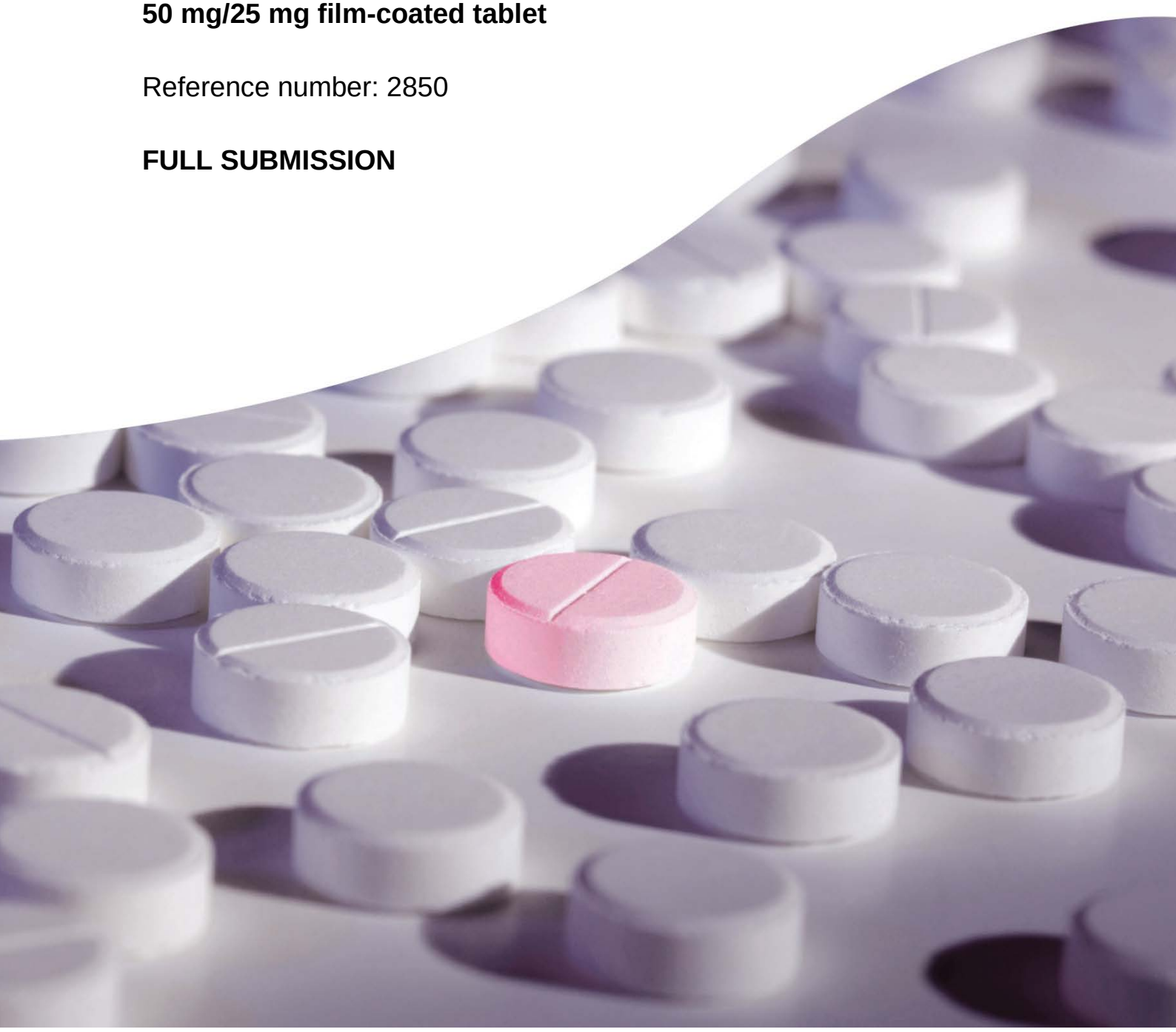
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Dolutegravir/rilpivirine (Juluca®)
50 mg/25 mg film-coated tablet

Reference number: 2850

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. Dolutegravir/rilpivirine (Juluca®) 50 mg/25 mg film-coated tablet. Reference number: 2850. November 2018.

AWMSG Secretariat Assessment Report
Dolutegravir/rilpivirine (Juluca®▼) 50 mg/25 mg film-coated tablet

1.0 KEY FACTS

Assessment details	Dolutegravir/rilpivirine (Juluca®▼) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/ml) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor. ▼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. Juluca® is the first licensed antiretroviral regimen which consists of two medicines. It combines an integrase inhibitor (dolutegravir) with a non-nucleoside reverse transcriptase inhibitor (rilpivirine) in a single tablet, taken once daily with a meal.
Current clinical practice	People with HIV-1 infection usually start on a triple therapy antiretroviral regimen of two nucleoside reverse transcriptase inhibitors plus either a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor or an integrase inhibitor. According to AWTTC-sought clinical experts the most common antiretrovirals currently used in Wales are: • dolutegravir/abacavir/lamivudine (Triumeq®) • emtricitabine/tenofovir disoproxil fumarate (Truvada®), darunavir, ritonavir • dolutegravir, rilpivirine, emtricitabine/tenofovir disoproxil fumarate (Truvada®), atazanavir, ritonavir • emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®) • elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (Stribild®) • efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®)
Clinical effectiveness	In two open-label phase III studies, SWORD-1 and SWORD-2, switching to the combination of dolutegravir and rilpivirine after patients had received first or second antiretroviral therapy and had a stable HIV-1 RNA for six months or longer was non-inferior to continuing with current antiretroviral therapy for maintaining suppression of viral load.
Cost-effectiveness	A cost-minimisation analysis compares Juluca® with other antiretroviral regimens in an adult population who are virologically suppressed (HIV-1 RNA < 50 copies per ml) and

	require a switch in treatment for reasons other than virological failure. The company base case suggests cost savings ranging between [commercial in confidence figure removed] (per patient/annum) when Juluca® is compared with generic Truvada® and Edurant® and [commercial in confidence figure removed] when compared with Genvoya®. However, the reported cost savings versus Genvoya® are unlikely to be realised since there is a Welsh Patient Access Scheme (WPAS) in place for this comparator. The analyses are therefore not all reflective of current cost differences in Wales. The model is limited to a comparison of acquisition costs only. A cost minimisation analysis is not deemed appropriate as clinical evidence has not been provided to demonstrate the equivalence of Juluca® with the comparators.
Budget impact	The company estimates that 26 people are eligible to receive treatment with Juluca® in Wales in Year 1, increasing to 53 people in Year 5. Using the Juluca® WPAS price, the company base case suggests cost savings of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. However, these estimates do not take into account the WPAS for comparator regimens. The model is limited to a comparison of acquisition costs only, and the choice of comparators is subject to uncertainty.

This assessment report is based on evidence submitted by ViiV Healthcare Ltd and an evidence search conducted by AWTTC on 12 and 13 July 2018[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[2]. This weakens the immune system and eventually leads to AIDS and AIDS-related illnesses. There is no cure for HIV-1 infection. Antiretroviral treatment aims to suppress the replication of HIV-1 in the blood and maintain levels of the virus that are below detectable limits (usually < 50 copies/ml)[2].

The British HIV Association guidelines recommend patients start on a triple therapy regimen of two nucleoside reverse transcriptase inhibitors plus either a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor or an integrase inhibitor[3]. Antiretroviral treatment is life-long[2]. However, the HIV genome can mutate during replication and may become resistant to a particular antiretroviral or class of antiretroviral agents. Therefore there is a continued need to develop new antiretroviral treatments[2]. The guidelines do not recommend treatment with two medicines. The guidelines were issued prior to the SWORD study results being available.

In people with HIV-1 infection who are taking viral suppressive treatments, the individual medicines of the antiretroviral combination are often switched[3]. Reasons for switching include:

- managing antiretroviral toxicity or intolerance;
- desire for once-daily dosing and reduced pill burden;
- managing potential medicine interactions; and
- individual preference and cost.

The British HIV Association guidelines state that although switching the individual components of antiretroviral therapy may improve adherence and tolerability, this should not be at the cost of virological efficacy[3].

2.2 Medicine

Juluca® is the first two-medicine regimen licensed combining an HIV integrase inhibitor (dolutegravir) with a non-nucleoside HIV reverse transcriptase inhibitor (rilpivirine) in a single tablet, taken once daily with a meal[2]. The European Medicines Agency (EMA) granted a marketing authorisation to Juluca® in May 2018 for treating HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/ml) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor[2]. Both components of Juluca® are indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection.

The applicant company states that it would expect Juluca® to be an alternative to tenofovir alafenamide-based regimens such as Descovy®, Genvoya® or Odefsey®, where a change to the current backbone regimen (either Truvada® or Kivexa®) is needed[1]. Juluca® is a nucleoside reverse transcriptase inhibitor (NRTI)-sparing alternative where a change to the backbone regimen is required. It is also an alternative where a change to the current third agent is required for people who have not tolerated, or are likely to encounter co-morbidities with, an alternative regimen[1].

2.3 Comparators

The comparator in the company's submission is combination antiretroviral triple therapy[1]. AWTTC-sought clinical expert opinion suggests that the most common antiretrovirals currently used in Wales are:

- dolutegravir/abacavir/lamivudine (Triumeq®)
- emtricitabine/tenofovir disoproxil fumarate (Truvada®) + darunavir + ritonavir or emtricitabine/tenofovir disoproxil fumarate (Truvada®) + atazanavir + ritonavir
- emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®)
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (Stribild®)
- efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®).

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 (2017) The EACS treatment guidelines version 9.0 (updated October 2017)[4]

The All Wales Medicines Strategy Group (AWMSG) has previously recommended dolutegravir (Tivicay®)[5], rilpivirine (Edurant®)[6], dolutegravir/abacavir/lamivudine (Triumeq®)[7], emtricitabine/tenofovir disoproxil fumarate (Truvada®)[8],

emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®)[9], and elvitegravir /cobicistat/emtricitabine/tenofovir disoproxil (Stribild®)[10] as options for use in NHS Wales.

2.5 Prescribing and supply

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

The company anticipates that dolutegravir/rilpivirine (Juluca®) may be supplied by a home healthcare provider[1].

3.0 CLINICAL EFFECTIVENESS

The company's submission includes two open-label, randomised, multicentre phase III studies: SWORD-1 and SWORD-2[1]. These compared current antiretroviral therapies to dolutegravir 50 mg tablets and rilpivirine 25 mg tablets taken together in adults with HIV-1 infection who were receiving antiretroviral therapy. A third study on the bioequivalence of a fixed-dose combination tablet formulation of Juluca® was included in the submission. The EMA stated that bioequivalence of Juluca to dolutegravir 50 mg tablet and a rilpivirine 25 mg tablet administered together with a meal was demonstrated and this study will not be discussed further in the report. The company also included results from a sub-study of the SWORD studies, which evaluated changes in bone mineral density[1].

3.1 SWORD-1 and SWORD-2 studies

These two international, open-label phase III studies were designed to demonstrate non-inferiority of once-daily dolutegravir and rilpivirine to current antiretroviral therapy in 1,028 patients with HIV-1 infection[11].

Patients enrolled were ≥ 18 years, who were receiving first or second antiretroviral therapy and who had stable plasma HIV-1 RNA (viral load < 50 copies/ml) for six months or longer at screening and no more than one instance of viral load > 50 copies/ml but lower than 200 copies/ml in the past 12 months[11]. Previous antiretroviral therapy regimens of two nucleoside reverse transcriptase inhibitors plus a third medicine (a non-nucleoside reverse transcriptase inhibitor, an integrase inhibitor or a protease inhibitor) were allowed, including pharmacokinetically boosted protease inhibitors or unboosted atazanavir. No more than 10% of patients had been previously exposed to dolutegravir or rilpivirine[11].

Patients were excluded if they had any major resistance-associated protease inhibitor, integrase inhibitor or reverse transcriptase inhibitor mutation or integrase resistance-associated substitution R263K, severe impaired liver function, concurrent hepatitis B infection, or expected need for hepatitis C therapy[11]. Patients who switched to a second-line regimen because of virological failure on the first-line regimen were also excluded[11].

In both studies patients were randomised 1:1 to receive dolutegravir 50 mg and rilpivirine 25 mg once daily for 52 weeks or to continue with their current antiretroviral therapy for 52 weeks[11]. Randomisation was stratified by baseline third-agent class (integrase inhibitor, non-nucleoside reverse transcriptase inhibitor or protease inhibitor), age group (over or under 50 years), and planned participation in a bone mineral density sub-study[11].

Patients were assessed at screening, day 1, weeks 4, 8, 12, 24, 36, 48 and week 52 (current antiretroviral therapy only) or withdrawal[11]. At week 52, patients assigned to current antiretroviral therapy could switch to treatment with dolutegravir and rilpivirine[1].

The primary efficacy endpoint was the proportion of patients in the intention-to-treat population who had a plasma viral load < 50 copies/ml at week 48, using the US FDA's snapshot algorithm[11]. Non-inferiority of the primary endpoint was based on the difference in response rates. Secondary endpoints included measuring change from baseline in bone, renal and cardiovascular biomarkers. A non-inferiority margin of −8% was chosen for a pooled analysis of SWORD-1 and SWORD-2[11].

Results showed that at week 48, 240 (95%) of 252 patients in SWORD-1 and 246 (94%) of 261 patients in SWORD-2 maintained viral loads under 50 copies/ml after switching to dolutegravir and rilpivirine, compared with 245 of 256 (96%) of patients in SWORD-1 and 240 of 255 (94%) in SWORD-2 who continued with current therapy[11]. A pooled analysis of the intention-to-treat population showed 95% of patients in the dolutegravir and rilpivirine groups maintained viral loads below 50 copies/ml with an adjusted treatment difference of −0.2% (95% confidence interval −3.0 to 2.5), confirming non-inferiority to current antiretroviral therapy. Dolutegravir and rilpivirine was non-inferior to current antiretroviral therapy for the proportions of patients who had virological failure (−0.5%, −1.4 to 0.5), with a predefined non-inferiority margin of 4%[11].

After 100 weeks, 89% of patients treated with dolutegravir and rilpivirine maintained virological suppression[1]. Patients who switched to dolutegravir and rilpivirine treatment late (at week 52) showed similar results to the primary endpoint: 93% maintaining viral suppression[1].

Results of the HIV treatment satisfaction questionnaire showed greater improvements in total score and lifestyle/ease score at weeks 48 and 100 in the dolutegravir and rilpivirine group, although the differences were not clinically meaningful because the mean changes from baseline were small[1]. Health status assessed using the EQ5D-5L questionnaire showed no statistically significant difference between the treatment groups at any time point (up to week 100). Self-reported patient adherence showed very little difference between the treatment groups (97.8% in the dolutegravir and rilpivirine group and 98.3% in the group that continued current antiretroviral treatment). Patients switched treatments because they were concerned about the long-term side effects of their current HIV medicines: 26% of patients treated with dolutegravir and rilpivirine and 27% of those who continued with antiretroviral therapy[1].

A sub-study (DXA) of the SWORD 1 and 2 studies evaluated change from baseline in bone mineral density. Mean bone mineral density increased from baseline to week 48 in patients who switched to dolutegravir and rilpivirine (1.34% total hip and 1.46% lumbar spine) compared with those who continued on treatment with a tenofovir disoproxil fumarate-containing antiretroviral regimen (0.05% total hip and 0.15% lumbar spine). Any beneficial effect on fracture rate was not studied[12].

3.2 Comparative safety

The percentages of patients reporting adverse events in the SWORD studies were 77% of dolutegravir and rilpivirine-treated patients and 71% of those patients who continued their current antiretroviral therapy[1]. The most frequent adverse events in patients taking dolutegravir and rilpivirine in the SWORD studies were nasopharyngitis, headache, upper respiratory tract infection, diarrhoea, back pain, bronchitis, influenza and arthralgia; very few were grade 2 or worse[11]. There were more adverse events leading to withdrawal from the study by week 48 reported in the dolutegravir and rilpivirine group (n = 17) than in the current antiretroviral therapy group (n = 3)[11].

3.3 Ongoing studies

The company reported that the SWORD studies and ongoing efficacy and safety analyses are planned to week 148[1]. The company has submitted a protocol for a study, COMBINE-2, real-world evidence for effectiveness of two-treatment regimen antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor[1].

3.4 AWTTC critique

- In the open-label SWORD-1 and SWORD-2 studies, switching to the combination of dolutegravir and rilpivirine was non-inferior to current antiretroviral therapy in maintaining viral suppression.
- Juluca® is the first medicine licensed for use as a two medicine regimen. This would provide an alternative which is NRTI-sparing and provide an option for people who require a third agent but they are either not tolerated or are likely to encounter co-morbidities with an alternative regimen[11]. Results from the SWORD studies showed that dolutegravir and rilpivirine maintained HIV suppression with no increased risk of developing resistance[11].
- The SWORD studies included patients in the UK and the results appear to be applicable to patients in Wales. The most commonly reported non-nucleoside reverse transcriptase inhibitor at baseline was efavirenz, the most commonly reported protease inhibitor was ritonavir-boosted darunavir, and the most commonly reported integrase inhibitor was raltegravir[11].
- There was a higher incidence of adverse events and withdrawals due to adverse events in the dolutegravir and rilpivirine arm of the SWORD studies. However, the EMA commented that the most commonly reported types of adverse events were largely comparable between the group taking dolutegravir and rilpivirine and the group who continued current antiretroviral therapy[2], and that no additional risks or safety issues were identified compared to the established safety profiles of the single agents. The EMA noted that it was plausible that people experience more adverse events when switching treatment than when continuing on stabilised treatment.
- The Medicines and Healthcare products Regulatory Agency (MHRA) have issued a safety signal of increased risk of neural tube defects with dolutegravir and states: do not prescribe to women seeking to become pregnant; exclude pregnancy before initiation and advise use of effective contraception[13].
- Adherence was reported as 98% in the SWORD studies which may not reflect adherence in clinical practice.
- The trial was open label which may have introduced bias.

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes a cost-minimisation analysis of Juluca® for an adult population who are virologically suppressed for HIV-1 (HIV-1 RNA < 50 copies per ml) and need a switch in treatment for reasons other than virological failure[1].

The simple one-year cost-minimisation analysis compares Juluca® to a range of comparators, taking the perspective of the NHS and Personal Social Services in Wales. The company assumes equivalence in efficacy and close comparability across all other relevant outcome domains based on clinical data from the open-label SWORD studies which compare Juluca® to current antiretroviral therapy. In the SWORD studies current antiretroviral therapies include two nucleoside reverse transcriptase inhibitors plus one HIV-1 integrase inhibitor, or one non-nucleoside reverse transcriptase inhibitor or one protease inhibitor.

Comparators are categorised as either primary or secondary. The primary comparators are those where Juluca® offers an alternative treatment to nucleoside reverse transcriptase inhibitors (that is, tenofovir disoproxil fumarate- or abacavir-based regimens) which may no longer be considered suitable due to higher risks of bone, renal and cardiovascular toxicities. The secondary comparator group considers the use of Juluca® as an alternative treatment where the current third agent (such as, efavirenz, a non-nucleoside reverse transcriptase inhibitor or protease inhibitor/booster containing regimens) is no longer considered suitable. A separate cost comparison is also presented between Juluca® and the single tablet regimens Stribild® and Symtuza®. Due to the short model time horizon, no discounting is applied. The Juluca® pricing follows a simple Wales Patients Access Scheme (WPAS) approach.

The cost-minimisation analysis compares the acquisition cost of Juluca® (WPAS price) with the range of primary and secondary comparators (list price[14]). Resource use costs are not included in the base case analysis.

The uncertainty surrounding the base case scenario is assessed in sensitivity analyses. These include applying known WPAS prices for the comparators Tivicay® and Triumeq® as well as exploring the impact of price discounts for Genvoya® in increments from 5% to 95%.

Other sensitivity analyses include an assessment of the cost impact of an additional follow-up appointment for Juluca® as well as a threshold analysis to assess the number of additional appointments required for Juluca® to stop being cost-saving. The disparity in adverse events is modelled in a scenario analysis that accounts for the adverse event frequency, type and healthcare resource costs needed for resolution; the impact of discontinuation and switching to alternative regimens is also considered.

4.2 Results

The results of the base case analysis are given in Table 1. Treatment with Juluca® (WPAS price) is less costly in the base case and the majority of the sensitivity analyses for both primary and secondary comparators. The cost saving per patient per year with Juluca® ranges from [commercial in confidence figure removed] (versus generic Truvada® and Edurant®) to [commercial in confidence figure removed] (versus Genvoya®, and versus Stribild®).

Sensitivity analyses report that including regimens with a listed WPAS price (Tivicay®, Triumeq® and Genvoya®) results in Juluca® ranging between having a positive cost impact of [commercial in confidence figure removed] (versus Triumeq®) to a cost saving of [commercial in confidence figure removed] (versus Descovy® and Tivicay®, and versus Truvada® and Tivicay®). Compared with Genvoya®, Juluca® is no longer cost-saving when a discount of [commercial in confidence figure removed] is applied to Genvoya®. The addition of a follow-up appointment results in Juluca® offering a cost saving of between [commercial in confidence figure removed] (versus Odefsey®) and [commercial in confidence figure removed] (versus Genvoya®). The impact of adverse events and discontinuation leading to switching had minimal impact on the results.

Table 1. Results of the base case analysis for primary comparators and secondary comparators including WPAS scenario analyses where known

Scenario Juluca® (WPAS price) versus	Costs	Juluca®	Comparator	Difference
Descovy® + Tivicay ® (WPAS price)	Medicine acquisition costs	¶¶	¶¶	¶¶
Descovy® + Isentress®	Medicine acquisition costs	¶¶	£10,064	¶¶
Descovy® + Prezista® + Norvir®	Medicine acquisition costs	¶¶	£8,188	¶¶
Genvoya® (list price)	Medicine acquisition costs	¶¶	£10,700	¶¶
Odefsey®	Medicine acquisition costs	¶¶	£6,399	¶¶
Truvada® + Tivicay® (list price)	Medicine acquisition costs	¶¶	£10,396	¶¶
Truvada® + Tivicay® (WPAS price)	Medicine acquisition costs	¶¶	¶¶	¶¶
Truvada® + Isentress®	Medicine acquisition costs	¶¶	£10,064	¶¶
Truvada® + Edurant®	Medicine acquisition costs	¶¶	£6,765	¶¶
Eviplera®	Medicine acquisition costs	¶¶	£6,399	¶¶
Kivexa® + Isentress®	Medicine acquisition costs	¶¶	£10,021	¶¶
Triumeq® (WPAS price)	Medicine acquisition costs	¶¶	¶¶	¶¶
Genvoya® (list price)	Medicine acquisition costs	¶¶	£10,701	¶¶
Stribild® (list price)	Medicine acquisition costs	¶¶	£10,701	¶¶
Symtuza®	Medicine acquisition costs	¶¶	£8,188	¶¶
¶¶: commercial in confidence figure removed				

4.3 AWTTC critique

The reliability of the cost minimisation analysis depends on the appropriateness of the assumption about clinical equivalence between Juluca® and the range of comparators. The company justifies using a cost minimisation analysis instead of a cost-utility analysis, on the basis that the supporting studies, SWORD-1 and SWORD-2, reported non-inferiority for dolutegravir and rilpivirine versus current antiretroviral therapy[15,16]. The results of the cost-minimisation analysis show that Juluca® (WPAS price) is cost saving versus the majority of comparators [commercial in confidence text removed], and when the WPAS discount for Genvoya® and Stribild® is [commercial in confidence figure removed].

Strengths and weaknesses of the economic analysis:

- The economic analysis is well conducted and includes a wide range of comparators.
- The company claims that Juluca® is non-inferior compared to current standard treatments with regards to virological efficacy based on clinical opinion, current guidelines and published evidence. However, in the absence of well-designed equivalence trials and evidence of close comparability of all other effects (including impact on health-related quality of life, adherence, administration requirements), there is no evidence to support the assumption that each individual regimen in the current antiretroviral therapy group is non-inferior to Juluca®. Therefore, AWTTC does not consider the cost-minimisation analysis criteria to be met.

- The open-label design of the SWORD-1 and SWORD-2 studies could introduce bias into the results.
- The company's submission assumes close comparability of all other effects between Juluca® and each of the different regimens in the current antiretroviral therapy group. Yet differences in grade 3/4 adverse events, quality of life and discontinuation rates were observed in the SWORD studies, though these may be transitory in effect. The effect of these differences was explored in sensitivity analysis provided by the company which contradicts the premise of equivalence which is the basis for cost-minimisation analysis.
- Any longer-term clinical or quality-adjusted life-year benefits associated with a difference in mortality or co-morbidities associated with the decreased risk of bone, renal and cardiovascular toxicities in patients switching to Juluca® have not been quantified and are uncertain.
- The analysis is limited to medicine acquisition costs, aside from considering the impact of health resource costs to resolve Grade 3 and 4 adverse events, or discontinuations through including additional follow-up consultations in the sensitivity analysis.
- The SWORD-1 and SWORD-2 studies reported outcomes from patients who were stable on their regimen for at least six months. While they may not be representative of the proposed population, the company states that the median time since first antiretroviral therapy was over 4 years which they consider generalisable to the Welsh population based on insights from Welsh HIV physicians.
- The time horizon used in the analysis is shorter than would be expected for a chronic condition.

4.4 Review of published evidence on cost-effectiveness

A literature search by AWTTC did not identify any studies relevant to the cost-effectiveness of Juluca® versus current antiretroviral therapy in the treatment of HIV in patients who may benefit clinically from a change in treatment regimen.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates that there are 1,835 people with HIV in Wales in Year 1, based on Welsh specific data reported by Public Health England[17]. Of these, an estimated 86% of people with HIV receive antiretroviral therapy, of whom 94% are virologically suppressed and a further 10% may need a treatment switch. Therefore it is estimated that 148 people are eligible for treatment with Juluca®. To calculate the number of people who need treatment in Wales, the company has combined prevalence estimates with an annual mortality rate of 0.14%[18,19] and an annual incidence rate of 141 patients per year, which relates to an additional 11 incident cases per year and is assumed to remain stable over the five-year horizon. The comparator regimen cost is estimated by equal weighting of the five primary comparators, each assumed to account for 20% of the population that would be eligible for Juluca®. An assumed market share of 16% in Year 1, increasing to 26% in Year 5 is further applied to estimate the number of people likely to be prescribed Juluca® in Wales.

5.2 Results

The budget impact is presented in Table 2. The company estimates the introduction of Juluca® (WPAS price) would lead to a saving of [commercial in confidence figure removed] in Year 1 rising to [commercial in confidence figure removed] in Year 5 when list prices for the comparators are used. When the WPAS price for Tivicay® is applied,

the cost savings are [commercial in confidence figure removed] in Year 1 increasing to [commercial in confidence figure removed] in Year 5. Also the scenario analyses exploring the impact of applying varying price discounts for Genvoya® on the overall budget impact show that the introduction of Juluca® is likely to result in cost-savings in all years [commercial in confidence text removed]. Resource implications and supportive medicines are not included into the analysis.

Table 2. Company reported costs associated with the use of Juluca® for the treatment of individuals with HIV

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Number of eligible patients (indication covered in this submission)	160	171	182	193	204
Uptake of Juluca® (%)	16	25	27	26	26
Number of patients receiving Juluca®, allowing for discontinuations	26	43	49	50	53
Medicine acquisition costs in a market without Juluca®	£1,459,486	£1,561,587	£1,663,554	£1,765,359	£1,867,031
Medicine acquisition costs in a market with Juluca® (WPAS)	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (WPAS)	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: Commercial in confidence figure removed					

5.3 AWTTC critique

Strengths of the budget impact model:

- The submission gives a detailed, transparent account of the methods and uses data sources relevant to Wales to estimate budget impact.
- The submission offers a comparison with a range of suitable comparators.

Weaknesses of the budget impact model:

- The budget impact is limited to the primary comparators only; there is no budget impact assessment for the secondary comparators, where the current third agents are no longer tolerated nor the other available single tablet regimens.
- The budget impact considerations are limited to acquisition costs only; other resource use is not included (for example, follow-up appointment costs and costs associated with adverse events).
- It is uncertain how the estimates for uptake have been calculated.
    - The mortality rate applied was based on an age range of 35–44 years and the mean age of the SWORD studies participants was 43 years. The mortality rate for the next age range 45–54 years (0.31%) is more than double that applied in the model (0.14%), which may lead to an underestimation of mortality rates. However, the company suggests that the impact of the increased mortality rate is minimal, with estimated cost savings of [commercial in confidence figure removed]

in Year 1 rising to savings of [commercial in confidence figure removed] in Year 5 (taking into account a WPAS discount of 50% for Genvoya®.

5.4 Comparative unit costs

Acquisition costs for treatments for HIV-1 infection are given in Table 3.

Table 3. Acquisition costs

Regimens	Cost per pack	Pack size	Example doses	Annual cost
Juluca® and primary comparators				
Juluca®	¶¶	30	1 tablet once daily	¶¶
Descovy®	£356	30	1 tablet once daily	£4,328
Tivicay®	£499	30	1 tablet once daily	£6,068
Isentress®	£471	60	1 tablet twice daily	£5,735
Prezista®	£298	30	1 tablet once daily	£3,623
Norvir®	£19	30	1 tablet once daily	£237
Genvoya®	£880	30	1 tablet once daily	£10,701
Odefsey®	£526	30	1 tablet once daily	£6,399
Secondary comparators				
Truvada®	£356	30	1 tablet once daily	£4,328
generic Truvada®	£311*	30	1 tablet once daily	£3,787
Kivexa®	£352	30	1 tablet once daily	£4,286
generic Kivexa®	£230**	30	1 tablet once daily	£2,797
Triumeq®	£798	30	1 tablet once daily	£9,711
Edurant®	£200	30	1 tablet once daily	£2,437
Eviplera®	£526	30	1 tablet once daily	£6,399
Stribild®	£880	30	1 tablet once daily	£10,701
Symtuza®	£673	30	1 tablet once daily	£8,188
WPAS regimens				
Tivicay®	¶¶	30	1 tablet once daily	¶¶
Triumeq®	¶¶	30	1 tablet once daily	¶¶

* Generic Truvada®, average NHS indicative price from generic manufacturers derived from British National Formulary, as of June 2018[20].
** Generic Kivexa®, average NHS indicative price from generic manufacturers derived from British National Formulary, as of June 2018[20].
¶¶: Commercial in confidence figure removed.
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[21-36].
Costs are predominantly based on the Monthly Index of Medical Specialities list prices as of August 2018[37].
This table does not imply therapeutic equivalence of medicines or the stated doses.
WPAS: Wales Patient Access Scheme

REFERENCES

1. ViiV Healthcare Ltd. Form B: Detailed appraisal submission. Dolutegravir/rilpivirine (Juluca®). Jul 2018.
2. European Medicines Agency. Assessment Report: Juluca®. Procedure No.: EMEA/H/C/004427/0000. Mar 2018. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004427/human_med_002254.jsp&mid=WC0b01ac058001d124. Accessed Aug 2018.
3. British HIV Association. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). Aug 2016. Available at: http://www.bhiva.org/HIV-1-treatment-guidelines.aspx. Accessed Aug 2018.
4. European AIDS Clinical Society. EACS guidelines. Version 9.0. Oct 2017. Available at: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed Aug 2018.
5. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2017. Dolutegravir (Tivicay®) 10 mg, 25 mg and 50 mg film-coated tablets. Oct 2017. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/3373. Accessed Aug 2018.
6. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1312. Rilpivirine (Edurant®) 25 mg film-coated tablets. Jun 2012. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2936. Accessed Aug 2018.
7. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0415. Dolutegravir/abacavir/lamivudine (Triumeq®) 50 mg/600 mg/300 mg film-coated tablet. May 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2365. Accessed Aug 2018.
8. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0507. Emtricitabine/tenofovir (Truvada®) film-coated tablet. Aug 2007. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/123. Accessed Aug 2018.
9. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1514. Emtricitabine/rilpivirine/tenofovir disoproxil (as fumarate) (Eviplera®) 200 mg/25 mg/245 mg film-coated tablet. Jul 2014. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2374. Accessed Aug 2018.
10. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2413. Elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild®) 150 mg/150 mg/200 mg/245 mg film-coated tablet. Dec 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1446. Accessed Aug 2018.
11. Llibre JM, Hung CC, Brinson C et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *The Lancet.* 2018;391(10123):839-849.
12. McComsey GA, Lupo S, Parks D et al. Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health. *Aids.* 2018;32(4):477-485.
13. Medicines and Healthcare products Regulatory Agency. Dolutegravir (Tivicay, Triumeq, Juluca): signal of increased risk of neural tube defects. Jun 2018. Available at: https://www.gov.uk/drug-safety-update/dolutegravir-tivicay-triumeq-juluca-signal-of-increased-risk-of-neural-tube-defects-do-not-prescribe-

to-women-seeking-to-become-pregnant-exclude-pregnancy-before-initiation-and-advise-use-of-effective-contraception. Accessed Nov 2018.
14. NHS Prescription Services. Drug Tariff. Sep 2018. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. Accessed Sep 2018.
15. ViiV Healthcare. NCT02429791: Regimen switch to dolutegravir + rilpivirine from current antiretroviral regimen in human immunodeficiency virus type 1 infected and virologically suppressed adults (SWORD-1). Apr 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT02429791. Accessed Aug 2018.
16. ViiV Healthcare. NCT02422797: Regimen switch to dolutegravir + rilpivirine from current antiretroviral regimen in human immunodeficiency virus type 1 infected and virologically suppressed adults (SWORD-2). Aug 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT02422797. Accessed Aug 2018.
17. Public Health England. United Kingdom. National HIV surveillance data tables to end December 2016. Tables No 1: 2017. 2017. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/648755/National_Tables.xls. Accessed Aug 2018.
18. Office for National Statistics. Mortality statistics. Deaths registered in England and Wales, 2016. 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables. Accessed Aug 2018.
19. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2016. Jun 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2016. Accessed Aug 2018.
20. British Medical Association, and Royal Pharmaceutical Society of Great Britain. British National Formulary. Aug 2018. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Aug 2018.
21. ViiV Healthcare UK Ltd. Juluca®. Summary of Product Characteristics. May 2018. Available at: https://www.medicines.org.uk/emc/product/9246/smpc. Accessed Aug 2018.
22. Gilead Sciences Ltd. Descovy® 200 mg/10 mg. Summary of Product Characteristics. Jun 2018. Available at: https://www.medicines.org.uk/emc/product/2107/smpc#. Accessed Aug 2018.
23. Gilead Sciences Ltd. Descovy® 200 mg/25 mg. Summary of Product Characteristics. Jun 2018. Available at: https://www.medicines.org.uk/emc/product/2108/smpc. Accessed Aug 2018.
24. ViiV Healthcare UK Ltd. Tivicay®. Summary of Product Characteristics. Jul 2018. Available at: https://www.medicines.org.uk/emc/product/5248. Accessed Aug 2018.
25. Merck Sharp & Dohme Limited. Isentress®. Summary of Product Characteristics. Jul 2018. Available at: https://www.medicines.org.uk/emc/product/6171/smpc. Accessed Aug 2018.
26. Janssen-Cilag Ltd. Prezista®. Summary of Product Characteristics. Jul 2018. Available at: https://www.medicines.org.uk/emc/product/4993/smpc. Accessed Aug 2018.
27. AbbVie Ltd. Norvir®. Summary of Product Characteristics. Jun 2018. Available at: https://www.medicines.org.uk/emc/product/510/smpc. Accessed Aug 2018.
28. Gilead Sciences Ltd. Genvoya®. Summary of Product Characteristics. Aug 2018. Available at: https://www.medicines.org.uk/emc/product/5063. Accessed Aug 2018.

29. Gilead Sciences Ltd. Odefsey®. Summary of Product Characteristics. May 2018. Available at: https://www.medicines.org.uk/emc/product/7262. Accessed Aug 2018.
30. Gilead Sciences Ltd. Truvada®. Summary of Product Characteristics. Aug 2018. Available at: https://www.medicines.org.uk/emc/product/3890. Accessed Aug 2018.
31. ViiV Healthcare UK Ltd. Kivexa®. Summary of Product Characteristics. Feb 2018. Available at: https://www.medicines.org.uk/emc/product/3881. Accessed Aug 2018.
32. ViiV Healthcare UK Ltd. Triumeq®. Summary of Product Characteristics. Jul 2018. Available at: https://www.medicines.org.uk/emc/product/3318. Accessed Aug 2018.
33. Janssen-Cilag Ltd. Edurant®. Summary of Product Characteristics. Aug 2017. Available at: https://www.medicines.org.uk/emc/product/4968. Accessed Aug 2018.
34. Gilead Sciences Ltd. Eviplera®. Summary of Product Characteristics. Aug 2018. Available at: https://www.medicines.org.uk/emc/product/2764. Accessed Aug 2018.
35. Gilead Sciences Ltd. Stribild®. Summary of Product Characteristics. Aug 2018. Available at: https://www.medicines.org.uk/emc/product/3154. Accessed Aug 2018.
36. Janssen-Cilag Ltd. Symtuza®. Summary of Product Characteristics. Jul 2018. Available at: https://www.medicines.org.uk/emc/product/8430. Accessed Aug 2018.
37. Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Aug 2018. Available at: http://www.mims.co.uk/. Accessed Aug 2018.