore uncertain whether treatment outcomes observed in the trials, and used in the economic model, will be matched by those in clinical practice.
- As noted by the company, there is a lack of long-term effectiveness data for rilpivirine and efavirenz[1]. Although a wide range of sensitivity analyses have been conducted by the company, all retain the small increased virological and immunological responses observed with rilpivirine compared with efavirenz in the pooled trials up to 96 weeks. The company has not explored the potential for lower relative efficacy of rilpivirine versus efavirenz than observed in the clinical trials. As may be expected from a scenario of equal efficacy, rilpivirine no longer dominates efavirenz, and QALY gains and cost differences are very small and comparable over the life time horizon.
- Sources of non-drug resource use and costs are dated and may not reflect those in current practice in Wales, although the model appears relatively insensitive to the assumed non-drug resource use and costs.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of rilpivirine within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Reportedly based on data from Public Health Wales[5], the company estimates there were 1,189 people diagnosed with HIV-1 in Wales in 2009, and an average incidence over the preceding four years of 157 cases per year. Assuming an annual mortality rate of 2%, the company has used these figures to predict the yearly net number of patients with HIV-1 in Wales as being 1,571 in 2012, rising to 2,047 in 2016. Of these, 78% are assumed to receive some antiretroviral therapy, based on Health Protection Agency data from 2009[18]. The number of patients predicted to be eligible for first-line therapy is therefore estimated as 22% of prevalent cases and 78% of incident cases. Of these, 87% are predicted to have a baseline viral load ≤ 100,000 copies/ml based on company-sought market research. Using 48-week pooled data from the ECHO and THRIVE trials, 9.8% of patients are assumed to discontinue rilpivirine each year. The company assumes market share of 6% in 2012, rising to 10% in 2013, then 8% in 2014 and 6% in each of 2015 and 2016[1]. The number of patients anticipated to receive rilpivirine is estimated as 23 in 2012, rising to 110 in 2016.

The company has used market research data to estimate the current proportion of use of the main NRTI background regimens in the UK (emtricitabine/tenofovir; abacavir/lamivudine; zidovudine/lamivudine). From these, the company has estimated the likely average annual costs of providing rilpivirine and efavirenz based regimens.

5.1.2 Results

The company anticipates cost savings from the use of a rilpivirine-based regimen instead of an efavirenz-based regimen, as detailed in Table 3. Alternative scenarios of the percentage of treatment-naive patients with viral loads of ≤ 100,000 copies/ml, the annual mortality rate and the assumed rilpivirine treatment discontinuation rate have also been provided; in all cases rilpivirine is estimated by the company to generate cost savings.

Table 3. Company-reported costs associated with rilpivirine treatment[1].

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients	383	407	431	454	476
Uptake (%)	6%	10%	8%	6%	6%
Treated patients*	23	52	84	98	111
Average annual cost per patient for rilpivirine + BR	£6,954	£6,954	£6,954	£6,954	£6,954
Average annual cost per patient for efavirenz + BR	£7,206	£7,206	£7,206	£7,206	£7,206
Net costs per patient	-£253	-£253	-£253	-£253	-£253
Primary care (displaced drug costs per patient)	-£253	-£253	-£253	-£253	-£253
Secondary & tertiary care	0	0	0	0	0
Staffing	0	0	0	0	0
Infrastructure	0	0	0	0	0
Personal social services	0	0	0	0	0
Overall net cost for whole population	-£5,815	-£13,017	-£21,330	-£24,845	-£28,147
* Takes into account a 9.78% discontinuation rate per year.					

5.1.3 AWTTC critique

- The company has made reasonable efforts to define the epidemiology of HIV-1 infection using Wales-specific data.
- The anticipated market uptake is a key component of the estimated cost savings and is, as in all budget impact analyses, a source of uncertainty.
- The key driver of the projected cost savings is the assumed costs of background treatment regimens used with rilpivirine and efavirenz. The company has used market research data to estimate the likely proportion of patients that will be treated with each of the three main NRTI background regimens for each of rilpivirine and efavirenz. The higher cost of the background regimen for efavirenz is due to the increased acquisition cost of the triple combination product efavirenz/emtricitabine/tenofovir (Atripla®) compared with where efavirenz is administered as a separate product to the NRTI background regimen. It should be noted that Atripla® is licensed only for use in patients who have already achieved stable virological suppression on the separate components, and not for initiation of treatment[19]. The estimated cost savings appear to assume the use of Atripla® as a first-line treatment, which would overestimate the costs of the background regimens assumed for efavirenz, and any cost savings associated with the use of rilpivirine.
- Rilpivirine 25 mg and efavirenz 600 mg tablets as single products have the same acquisition costs, and it is unlikely that the adoption of rilpivirine in NHS Wales would have a significant net budgetary impact.
- A triple combination product of emtricitabine/rilpivirine/tenofovir (Eviplera®▼) is also available and is subject to a separate AWMSG appraisal[12].

5.2 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. Table 4 provides example comparative costs for the most common first-line NNRTI/NRTI regimens.

Table 4. Examples of drug acquisition costs for first-line NNRTI/NRTI regimens.

Example regimens	Dose	Approximate annual cost
NNRTI		
Rilpivirine 25 mg (Edurant®▼) tablets	One tablet daily in combination with a BR of two NRTIs	£2,438 plus two NRTI BR costs
Efavirenz 600 mg (Sustiva®) tablets	One tablet daily in combination with a BR of two NRTIs	£2,438 plus two NRTI BR costs
Two NRTI BR		
Tenofovir disoproxil fumarate 245 mg/ emtricitabine 200 mg (Truvada®)	One tablet daily in addition to NNRTI	£5,095
Abacavir 600 mg/lamivudine 300 mg (Kivexa®)	One tablet daily in addition to NNRTI	£4,289
Zidovudine 300 mg/lamivudine 150 mg (Combivir®)	One tablet twice daily in addition to NNRTI	£3,654
NNRTI with two NRTI combination products		
Emtricitabine 200mg/rilpivirine 25mg/tenofovir disoproxil fumarate 245 mg (Eviplera®▼)*	One tablet daily	£7,534
Efavirenz 600 mg/tenofovir disoproxil fumarate 245 mg/ emtricitabine 200 mg (Atripla®)†	One tablet daily	£7,633

BR: background regimen; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitors.
* Eviplera®▼ is currently undergoing appraisal by AWMSG[12].
† Atripla® is not licensed for initiation of first-line treatment; patients who are stabilised on individual components may switch to Atripla® when sustained virological suppression is achieved[19].
Costs based on MIMS list prices as of 3 Feb 2012[20].
This table does not imply therapeutic equivalence of the stated drugs and doses.
See all relevant SPCs for full dosing details[2,19,21–25].

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that rilpivirine is appropriate for specialist only prescribing within NHS Wales for the stated indication.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months:

- TMC278-C204: a phase IIb randomised, partially blinded, dose-finding trial of rilpivirine in antiretroviral-naive HIV-1 infected subjects[26]. Analyses from weeks 96 and 192 have been published[27,28].
- ECHO: a phase III clinical trial in treatment-naive HIV-1 patients comparing rilpivirine to efavirenz in combination with tenofovir and emtricitabine[29]. Week 96 analyses are awaiting publication.
- THRIVE: a phase III clinical trial in treatment-naive HIV-infected patients comparing rilpivirine to efavirenz in combination with two NRTIs[30]. Week 96 analyses are awaiting publication.
- NCT01286740: a phase IIb study to evaluate switching from a regimen consisting of an efavirenz/emtricitabine/tenofovir disoproxil fumarate single tablet regimen (STR) to an emtricitabine/rilpivirine/tenofovir disoproxil fumarate STR[31].

- NCT01309243: a phase IIIb study to evaluate the safety and efficacy of an emtricitabine/rilpivirine/tenofovir disoproxil fumarate STR compared with an efavirenz/emtricitabine/tenofovir disoproxil fumarate STR in HIV-1 infected, antiretroviral treatment-naive adults[32].
- NCT01252940: a phase III study to evaluate switching from regimens consisting of a ritonavir-boosted protease inhibitor and two NRTIs to a fixed-dose tablet containing emtricitabine/rilpivirine/tenofovir disoproxil fumarate[33].

6.3 AWMSG review

This ASAR will be considered for review three years from Ministerial ratification (date will be disclosed on 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.

GLOSSARY

Virological failure (efficacy endpoint)
A patient with virological failure was classified as one of the following:

- Rebounder: achieved plasma viral load < 50 HIV-1 RNA copies/ml on two consecutive visits before week 48, but then obtained viral load values ≥ 50 RNA copies/ml on two successive visits.
- Never suppressed: did not achieve viral load < 50 HIV-1 RNA copies/ml on two consecutive visits before week 48[13,14].

Virological failure (resistance analysis)
Virological failure as determined by resistance analysis was defined as any patient who received at least one dose of therapy and then had a treatment failure, regardless of treatment status, reason for discontinuation or time of failure (whether before or after week 48), providing one of the following criteria had been met:

- Achieved plasma viral load < 50 HIV-1 RNA copies/ml on two consecutive visits, but then obtained viral load values ≥ 50 RNA copies/ml on two successive visits.
- Did not achieve viral load < 50 HIV-1 RNA copies/ml on two consecutive visits and had an increase in viral load of at least 0.5 log10 copies/ml above the lowest point[13,14].

Virological response
A virological response was defined as two consecutive viral load values that were < 50 HIV-1 RNA copies/ml. Loss of response occurred where two consecutive values of ≥ 50 RNA copies/ml were obtained. Following loss of response, patients were considered non-responders, even if re-suppression was obtained[1].

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Appendix 1. Additional clinical information.

Table 1. Week 48 endpoint analysis from THRIVE and ECHO studies.

	THRIVE[13,16,17]		ECHO[14,15,17]		Pooled analysis in patients with low viral load[1,17]	
	Rilpivirine	**Efavirenz**	**Rilpivirine**	**Efavirenz**	**Rilpivirine**	**Efavirenz**
Number of patients included in analysis	340	338	346	344	368	329
Primary endpoint						
Proportion of virological responders at week 48	291 (86%)	276 (82%)	287 (83%)	285 (83%)	332 (90.2%)	276 (83.9%)
Difference (95% CI)	3.9% (-1.6, 9.5)		0.1% (-5.5, 5.7)		6.1% (1.6, 11.5)	
Secondary endpoints						
Mean change in $CD4^+$ cell count from baseline	189 cells per microlitre	171 cells per microlitre	196 cells per microlitre	182 cells per microlitre	185 cells/mm^3	160 cells/mm^3
Proportion of patients where self-reported adherence > 95%	272/308 (88.3%)	241/284 (84.9%)	275/319 (86.2%)	267/317 (84.2%)	Not available	Not available
Treatment discontinuation						
Discontinuation	44 (13%)	56 (17%)	50 (14%)	56 (16%)	36 (9.8%)	47 (14.3%)
Due to virological failure	13 (4%)	8 (2%)	23 (7%)	6 (2%)	7 (1.9%)	3 (0.9%)
Due to AEs	15 (4%)	25 (7%)	8 (2%)	28 (8%)	15 (4.1%)	20 (6.1%)
Virological failure and RAM						
Virological failures (efficacy endpoint)	24 (7%)	18 (5%)	38 (11%)	15 (4%)	14 (3.8%)	11 (3.3%)
Virological failures (resistance analysis)	27 (8%)	20 (6%)	45 (13%)	19 (6%)	19 (5.2%)	16 (4.8%)
Proportion of virological failures with treatment emergent RAM	15/22 (68%)	8/15 (53%)	29/40 (73%)	8/13 (62%)	8/16 (50%)	6/12 (50%)
NNRTI RAM	13/22 (59%)	7/15 (47%)	26/40 (65%)	8/13 (62%)	6/16 (38%)	5/12 (42%)
NRTI RAM	14/22 (64%)	5/15 (33%)	28/40 (70%)	4/13 (31%)	7/16 (44%)	2/12 (17%)

AE: adverse event; CI: confidence interval; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitors; RAM: resistance-associated mutation.

Appendix 2. Additional health economic information.

Table 1. Health economic model detail

	Base case model	Appropriate?
Comparator(s)	Rilpivirine 25 mg once daily is compared against efavirenz 600 mg once daily, both given in addition to background regimens as observed in patients with baseline HIV viral load ≤ 100,000 copies/ml in the ECHO and THRIVE trials.	Yes. AWTTC originally requested a comparison against efavirenz and nevirapine, but the company has noted efavirenz is the most relevant comparator.
Population	Treatment-naive HIV-1 patients with baseline viral load ≤ 100,000 copies/ml.	Yes, as per the licensed indication[2].
Model type and description	Cost utility analysis (CUA) based on a Markov model. Patients enter the model in one of six $CD4^+$-defined health states. Patients may move between $CD4^+$ health states or to a final state of death based on virological response and change in $CD4^+$ cell count over time. For the initial treatment regimen, virological response at 48 weeks determines whether patients remain on therapy or switch due to lack of viral suppression or emergence of AEs. Subsequent treatment options are assumed to be the same for patients treated initially with rilpivirine or efavirenz. Virological response for subsequent lines of therapy is considered at 24 weeks. Up to four lines of therapy are modelled, after which patients are assumed to remain on their current therapy until death. A three month cycle length has been adopted.	CUA is the preferred type of analysis. A similar approach to other HIV models has been adopted, in which treatment duration with each line of therapy is determined primarily by virological response or AEs and health states and outcomes are determined mainly by $CD4^+$ cell counts. The model assumes the proportion of patients treated with each second and subsequent treatment regimen is the same for rilpivirine and efavirenz.
Perspective	NHS Wales	Yes.
Time horizon	Life time analytical horizon assumed with 10- and 15-year time horizons explored in sensitivity analyses.	Yes, appropriate for life-long treatment of a conditions such as HIV.
Discount rate	3.5% discount rate for costs and outcomes, with 0% and 6% explored in sensitivity analyses.	Yes, appropriate.

Table 1. Continued.

	Base case model	Appropriate?
Efficacy	$CD4^+$ cell count changes and virological response with first-line treatment are derived from the subpopulation of the pooled ECHO and THRIVE trials with a baseline viral load ≤ 100,000 copies/ml. $CD4^+$ cell counts increase rapidly in the first 24 weeks, and then at a slower rate between weeks 24 and 96, unless treatment is discontinued due to lack of virological response or AEs. Historical data on time to switching of drug classes, obtained from the UK[34], is used to determine the duration of stable $CD4^+$ counts, after which patients are assumed to switch to the next line of therapy. $CD4^+$ cell count changes and virological response for second-line therapy, assumed to be protease inhibitor-based, is modelled using data from a formal mixed treatment comparison. Efficacy of subsequent lines of therapy is reported to be derived from pooled results of pivotal phase III trials. $CD4^+$ decline is permitted only after fourth-line treatment. HIV and non-HIV-related deaths are modelled using historical data from European centres and Welsh all-cause mortality data.	Efficacy of first-line treatment is derived from the ECHO and THRIVE trials, and the company acknowledges these were not powered for analyses in the relevant subpopulation of participants. The EPAR noted that treatment adherence needs to be high for rilpivirine, and it must be taken in strict accordance with the SPC to maximise exposure, to combat a potentially greater risk of virological failure[17]. There is a risk that efficacy in clinical practice may therefore be reduced for rilpivirine compared with that observed in the clinical trial setting. Although the risk of development of resistance with rilpivirine in the licensed subpopulation appeared low and comparable to efavirenz in the trial, it appears uncertain whether this would also be the case in practice if patient adherence and rilpivirine exposure is reduced compared with that observed in the trial. As noted by the company, there is a lack of long term effectiveness data for rilpivirine and efavirenz. The company has adopted a pragmatic approach to modelling outcomes with second and subsequent lines of therapy, although this inevitably introduces a degree of uncertainty. A mixed treatment comparison informs second-line treatment efficacy of protease inhibitors, although it appears that most trials included in that analysis were conducted in patients with prior protease inhibitor experience and many patients were heavily pre-treated. No details are provided around the methods of identifying and selecting trials, and pooling efficacy data, for darunavir as a second-line protease inhibitor therapy, or other classes used in subsequent lines of therapy.
Adverse effects	The model considers AEs related to first-line treatment only. Pooled rates of grade 2 or greater AEs observed in the pooled ECHO and THRIVE trial populations have been used to inform utility estimates. The costs of AEs are assumed to be encompassed within non-drug costs.	AE rates are based on 48-week data from the trials. The impact of AEs is assumed to occur within the first cycle and to be resolved within the three month cycle. It is not clear that all included AEs would resolve in this time frame.
Utility values	A published study of predicted utility values, derived from treatment-naive and treatment-experienced HIV patients in five open-label trials using the SF-36 instrument, has been used to weight the $CD4^+$-defined health states in the base case analysis[35]. Utility decrements associated with AEs are reported to be taken from this same study. Alternative utility weights from a published CUA of other agents, and those derived using the SF-36 in ECHO and THRIVE trial participants, were explored in sensitivity analyses.	It is not possible to verify the reported utility weights obtained from the ECHO and THRIVE trial participants. The utility weights attached to AEs in the base case analysis are inconsistent with those reported in the cited reference, and it is not possible to verify those utility decrements assumed for lab abnormalities which may typically be asymptomatic (e.g. cholesterol and triglyceride abnormalities). As the rates of AEs included in the model are generally greater for efavirenz than rilpivirine, this analysis would appear to be biased in favour of rilpivirine; however, one way sensitivity analyses, including the removal of utility decrements associated with AEs, indicate that the model is relatively insensitive to the assumed utility weights.

Table 1. Continued.

	Base case model	Appropriate?
Resource use and costs	Antiretroviral drug acquisition costs are based on BNF list prices[36]. Costs of background regimen drugs are based on weighted average costs of those observed in the THRIVE and ECHO trials, and other trials for later lines of therapy. Non-antiretroviral costs are reportedly derived from a retrospective UK database study of HIV-related resource use conducted in 2006, with costs inflated to 2010 prices. These include inpatient and outpatient costs, and non-antiretroviral drug costs.	Non-antiretroviral resource use and costs are based on historical data and costs from two centres in London, and it is possible that these do not reflect current resource use and costs in a range of other centres in the UK. AE costs are assumed to be encompassed within these costs, and so are not specifically modelled separately.
Uncertainty	A wide range of one-way sensitivity and scenario analyses, and probabilistic sensitivity analysis, has been conducted.	One way scenario analyses indicate the model is most sensitive to the rate of $CD4^+$ count changes and the costs of third- and fourth-line regimens. All of the reported sensitivity analyses demonstrate that first-line rilpivirine is less costly and generates more QALYs than efavirenz. PSA suggests that around 65% of 1,000 simulations fall below a threshold of £20–30k/QALY, although a proportion of these were in the SW quadrant of the cost-effectiveness plane. Rilpivirine was dominant (both more effective and less costly) in around 49% of simulations. Although a wide range of sensitivity analyses have been conducted to explore the impact of efficacy parameters based on the ECHO and THRIVE trials, these trials were not powered for the subgroup analyses in the licensed population. The EPAR notes that (when adherence is high) efficacy outcomes are comparable between rilpivirine and efavirenz in the licensed population[17], but the company has not explored the possibility of equal virological and immunological response. AWTTC analyses using the company's model indicate that if virological and immunological responses, and rate of change in $CD4^+$ cell counts, for rilpivirine are equal to that of efavirenz, then rilpivirine is marginally more costly than efavirenz and offers a negligible QALY gain. Under this scenario the actual costs and QALY gains over the modelled lifetime are very small, which can make the modelled ICER appear very sensitive to small incidental changes in some parameter values.
Model Provided?	Yes	Yes, model appears to generate results as reported in the submission.
Other considerations		

AE: adverse event; AWTTC: All Wales Therapeutics and Toxicology Centre; CUA: cost utility analysis; EPAR: European Public Assessment Report; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years.