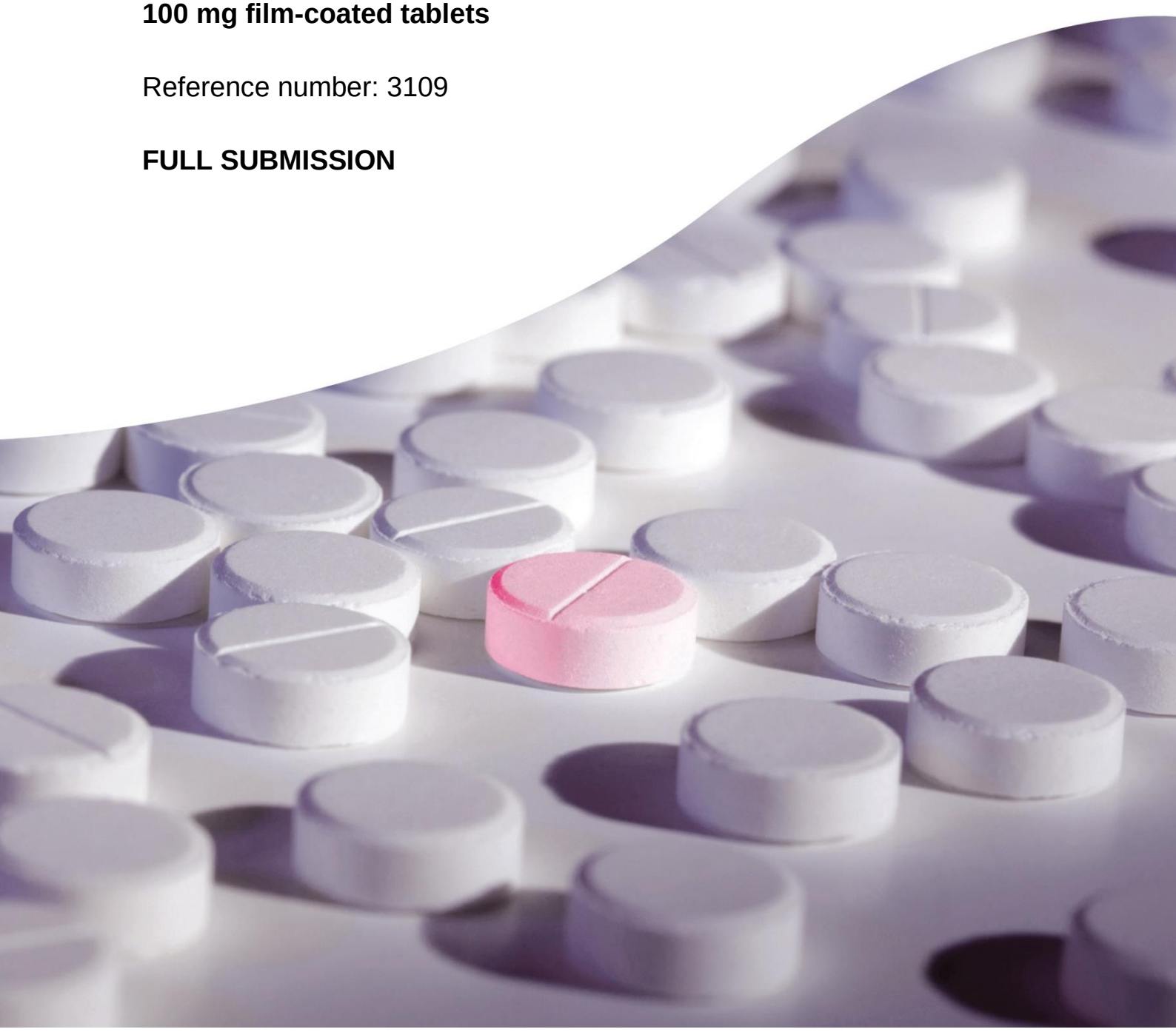
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Doravirine (Pifeltro®)
100 mg film-coated tablets

Reference number: 3109

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Doravirine (Pifeltro®) 100 mg film-coated tablets. Reference number: 3109. July 2020.

AWMSG Secretariat Assessment Report
Doravirine (Pifeltro®▼) 100 mg film-coated tablets

1.0 KEY FACTS

Assessment details	Doravirine (Pifeltro®▼), in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Current clinical practice	British HIV Association guidelines recommend that people with HIV-1 infection start on a triple therapy antiretroviral regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor. The company states that doravirine represents an additional third agent option for first-line use either in combination with an NRTI backbone as Pifeltro® or as the single tablet regimen doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®). Etravirine and rilpivirine, which are also NNRTIs are the main comparators. Doravirine may also be used as a second- or subsequent-line switch treatment option where existing treatment is not tolerated or has failed.
Clinical effectiveness	The main evidence comes from three phase III studies in adults with HIV-1 infection. One study compared doravirine with ritonavir-boosted darunavir, when given in combination with either: emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine. Another study compared fixed-dose combinations of doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®) and efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®). A third study evaluated the effect of switching treatment from a stable antiretroviral regimen to a once-daily, single tablet of Delstrigo®. The studies showed that doravirine was non-inferior to the comparators, or to switching treatment. A simplistic network meta-analysis of doravirine versus rilpivirine in treatment-naive patients showed no statistical differences in terms of viral suppression; no comparison was made for safety. No indirect comparison versus etravirine was possible because of heterogeneity in patient populations and study design.

Costeffectiveness	A cost analysis compares prescription costs of doravirine with rilpivirine as third agents, given in combination with two NRTI backbones, in the treatment of HIV infection. [Commercial in confidence text removed] A cost-minimisation analysis is inappropriate in this instance given that for the base case analysis, equivalence is based on the results of a network meta-analysis comparing doravirine and rilpivirine only and not on the basis of well-designed equivalence trials. The model does not take into account any other resource use or costs apart from the prescription costs of doravirine and rilpivirine. Potential for discontinuation is not considered which would have resource implications. Only treatment-naïve patients are included in the base case comparison, which does not reflect the indicated population. The time horizon is restricted to one year although it is likely that treatment would be continued over a longer time period. The sensitivity analysis compares doravirine with other branded third agents: etravirine, dolutegravir and darunavir. No clinical comparative data are presented for the comparators in the sensitivity analysis.
Budget impact	[Commercial in confidence text removed] Only the prescription costs of the medicines are reported, no other resource use or costs are included in the analysis. No description of the settings is reported or differences in resource use by different settings. The cost of dolutegravir is varied in a sensitivity analysis to investigate the impact of the Wales Patient Access Scheme (WPAS) discount.
Additional factors to consider	Delstrigo® (the single tablet combination of doravirine, lamivudine, tenofovir disoproxil fumarate) is being appraised separately to doravirine (Pifeltro®) as a limited submission. AWMSG criteria require doravirine (Pifeltro®) to be recommended before Delstrigo® can be appraised.

This assessment report is based on evidence submitted by Merck Sharp and Dohme UK Ltd and an evidence search conducted by AWTTC on 3 February 2020[1].

2.0 BACKGROUND

2.1 Condition and clinical practice

HIV type 1 (HIV-1) infection is a retroviral infection causing chronic activation of the immune system resulting in a gradual loss of CD4 T cells and weakening of the immune system[2]. Antiretroviral treatment aims to suppress and maintain HIV-1 RNA levels in the blood to below detectable limits (usually < 50 copies/ml)[3].

British HIV Association (BHIVA) guidelines recommend treating HIV-1 infection with a triple therapy antiretroviral regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) plus either: a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor[3]. The guidelines recommend

emtricitabine and tenofovir disoproxil fumarate (or tenofovir alafenamide) as the two NRTIs[3]; NNRTIs that could be used as the third agent include: efavirenz, rilpivirine, nevirapine and etravirine. Antiretroviral therapies are tabulated in Appendix 1.

There are limitations to the NNRTI class for reasons of tolerability, efficacy and resistance: efavirenz is associated with central nervous system side effects, nevirapine with liver reactions and rash, and rilpivirine is not indicated for people with a high baseline viral load, or where proton pump inhibitors are contra-indicated[4]. Etravirine is indicated in previously treated patients but not in treatment-naive patients. In addition there is evidence of resistance to NNRTIs[4].

According to clinical experts in Wales, the choice of antiretrovirals used in triple therapy depends on cost and factors such as resistance, tolerability, adherence, baseline viral load, hepatitis B status, co-morbidities, drug-drug interactions and patient choice.

2.2 Medicine

Doravirine (Pifeltro) is an NNRTI that is taken orally, once-daily, with or without food[5]. The European Medicines Agency granted it marketing authorisation in November 2018 to treat HIV-1 infection in adults without past or present evidence of resistance to other NNRTIs[5].

Doravirine would be an additional third medicine option for first-line treatment in combination with antiretroviral therapy[1]. The company acknowledges that given the availability of generic third agents it anticipates doravirine will be limited to use as an alternative option to other branded third agents. The company suggests it may also be used as a second- or subsequent-line switch treatment option where treatment with an alternative antiretroviral agent has not worked or is not tolerated[1].

The company has developed a fixed-dose combination product containing doravirine 100 mg, lamivudine 300 mg and tenofovir disoproxil fumarate 245 mg (Delstrigo®).

2.3 Comparators

The comparator(s) included in the company's submission are:

- rilpivirine;
- etravirine;
- dolutegravir; and
- darunavir[1].

2.4 Guidance and related advice

- British HIV Association (BHIVA) guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)[3]
- European AIDS Clinical Society (EACS) (2017) The EACS treatment guidelines version 9.0 (updated October 2017)[6]

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the comparator third agents for the treatment of HIV-1 infection in adults in Wales:

- rilpivirine (Edurant®)[7];
- etravirine (Intelence®)[8];
- dolutegravir (Tivicay®)[9]; and
- darunavir/cobicistat (Rezolsta®)[10].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, doravirine (Pifeltro®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that doravirine (Pifeltro®) may be supplied by a home healthcare provider.

3.0 CLINICAL EFFECTIVENESS

The main evidence comes from three phase III studies conducted in adults with HIV-1 infection:

- DRIVE-FORWARD compared doravirine with ritonavir-boosted darunavir, each given in combination with two different NRTI fixed-dose combinations: emtricitabine/tenofovir disoproxil fumarate; or abacavir/lamivudine.
- DRIVE-AHEAD compared fixed-dose combinations of doravirine/ lamivudine/tenofovir disoproxil fumarate (Delstrigo®) and efavirenz/ emtricitabine/tenofovir disoproxil fumarate (Atripla®).
- DRIVE-SHIFT evaluated the effect of switching treatment from a stable antiretroviral regimen to a once-daily, single tablet regimen of doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®).

The company also conducted a literature review and a network meta-analysis to provide indirect comparison of doravirine with rilpivirine.

3.1 DRIVE-FORWARD study

This randomised, double-blind, parallel-group, phase III non-inferiority study was conducted at 125 centres worldwide, including 11 sites in the UK[11]. It enrolled adults (aged over 18 years) with HIV-1 infection who had not yet received any antiretroviral therapy and who had plasma HIV-1 levels of at least 1,000 copies per ml. Patients were excluded if they had documented or known resistance to study medicines including ritonavir, darunavir, tenofovir, abacavir, emtricitabine or doravirine. A total of 769 patients were randomised to receive up to 96 weeks of oral, once-daily treatment with either doravirine 100 mg or darunavir 800 mg plus ritonavir 100 mg in combination with either emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, or abacavir 600 mg/lamivudine 300 mg. Most patients (87% in each group) received the emtricitabine/tenofovir disoproxil regimen[11].

The study's primary endpoint was the proportion of patients who had plasma HIV-1 RNA levels of less than 50 copies per ml at Week 48, as defined by the US FDA snapshot algorithm[11]. Secondary endpoints included HIV-1 RNA less than 40 copies/ml and change from baseline in CD4 T-cell count. Development of viral resistance to the study medicines was an exploratory endpoint. Safety outcomes included change from baseline in LDL-cholesterol and non-HDL-cholesterol, incidence of adverse events and time to discontinuation because of adverse events. Non-inferiority was established if the lower bound of the two-sided 95% confidence interval (CI) for the treatment difference (doravirine minus darunavir) was greater than −10 percentage points. Three patients who had been randomised did not receive any treatment and efficacy analyses were conducted in the full analysis set (n = 766), defined as all randomised patients who received at least one dose of study treatment. This comprised 645 men and 121 women; median age was 33 years[11].

At Week 48, 321 of 383 patients (84%) in the doravirine group and 306 of 383 (80%) in the darunavir group had plasma HIV-1 RNA of < 50 copies/ml (Table 1)[11]. The lower bound of the CI was −1.6 showing that doravirine was non-inferior to darunavir. Doravirine showed antiretroviral efficacy comparable to that of ritonavir-boosted

darunavir for the subgroups with the two different NRTI combinations. Results for secondary virological endpoints were consistent with those for the primary endpoint[11].

3.2 DRIVE-AHEAD study

This randomised, double-blind, phase III non-inferiority study was conducted at 126 centres worldwide, including seven centres in the UK[12]. It enrolled adults (aged over 18 years) with HIV-1 infection who had not yet received any antiretroviral therapy and who had plasma HIV-1 levels of at least 1,000 copies per ml. Patients were excluded if they had documented or known resistance to any of the study medicines. In total, 734 patients were randomised to receive up to 96 weeks of oral, once-daily treatment with fixed-dose combinations of either: doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (Delstrigo®), or efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Atripla®)[12].

The primary and secondary endpoints were the same as those used in DRIVE-FORWARD. The pre-specified non-inferiority margin for the primary endpoint was −10%[12]. Six patients were randomised but did not receive any treatment so were not included in the full analysis set of 728 patients (616 men; median age 31 years)[12].

At Week 48, 307 of 364 patients (84%) in the Delstrigo® group and 294 of 364 patients (81%) in the Atripla® group had plasma HIV-1 RNA of < 50 copies/ml (Table 1)[12]. The lower bound of the CI was −2.0 showing that Delstrigo® was non-inferior to Atripla®. Similar results were seen for the secondary endpoints[12].

3.3 DRIVE-SHIFT study

This open-label, randomised, active-controlled, non-inferiority phase III study was conducted at 122 centres worldwide[13]. It enrolled adults with HIV-1 infection who had no history of virological failure and had been virologically suppressed for at least six months on a stable antiretroviral regimen consisting of a ritonavir- or cobicistat-boosted protease inhibitor (atazanavir, darunavir or lopinavir), a cobicistat-boosted integrase inhibitor (elvitegravir), or an NNRTI (efavirenz, nevirapine or rilpivirine), each in combination with two NRTIs[13].

Patients were randomly assigned (2:1) to switch to Delstrigo® on Day 1 (switch group) or to continue their baseline regimen until Week 24 (baseline group)[13]. The primary endpoint was patients with HIV-1 RNA < 50 copies/ml. This was measured at 48 weeks from switching baseline treatment (switch group) or after 24 weeks of continuing baseline treatment (baseline group).

Delstrigo® was non-inferior if the lower bound of the 95% CI was above −8%. The analyses included all patients who received at least one dose of study medicine. There were 447 patients in the switch group and 223 in the baseline group. Of these 670 patients, 566 (84%) were men and the median age was 43 years[13].

At Week 48, 406 patients (91%) in the switch group had maintained HIV-1 RNA < 50 copies/ml and at Week 24, 211 of 223 patients (95%) in the baseline group had HIV-1 RNA < 50 copies/ml (Table 1)[13]. The lower bound of the CI was −7.87 so switching to Delstrigo® was non-inferior to continuing the baseline regimen for 24 weeks[13].

Table 1 Primary endpoint results from DRIVE-FORWARD, DRIVE-AHEAD and DRIVE-SHIFT studies[11-14]

DRIVE FORWARD	Doravirine (100 mg) n=383	Darunavir plus ritonavir (800/100 mg) n=383	Treatment difference (95% CI)
Number of patients with HIV-1 RNA <50 copies/ml at Week 48 (%)	321 (83.8%)	306 (79.9%)	3.91* (−1.59 to 9.42)
DRIVE AHEAD	**Delstrigo® (100/300/300 mg) n=364**	**Atripla® (600/200/300 mg) n=364**	**Treatment difference (95% CI)**
Number of patients with HIV-1 RNA <50 copies/ml at Week 48 (%)	307 (84.3)	294 (80.8%)	3.54* (−1.95 to 9.03)
DRIVE SHIFT	**Switch group - Delstrigo® (100/300/300 mg) at Week 48† n=447**	**Baseline group at Week 24§ n=223**	**Treatment difference (95% CI)**
Number of patients with HIV-1 RNA <50 copies/ml (%)	406 (90.8%)	211 (94.6%)	−3.78* (−7.87 to 0.31)

* non-inferior

† Switch group: patients switched from baseline treatment to Delstrigo®

§ Baseline group: patients continued their baseline regimen

Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg; CI: confidence intervals; Delstrigo®: doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

3.4 Indirect treatment comparisons

There were no direct studies of doravirine versus the comparators therefore the company conducted a literature search to identify studies which could inform indirect comparison. The search found nine clinical studies, including DRIVE-FORWARD, DRIVE-AHEAD and DRIVE-SHIFT which could have been used to compare the efficacy of doravirine versus rilpivirine and etravirine[1]. A single comparative analysis was not possible because of significant heterogeneity in study designs and patient populations. Therefore, the company conducted two separate analyses[1].

In treatment-naive patients, a simplistic network meta-analysis of doravirine versus rilpivirine compared the efficacy in terms of viral suppression only[1]. The analysis based on five studies (see Appendix 2) showed no statistical differences between doravirine and rilpivirine, based on viral suppression at 48 and 96 weeks. The same result was obtained with fixed effects and random effects models[1].

In treatment-experienced patients, the three studies identified had significant heterogeneity in the study designs and patient populations, therefore comparison between doravirine and etravirine (only licensed in treatment-experienced patients) could not be done[1].

3.5 Comparative safety

The EMA's Committee for Medicinal Products for Human Use (CHMP) viewed the safety profile of doravirine as favourable, with comparable or superior tolerability compared to darunavir (plus ritonavir), and superior tolerability compared with efavirenz[4].

Doravirine-treated patients showed statistically significant reductions from baseline in low-density lipoprotein (LDL) cholesterol and non-high density lipoprotein (HDL)

cholesterol compared to those treated with darunavir (a protease inhibitor) plus ritonavir[11]. The favourable effects of doravirine treatment on blood lipids were maintained throughout the 96 weeks[14]. Doravirine-treated patients had significantly fewer medicine-related diarrhoea adverse events compared with darunavir-treated patients[11]. Compared to efavirenz (an NNRTI) subjects treated with doravirine present with statistically fewer neuropsychiatric adverse events, a lower risk of rash and a more favourable lipid profile[4].

The number of patients failing therapy with de-novo resistance was very low in the DRIVE-FORWARD study: one of 383 patients treated with doravirine versus none of 383 treated with darunavir. In DRIVE-AHEAD de-novo resistance was confirmed in six of 364 patients treated with doravirine versus 12 of 364 treated with efavirenz[4].

3.6 AWTTC critique

- Evidence from two phase III studies showed that doravirine (in combination therapy) was non-inferior to ritonavir-boosted darunavir (DRIVE-FORWARD study) and to efavirenz (DRIVE-AHEAD study) for the primary endpoint of suppressing HIV[11,12].
- In the DRIVE-AHEAD study doravirine was used in combination with an NRTI backbone which differed from that used in the Atripla® arm, therefore there is uncertainty whether differences were due to doravirine versus efavirenz or differences between backbones. In DRIVE-SHIFT patients were switched from a large number of different third agents and different NRTI backbones creating uncertainty as to whether outcomes were due to doravirine.
- Clinical expert opinion, sought by AWTTC has advised that patients can exhaust treatment options through a combination of allergy, adverse reaction, intolerance and resistance, and doravirine would provide an alternative treatment option.
- Neuropsychiatric adverse events were significantly fewer with doravirine compared with efavirenz[4]. Doravirine-treated patients had significantly fewer medicine-related diarrhoea adverse events and had significantly favourable cholesterol profiles, compared with darunavir-treated patients[11]. Clinicians in Wales have highlighted that doravirine offers advantages over other NNRTIs which may be useful when choosing treatment for individual characteristics and balancing risks for individual patients. The company has not provided a comparison of adverse effects with the comparators: rilpivirine, etravirine and dolutegravir.
- The company's indirect treatment comparison is limited to comparing the efficacy of doravirine versus rilpivirine in a simplistic network meta-analysis, which showed no differences for the primary endpoint. Indirect comparison is limited to comparison via a single medicine, efavirenz. There is no indirect comparison of the safety of doravirine. The company was unable to compare doravirine with etravirine in treatment-experienced patients because of heterogeneity in the patient populations and study endpoints. No comparison versus dolutegravir has been made.
- The licence for doravirine has no restrictions on its use, whereas some other NNRTIs are restricted, such as etravirine (only for treatment-experienced patients) or rilpivirine (only for patients with a viral load < 100,000 copies/ml).
- Doravirine has a novel resistance profile among the NNRTI class and may have a higher barrier to resistance in contrast with other agents in that class. The EMA noted that the resistance barrier seemed higher with doravirine than with efavirenz whereas ritonavir-boosted darunavir was associated with the lowest risk of treatment failure[4].

- Patients with resistance to the study medicines were excluded in the clinical studies so these may not reflect the licensed indication or how the medicine will be used in practice[4].

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes a base case cost analysis comparing the prescription cost for one year of doravirine 100 mg once daily with rilpivirine 25 mg once daily (third agent NNRTIs) both given orally in combination with two NRTI backbones in adults (≥ 18 years) with HIV infection.

A simple cost comparison is used to estimate the difference in medicine costs between doravirine and rilpivirine based on the first year of the five-year budget impact analysis. An NHS Wales/Personal and Social Services perspective is used. Doravirine has a Wales Patient Access Scheme (WPAS). The indication for doravirine covers adults with HIV infection (treatment-naïve or treatment-experienced without past or present mutations in the NNRTI class) but the base case costing scenario reflects a first-line treatment subset of the licensed population, as rilpivirine is restricted to first-line treatment and plasma HIV-1 RNA concentration of ≤ 100,000 copies/ml.

Costs for a full course of oral treatment are calculated as the sum of the costs of medicine acquisition over a year. The acquisition cost for rilpivirine is sourced from the British National Formulary. No other resources or direct costs were anticipated with the use of doravirine. Monitoring costs, costs related to discontinuations of treatment or treatment switching, and costs related to adverse events are not included. The company stated that monitoring costs were not included as the current British HIV Association (BHIVA) guidelines recommend the same monitoring frequency regardless of ART regimen[15].

No discounting is applied as the time horizon is limited to one year. Results from a network meta-analysis comparing doravirine to rilpivirine informed the basis for equivalence of efficacy that supported the costing approach. Based on data from two trials, no statistically significant differences in efficacy were found based on viral suppression at 48 and 96 weeks. Resource use related to adverse events is not included in the analysis. Costs related to switching between ART regimens was not included. When patients switch ART regimens, there may be additional monitoring requirements if the original treatment fails, or there are new HIV-related symptoms or adverse events[15]. The company did not include resource use related to switching treatment as these would not be specific to treatment switching onto, or away from, doravirine (rather than another HIV treatment) and as such it was considered that they do not represent an additional incremental cost with doravirine.

The company conducted scenario analyses to test the influence of different comparators. Other comparators tested in scenario analyses are: etravirine 200 mg twice daily, dolutegravir 50 mg once daily, and darunavir 800 mg once daily. No evidence is presented for equivalence of efficacy of doravirine compared with etravirine, dolutegravir or darunavir. Dolutegravir is the only medicine of the four comparators with a WPAS.

4.2 Results

The results of the base case and scenario analyses based on the WPAS discounted price of doravirine are detailed in Table 2. [Commercial in confidence text removed][16]. The cost differences are due to the difference in prescription cost only.

Table 2. Results of the base case analysis and scenario/sensitivity analyses

Scenario	Costs	Doravirine (WPAS price)	Comparator	Difference	Plausibility
Base case: comparator rilpivirine 25 mg once daily					
Doravirine versus rilpivirine	Medicine acquisition costs	¶¶	**£2,438.29**	¶¶	Rilpivirine is restricted to HIV infection not previously treated with antiretroviral therapy and plasma HIV-1 RNA concentration less than or equal to 100,000 copies/mL. Doravirine can be used in treatment experienced patients and there is no restriction on RNA concentration.
Scenario analysis: comparator etravirine 200 mg twice daily					
Doravirine versus etravirine	Medicine acquisition costs	¶¶	**£3,667.96**	¶¶	Etravirine is restricted to antiretroviral treatment-experienced patients and therefore would not be a first-line agent. Doravirine can be used as a first- line agent. The company states that etravirine would typically be used infrequently and only in highly treatment-experienced patients whose disease does not respond to or is not adequately controlled on alternative antiretroviral therapy regimens
Scenario analysis: comparator dolutegravir 50 mg once daily					
Doravirine versus dolutegravir	Medicine acquisition costs	¶¶	**£6,072.28**	¶¶	Dolutegravir may be a suitable comparator to doravirine. It can be used in treatment naïve or treatment experienced patients. [Commercial in confidence text removed]
Scenario analysis: comparator – darunavir 800 mg once daily + ritonavir 100 mg once daily					
Doravirine versus ritonavir boosted darunavir	Medicine acquisition costs	¶¶	**£3,826.85**	¶¶	Darunavir is restricted to patients who have been previously treated with antiretroviral therapy.

¶¶ Commercial in confidence figure removed.

Only medicine acquisition costs are included. Other costs, e.g. administration costs, adverse event costs, diagnosis and monitoring, and hospitalisation costs, are not included

4.3 AWTTC critique

The reliability of the cost-minimisation analysis (CMA), presented as a cost analysis, depends on the extent to which doravirine is considered to be therapeutically equivalent to the comparators. The company justified using a CMA, as opposed to a cost utility analysis (CUA), based on a network meta-analysis comparing doravirine to rilpivirine using two studies in treatment-naïve patients with HIV infection.
The submission is characterised by strengths and limitations.

Strengths:

- The analysis adopts an appropriate perspective.

Limitations:

- The criteria for a CMA have not been met. Equivalence studies have not been conducted and the company has used an indirect treatment comparison. In

addition differences in side effects and barriers to resistance were found in clinical studies and a CUA may have been able to include these differences.

- The comparators have treatment restrictions: rilpivirine is restricted to HIV infection not previously treated with antiretroviral therapy and plasma HIV-1 RNA concentration ≤ 100,000 copies/mL drugs[16]; etravirine is restricted to HIV infection resistant to other NNRTIs and protease inhibitors in combination with other antiretroviral drugs[16], and darunavir is restricted to patients who have previously been treated with antiretroviral therapy[16]. The company reports in Form B that according to clinical opinion, including Welsh HIV clinicians, etravirine would typically be used infrequently and only in highly treatment-experienced patients whose HIV infection does not respond to or is not adequately controlled on alternative antiretroviral therapy regimens.
- The analysis presented is a simple cost analysis including only prescription costs. No other resource use such as monitoring costs, treatment for adverse events, or discontinuation and treatment switching costs have been included and the company does not justify excluding other resource use.

4.4 Review of published evidence on cost effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre identified a CUA of doravirine versus dolutegravir, or ritonavir-boosted darunavir of HIV-1 infected treatment-naïve adult patients submitted to the Canadian Agency for Drugs and Technologies in Health[17]. In the model, treatment with doravirine resulted in more QALYs (22.40) compared to ritonavir-boosted darunavir (22.32 QALYs) but less QALYs than dolutegravir (22.54 QALYs) over a lifetime time horizon. Limitations in the review included that clinical effectiveness evidence and utility value assumptions were highly uncertain[17].

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there are 2,644 people with HIV infection in Wales. This estimate is based on Welsh specific prevalence data published by Public Health England[18]. To calculate the number of people who need treatment in Wales, the company has extrapolated prevalence data from 2017 using an 8% annual increase in prevalence based on the average increase from 2008 to 2017[18]. The Public Health England data reported that 97% of people with HIV infection were receiving antiretroviral therapy in Wales, and 99% of patients are ≥ 18 years old[18]. The proportion of patients prescribed a third agent rather than a single tablet regimen was estimated as 65%.

[Commercial in confidence text removed] The company considers the impact of introducing doravirine to a current market consisting of the comparators rilpivirine, etravirine, dolutegravir and darunavir and provides a breakdown of how these comparator medicines are likely to be displaced as a result. For doravirine, the WPAS price was applied, whilst list prices were used for all the comparators (of the four comparators only dolutegravir has a WPAS). The cost of darunavir included ritonavir as a boosting agent. Sensitivity analysis of the cost for dolutegravir is presented to show the influence of the WPAS on the budget impact. No other sensitivity analyses were carried out.

Clinical expert opinion, sought by AWTTC has advised that patients can exhaust treatment options through a combination of allergy, adverse reaction/ intolerance and resistance, and doravirine would provide an alternative treatment option. In the absence of real-world data on the distribution of use of doravirine, a simplifying assumption of the same percentage displacement for all comparators was made.

However, the primary comparator for this analysis is rilpivirine (as another NNRTI third agent used in Wales), based on Welsh clinical expert opinion to the AWTTC prior to submission.

5.2 Results

The budget impact results are presented in Table 3. [Commercial in confidence text removed]

Table 3. Company-reported costs associated with use of doravirine for the treatment of HIV infection

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of people with HIV	2,644	2,848	3,069	3,306	3,562
Number of patients prescribed a third agent	1,541	1,660	1,789	1,927	2,077
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations (6% discontinuation)	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	£7,070,308	£7,617,368	£8,206,758	£8,841,750	£9,525,875
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figure removed					

The company estimated that no additional resources or direct costs (or savings) are anticipated arising from the introduction of doravirine.

5.3 AWTTC critique

- The company has included population growth and mortality in the calculations.
- The company reports that the "number of patients eligible for treatment with doravirine is anticipated to be the full HIV adult population (naïve and experienced populations)": 6.6% of patients are estimated to be resistant to NNRTI/NRTI and of the remaining patients, 35% receive a single tablet regimen. The calculations for the budget impact analysis include all the remaining 65% of patients who would have a regimen requiring a third agent, therefore all these patients receive branded medicines in the analysis. The company has assumed doravirine would be used as an alternative to other branded agents.
- In the Public Health England data % incidence decreases after 2014 therefore using the average 8% annual increase in HIV population may overestimate the projected patient numbers in Years 1 to 5.
- The budget impact analysis considerations are limited to acquisition costs only; other resource use is not included (e.g. monitoring costs, costs associated with adverse events, costs associated with discontinuation and switching).
- The budget impact does not explore whether patients are treatment-naïve or treatment-experienced even though the comparators have different indications for this aspect.

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Appendix 1
Antiretroviral therapy combination options for HIV-1 infection

NRTI "backbone"	+	NNRTI		Protease inhibitor		Integrase inhibitor		Single tablet regimens
Emtricitabine + tenofovir disoproxil fumarate **or** Truvada® (emtricitabine/ tenofovir disoproxil fumarate)	**plus**	Efavirenz	**or**		**or**			Atripla® (emtricitabine/tenofovir disoproxil fumarate/efavirenz)
		Rilpivirine						
		Etravirine*						
		Nevirapine						
		Doravirine						
				Darunavir + ritonavir				
				Darunavir + cobicistat **or** Rezolsta®(darunavir/cobicistat)				
				Atazanavir + ritonavir				
						Dolutegravir		
						Elvitegravir (+ cobicistat)		Stribild® (emtricitabine/tenofovir disoproxil fumarate/ elvitegravir/ cobicistat)
						Raltegravir		
Emtricitabine + tenofovir alafenamide **or** Descovy® (emtricitabine/tenofovir alafenamide)	**plus**	Efavirenz						
		Rilpivirine						Odefsey® (emtricitabine/tenofovir alafenamide/rilpivirine)
		Etravirine						
		Nevirapine						
		Doravirine						
				Darunavir + ritonavir				
				Darunavir + cobicistat OR Rezolsta®(darunavir/cobicistat)				Symtuza® (emtricitabine/tenofovir alafenamide/darunavir/cobicistat)
				Atazanavir +ritonavir				
						Dolutegravir		
						Bictegravir**		Biktarvy® (emtricitabine/tenofovir alafenamide/bictegravir)
						Elvitegravir (+ cobicistat)		Genvoya® (emtricitabine/tenofovir alafenamide/elvitegravir/cobicistat)
						Raltegravir		
Abacavir + lamivudine **or**	**plus**	Efavirenz						
		Rilpivirine						
		Etravirine						

NRTI "backbone"	+	NNRTI		Protease inhibitor		Integrase inhibitor		Single tablet regimens
Kivexa® (abacavir/lamivudine)		Nevirapine						
		Doravirine						
				Darunavir + ritonavir				
				Darunavir + cobicistat OR Rezolsta®(darunavir/cobicistat)				
				Atazanavir +ritonavir				
						Dolutegravir		Triumeq® (abacavir/lamivudine/ dolutegravir)
						Elvitegravir (+ cobicistat)		
						Raltegravir		
Lamivudine + tenofovir disoproxil fumarate	**plus**	Doravirine						Delstrigo® (lamivudine/tenofovir disoproxil fumarate/doravirine)

NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleotide reverse transcriptase inhibitor

Appendix 2

Studies included in the company's network meta-analysis

Study name	Study design	Patient population	Interventions used	Time	Primary endpoint measure
STaR	Randomized, open-label, 96-week study directly comparing the safety and efficacy of the two NNRTI-based single tablet regimens	Treatment-naive adults with HIV-1 infection (≥2,500 copies/ml (n=786)	Rilpivirine/emtricitabine/tenofovir DF (n=394) vs. Efavirenz/emtricitabine/tenofovir DF (n=392)	96 weeks	Proportion of subjects with HIV-1 RNA <50 copies/ml at Week 48 by the FDA snapshot algorithm
ECHO	Phase 3, randomised, double-blind, double-dummy, active-controlled trial of rilpivirine vs efavirenz, in combination with emtricitabine and tenofovir DF (non-inferiority study)	Treatment-naive adults with HIV-1 infection (≥5,000 copies/ml (n=690)	Rilpivirine plus emtricitabine plus tenofovir DF (n=346) vs. Efavirenz plus emtricitabine plus tenofovir DF (n=348)	96 weeks	Proportion of subjects with HIV-1 RNA <50 copies/ml at Week 48
THRIVE	Phase 3, randomised, double-blind, double-dummy, non-inferiority trial comparing rilpivirine with efavirenz, in combination with two NRTIs	Treatment-naive adults with HIV-1 infection (≥5,000 copies/ml) and viral sensitivity to NRTIs (n=680)	Rilpivirine plus emtricitabine plus tenofovir DF (n=204), or rilpivirine plus zidovudine plus lamivudine (n=101), or rilpivirine plus abacavir plus lamivudine (n=35) vs. Efavirenz plus emtricitabine plus tenofovir DF (n=202), or efavirenz plus zidovudine plus lamivudine (n=103), or efavirenz plus abacavir plus lamivudine(n=33)	96 weeks	Proportion of subjects with HIV-1 RNA <50 copies/ml at Week 48
DRIVE-AHEAD	Phase 3 randomised, double-blind, non-inferiority study comparing single-treatment regimens of Delstrigo and Atripla	Treatment naïve adults with HIV-1 infection (at least 1,000 copies/ml) (n=728)	Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate) (n=364) vs. Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) (n=364)	96 weeks	Proportion of patients with HIV-1 RNA <50 copies per ml at Week 48, as defined by the US FDA snapshot algorithm.
DRIVE	Phase 2 randomised, double-blind, dose-ranging study comparing doravirine plus emtricitabine/tenofovir disoproxil fumarate versus efavirenz plus emtricitabine/tenofovir disoproxil fumarate	Treatment naïve patients with HIV-1 infection	Doravirine (100 mg arm only) plus emtricitabine/tenofovir disoproxil fumarate (n=108) vs. efavirenz plus emtricitabine/tenofovir disoproxil fumarate (n=108)	48 weeks	Proportion of patients with HIV-1 RNA <50 copies per ml at Weeks 48 & 96, as defined by the US FDA snapshot algorithm