AWMSG Secretariat Assessment Report – Limited submission

Dolutegravir (Tivicay®▼) 10 mg and 25 mg film-coated tablets

Company: ViiV Healthcare UK Ltd.

Licensed indication under consideration: In combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected children aged 6–12 years.

▼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.

Date of licence extension: 23 February 2017.

Comparator(s)

- Raltegravir (Isentress®).

Limited submission details

The limited submission criteria were met based on:

- A minor licence extension.
- Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.
- Estimated small difference in cost compared to comparator(s).

Clinical effectiveness

- Dolutegravir (Tivicay®) is a new generation integrase inhibitor (INI) with once-daily dosing that does not require boosting with a pharmacokinetic enhancer.
- Dolutegravir has a high barrier to resistance and is generally active against viral strains resistant to first-generation INIs.
- The All Wales Medicines Strategy Group (AWMSG) has previously recommended dolutegravir in combination with other antiretroviral treatments (ART), as an option for use for the treatment of HIV infected adults and adolescents above 12 years of age.
- The extension of the licensed indication to include children aged 6–12 years is supported by data from a 48-week, open-label, pharmacokinetic, safety, dose finding study of dolutegravir plus optimized background regimen in treatment-experienced, INI-naive children with HIV-1 RNA > 1000 copies/ml.
- Dolutegravir treatment for 48 weeks had significant and sustained virologic efficacy. HIV RNA < 400 c/ml was achieved in 78.3% of children (18/23; 95% confidence interval [CI]: 56.3% to 92.5%); HIV RNA < 50 c/ml was achieved in 73.9% (17/23; 95% CI: 51.6% to 89.8%). The median gain in CD4 cell count and percentage at Week 48 was 387 cells/mm^3 (49, 575) and 9% (7, 14), respectively.
- Dolutegravir was found to be well tolerated: none of the adverse events were related to dolutegravir treatment. There were no serious adverse events or

discontinuations due to adverse events. There were no additional types of adverse reactions beyond those observed in the adult population.

Budget impact

- The company estimates that seven children in Wales would be eligible for dolutegravir within the indication under consideration. This is based on Welsh data obtained by Public Health England, which report 15 children under the age of 15 were seen for HIV care in 2014, and data from the Collaborative HIV Paediatric Study which suggests 48% would be aged 6–12 years; equating to seven children.
- The company estimates that of the seven children eligible, only two or three would receive dolutegravir based on a market uptake of 35%. The company expects the number of children treated each year to decrease as children transition into ages above 12 years of age resulting in a falling incidence rate with two children in Year 1 and no patients being treated in Year 5.
- The recommended dose of dolutegravir is dependent on the child's weight. AWTTC has calculated that the annual costs for treating patients aged 6–12 years with dolutegravir (dose range: 20 mg to 50 mg daily) ranges from [commercial in confidence figures removed], based on a Wales Patient Access Scheme (WPAS) price. The annual cost per patient for raltegravir based on a dose range of 75 mg twice daily to 300 mg twice daily is £538 to £2152. The budget impact based on two patients in Wales and raltegravir being displaced would range from [commercial in confidence figures removed], depending on the weight of the child.

Additional information

- AWTTC is of the opinion that, if recommended, dolutegravir (Tivicay®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company anticipate that dolutegravir (Tivicay®) may be supplied by a home healthcare provider.

Evidence search

Date of evidence search: 25 May 2017.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Dolutegravir (Tivicay®) 10 mg and 25 mg film-coated tablets. Reference number: 3373. September 2017.

Appendix: Previous AWMSG secretariat assessment report (published September 2014)

This report was published as part of a previous AWMSG appraisal of dolutegravir (Tivicay®) (Advice number 2314). The advice from this appraisal has been superseded by advice number 2017. The original appraisal documentation is included here for completeness.

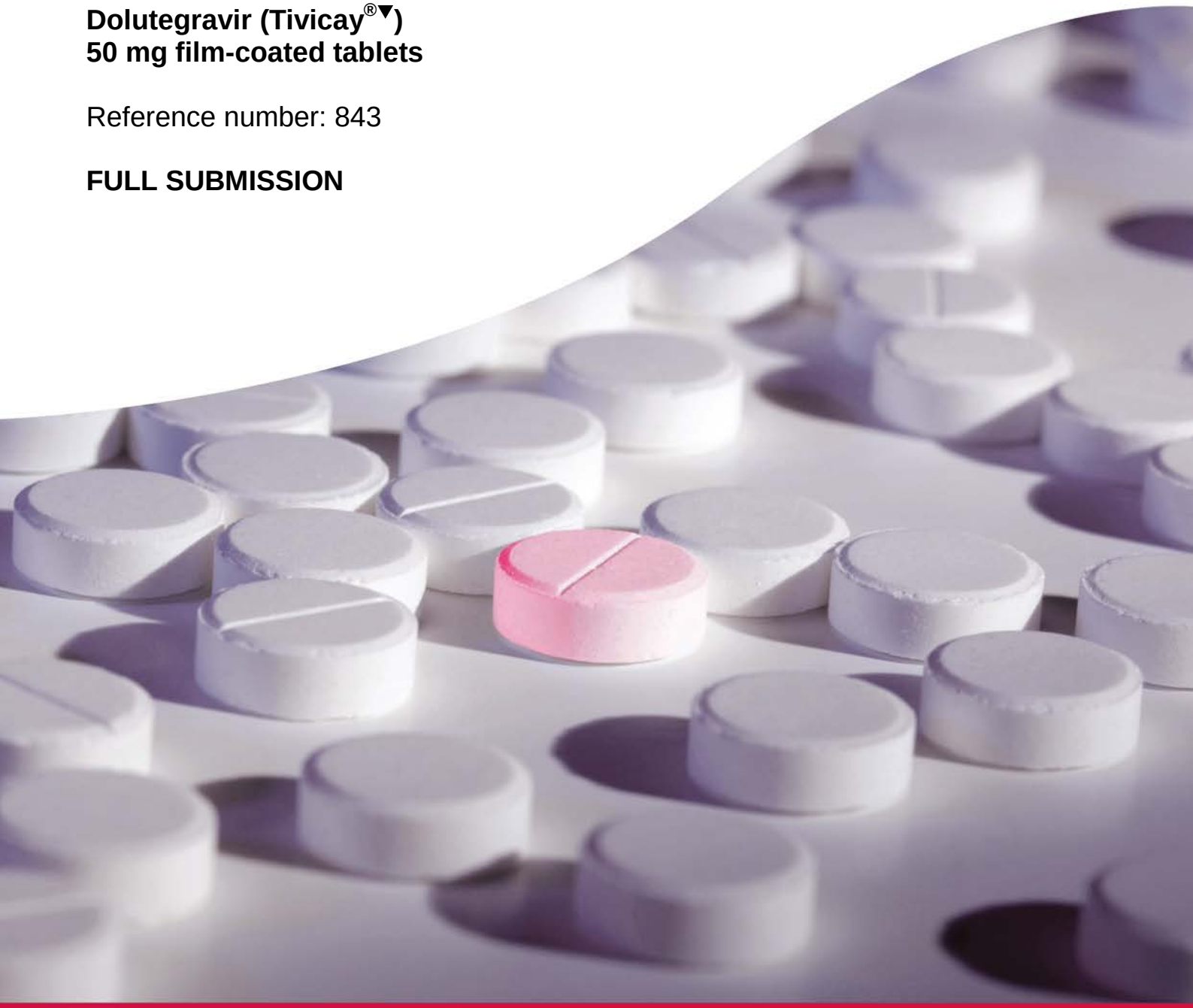
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Dolutegravir (Tivicay®▼)
50 mg film-coated tablets

Reference number: 843

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Dolutegravir (Tivicay®▼) 50 mg film-coated tablets

This assessment report is based on evidence submitted by ViiV Healthcare UK Ltd on 25 April 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Dolutegravir (Tivicay®▼) is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age[2].
Dosing	In adult patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class, the recommended dose of dolutegravir is 50 mg (one tablet) orally once daily. Dolutegravir should be administered twice daily in this population when co-administered with some medicines (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). In adult patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected), the recommended dose of dolutegravir is 50 mg (one tablet) twice daily. The decision to use dolutegravir for such patients should be informed by the integrase resistance pattern. Co-administration of dolutegravir with some medicines should be avoided in this population (e.g. efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin). In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	16 January 2014[3]

2.0 DECISION CONTEXT

2.1 Background

Human immunodeficiency virus (HIV) is a retrovirus that infects cells in the human immune system, such as $CD4^+$ lymphocytes, causing their destruction which results in the progressive suppression of the host immune system. Untreated HIV is a progressive disease leading to the development of acquired immunodeficiency syndrome (AIDS)[4]. In 2012, there were 1,535 patients with HIV resident in Wales (74% male, 75% white), of whom 1,307 were receiving antiretroviral therapy (ART)[5].

Current British HIV Association guidelines for the treatment of HIV recommend a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one ritonavir-boosted protease inhibitor (PI/r) or non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI) in ART-naive patients[6]. The choice of ART should take into consideration drug interactions, co-morbidities, pregnancy and cardiovascular risk factors. Over time HIV mutations resistant to ART can develop,

particularly if adherence is suboptimal, resulting in virological failure (viral load [VL] > 50 copies/ml)[4,6]. If therapy starts to fail, resistance testing is performed and the results reviewed along with any archived mutations. The ART regimen should be then changed as quickly as possible to avoid the accumulation of resistant mutations[6]. Dolutegravir is an INI which does not require boosting with a pharmacokinetic enhancer[1]. Dolutegravir inhibits HIV integrase by blocking the strand transfer step of the retroviral DNA integration, essential for HIV replication[2].

2.2 Comparators

The comparators included in the company submission were:

- ART-naive patients: efavirenz (Sustiva®) + ritonavir-boosted darunavir (Norvir® + Prezista®) + raltegravir (Isentress®)
- ART-experienced INI-naive patients: raltegravir (Isentress®).

2.3 Guidance and related advice

- British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013)[6].
- European AIDS Clinical Society. European guidelines for the treatment of HIV-infected adults in Europe. Version 7.02 (2014)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of INIs and combination products containing an INI in adult patients:

- Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®▼) is recommended as an option for use within NHS Wales for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral-treatment-naive or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild®▼ (2013)[8].
- Raltegravir (Isentress®▼) is recommended in combination with other antiretroviral medicinal products as an option for restricted use within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients in accordance with British HIV Association (BHIVA) guidance. Raltegravir (Isentress®▼) should be restricted for use in patients who are resistant or intolerant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) or for whom these options are compromised due to drug-drug interactions (2010)[9].
- Raltegravir (Isentress®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-experienced adults in accordance with British HIV Association (BHIVA) guidance (2008)[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The applicant company included evidence from five studies in support of their submission. SPRING-1 was a phase IIb dose-finding study which established the optimum dose of dolutegravir in ART-naive patients and as such will not be discussed further in this report[1,11]. Three phase III comparative studies in ART-naive patients were provided: SPRING-2, SINGLE and FLAMINGO are summarised in Section 3.1.1. A further phase III comparative study in ART-experienced, INI-naive patients, SAILING, was provided and is summarised in Section 3.1.2.

3.1.1 SPRING-2, SINGLE and FLAMINGO studies: ART-naive patients

All three studies were phase III, randomised, active-controlled, noninferiority studies designed to assess the efficacy and safety of dolutegravir in ART-naive, adult patients (aged ≥ 18 years) with HIV-1 infection (HIV-1 RNA ≥ 1,000 copies/ml). SPRING-2 and SINGLE were double-blinded studies, and FLAMINGO was an open-label study[12–14]. In the SPRING-2 study, patients (n = 827) were randomised to receive either dolutegravir (50 mg once daily) or raltegravir (400 mg twice daily); administered with co-formulated tenofovir/emtricitabine or abacavir/lamivudine as selected by the investigator. In the SINGLE study, patients (n = 844) were randomised to receive either dolutegravir (50 mg) plus abacavir-lamivudine (n = 414) once daily or efavirenz-tenofovir disoproxil fumarate-emtricitabine (Atripla®) (n = 419) once daily[14]. In the FLAMINGO study, patients (n = 484) were randomised to receive either dolutegravir 50 mg (n = 242) once daily or darunavir 800 mg plus ritonavir 100 mg (n = 242) once daily with either tenofovir-emtricitabine or abacavir-lamivudine as selected by the investigator[12].

The primary endpoint, the proportion of patients with HIV-1 RNA < 50 copies/ml at week 48 by snapshot analysis, was met in all studies (refer to Table 1)[12–14]. Noninferiority was demonstrated in the SPRING-2 study versus raltegravir[12,13]. Superiority of dolutegravir versus Atripla® was demonstrated in the SINGLE study and versus darunavir plus ritonavir in the FLAMINGO study[12,14]. Secondary endpoints were found to be supportive of the primary endpoint[12–14].

Table 1. Primary endpoint results for the SPRING-2, SINGLE and FLAMINGO studies[1,12–16]

	SPRING-2			SINGLE			FLAMINGO		
	Dolutegravir 50 mg*	Raltegravir 400 mg *	Adjusted difference (95% CI)	Dolutegravir 50 mg plus abacavir-lamivudine	Atripla® 600 mg	Adjusted difference (95% CI)	Dolutegravir 50 mg*	Darunavir 800 mg plus ritonavir 100 mg*	Adjusted difference (95% CI)
	n = 411	n = 411		n = 414	n = 419		n = 242	n = 242	
Proportion of patients with HIV-1 RNA < 50 copies per ml at week 48 by snapshot analysis	88% (361/411)	85% (351/411)	2.5% (−2.2 to 7.1)†	88% (364/414)	81% (338/419)	7% (2 to 12)	90% (217/242)	83% (200/242)	7.1% (0.9 to 13.2)
Proportion of patients with HIV-1 RNA < 50 copies per ml at week 96	81% (332/411)	76% (314/411)	4.5% (−1.1 to 10.0)†	80% ¶	72% ¶	8.0% (2.3 to 13.8%)	–	–	–
Virologic non-responders at week 48	5% (20/411)	8% (31/411)	–	5% (21/414)	6% (26/419)	–	6% (15/242)	7% (18/242)	–
Virologic non-responders at week 96	5% (22/411)	10% (43/411)	–	¶	¶	–	–	–	–

CI: confidence interval
*The study drug was given with investigator-selected tenofovir/emtricitabine or abacavir/lamivudine backbone.
†The lower bound of the 95% CI for the treatment difference was not above 0%; therefore superiority could not be concluded[1]
¶Commercial in confidence figures removed

3.1.2 SAILING study: ART-experienced, INI-naive patients

SAILING was a 48-week phase III, randomised, double-blind active-controlled, noninferiority study[17] which investigated the efficacy and safety of dolutegravir versus raltegravir. Adult patients (> 18 years) with HIV-1 RNA ≥ 400 copies/ml on two consecutive assessments (unless > 1000 copies/ml on screening), resistant to two or more classes of ART, INI-naive, and with one to two fully active drugs for background were considered eligible. Patients (n = 724) were randomised 1:1 to receive dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background therapy.

The primary endpoint was the proportion of patients with HIV-1 RNA < 50 copies per ml at week 48 by snapshot analysis including all patients who had received at least one dose of the study medicine (n = 715). At week 48, 251/354 (71%) of patients in the dolutegravir group had HIV-1 RNA < 50 copies per ml versus 230/361 (64%) in the raltegravir group (treatment difference: 7.4%; 95% CI: 0.7–14.2). Superiority of the dolutegravir regimen was demonstrated (p = 0.03). Significantly fewer patients in the dolutegravir group had virological failure with treatment-emergent genotypic or phenotypic evidence of INI resistance at week 48 (1% versus 5% [p = 0.003]; adjusted difference −3.7%; 95% CI −6.1 to −1.2 [p = 0.003])[11,17]. Other secondary endpoints were supportive of the primary endpoint.

3.1.3 Safety

In the SPRING-2 and SAILING studies, adverse events (AEs) at week 48 were found to be similar between treatment groups[13,17]. In the FLAMINGO and SINGLE studies, medicine-related AEs were found to be lower in patients receiving dolutegravir compared to those receiving comparator treatments ([Commercial in confidence data removed]; SINGLE: 66% in the Atripla® group versus 43% in the dolutegravir group)[1,14]. The most commonly reported AEs in the SPRING-2, SAILING and FLAMINGO studies were diarrhoea, nausea, headache, nasopharyngitis and upper respiratory tract infection. Discontinuations due to AEs were found to be the same or lower in patients receiving dolutegravir compared to the respective comparators. In the SPRING-2 and SAILING studies, numerically higher rates of transaminase increases (alanine transaminase [ALT] greater than ten times the upper limit of normal) were reported in the dolutegravir groups versus the comparator groups[11]. In the FLAMINGO study, nine patients receiving dolutegravir and six patients receiving darunavir had treatment-emergent increases in ALT (more than three times the upper limit of normal), although there was no tendency for more frequent liver reactions with dolutegravir than darunavir plus ritonavir in the FLAMINGO study[11]. Combined results for the SPRING-2 and SAILING studies showed that treatment-related serious AEs (SAEs) were reported in fewer patients receiving dolutegravir (five patients) compared to those receiving raltegravir (nine patients)[17,18]. In the FLAMINGO study, one SAE (attempted suicide) was considered to be treatment-related in a patient with a previous history of suicidal ideation receiving dolutegravir[12]. In the SINGLE study, one treatment-related SAE was reported in the dolutegravir group and eight were reported in the Atripla® group[14].

The Committee for Medicinal Products for Human Use (CHMP) noted that, over all studies, there was one case of severe hypersensitivity including a severe liver reaction which resolved on stopping dolutegravir. The potential risk for infrequent but potentially severe hypersensitivity reactions is to be investigated further by the applicant company through a prospective observational cohort study. CHMP concluded that overall the safety profile of dolutegravir is favourable and well tolerated. The metabolic profile is favourable as with other medicines in its class[11].

3.2 AWTTC critique

- CHMP noted the high barrier to resistance of dolutegravir, which was demonstrated in all of the studies. This barrier was protective not only to the study medicine but also to co-treating agents[11]. In the SPRING-2 and SINGLE

studies, no resistance to the INI or NRTI class was detected in ART-naive patients during the 48 week study period. In the SAILING study, no integrase resistance of clear clinical relevance was reported in ART-experienced patients receiving dolutegravir[11].

- Dolutegravir is the first INI with once-daily dosing not requiring boosting with a pharmacokinetic enhancer[1]. FLAMINGO was an open-label study where the effect of a reduced pill burden was assessed. Dolutegravir had higher scores for ease and convenience over the darunavir plus ritonavir in the HIV Treatment Satisfaction Questionnaire[1,12]. The benefit of once-daily dosing does not apply to patients with resistance to the INI class in which case twice daily dosing is required[2].
- A study outlined by CHMP in their assessment report, VIKING-3, showed that in patients with baseline Q148 + 1 secondary mutation the efficacy of dolutegravir is lowered but still relevant. In patients with Q148 + ≥ 2 mutations, efficacy is significantly reduced [11]. This evidence has been included in the SPC[2].
- An ongoing phase I/II open-label study to assess the pharmacokinetics, tolerability, efficacy and safety of dolutegravir in children and adolescents, provided CHMP with limited preliminary results in adolescents (aged 12 to 18 years). CHMP concluded that dolutegravir provided similar exposure in this age group to adults; therefore, efficacy results observed in adults could be extrapolated to the adolescent population providing that patients weigh > 40 kg[11]. The SPC includes dosage regimens for treatment naive adolescents[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a primary cost-utility analysis (CUA) in which dolutegravir is compared with a) efavirenz and b) darunavir/ritonavir, and a secondary cost-minimisation analysis (CMA) in which dolutegravir is compared with raltegravir for ART-naive patients with HIV and with raltegravir for ART-experienced but INI-naive patients with HIV[1].

The CUA uses the Anti-Retroviral Analysis by Monte Carlo Individual Simulation for dolutegravir (ARAMIS-DTG) model, claimed by the company to be one of the most widely used models to evaluate the cost-effectiveness of various ART regimens. This transitions individual patients through mutually exclusive health states by continually adjusting the probability of disease progression based on their characteristics and disease history.

The model includes six HIV health states (no infection plus five states with different acute infections), two cardiovascular disease (CVD) states (with and without CVD) and death. Transition probabilities are determined by change in individual $CD4^+$ cell count, with low cell counts associated with increased HIV morbidity, higher probability of infection, other AEs and death. Late failure, defined as patients who initially achieve viral suppression at week 48 but experience viral rebound thereafter, is included. CVD risk is a function of patient characteristics and lipid profile. HIV-related mortality depends on $CD4^+$ cell count and infections, with rates derived from a cohort study and adjusted for antiretroviral therapy exposure.

Treatment success is defined as having HIV-RNA of < 50 copies/ml at weeks 48 and 96, consistent with the clinical trials. Patients with treatment success and no grade 2–4 AEs continue on their current treatment regimen until viral rebound, AE or death. Switching decisions are determined by treatment history and resistance status, with up

to six treatment lines modelled, including three described as 'salvage'. The number of active drugs (three, two or one) prescribed in these salvage lines depends on class resistance. A lifetime horizon of analysis and an NHS in Wales perspective are adopted.

Baseline patient characteristics are sampled from the populations included in the dolutegravir phase III clinical trials. Data from these trials are used to model monthly transitions between states for first-line treatment (SINGLE for Atripla® versus dolutegravir[19] and FLAMINGO for darunavir/ritonavir versus dolutegravir to week 48[20], and SPRING-2 from week 48 to 96[21]). Beyond week 96, dolutegravir and the comparators are assumed to have similar efficacy, at the rate observed in a five-year efficacy trial of raltegravir and efavirenz-based combination therapies among ART-naive patients[22]. The late failure rate was maintained at week 55 levels.

Efficacy data for second-line treatment come from trials of darunavir/ritonavir[23–28]; whilst for third-line treatments, evidence is from studies of raltegravir for ART-experienced patients with triple-class drug-resistance[29–32]. For salvage therapy, efficacy data were derived from studies of maraviroc[33–35]. Late failure rates were doubled or tripled to reflect those expected in clinical practice due to poor adherence.

Event rates for AEs in first line treatment are from the clinical trials[19–21]. For subsequent treatment lines only AEs causing discontinuation are modelled.

The risk of developing an infection was derived from observational cohort data from Europe and North America[36]. The cost of primary and secondary prophylaxis was modelled and its benefit is assumed to be captured in the risk rates.

Resources in the model include medication, hospital attendances as an inpatient, outpatient, or day case and at GP practices, and tests for AEs. Medication doses and costs are taken from the British National Formulary (BNF)[37], except for dolutegravir which uses the Wales Patient Access Scheme (WPAS) cost; NHS resources and costs to manage patients with HIV are from a study set in London[38]; CVD events and costs are from the National Institute for Health and Care Excellence (NICE)[39], and NHS palliative care costs are from a study of three settings in England[40]. The resources to manage AEs are from a publication reporting outcomes from a Delphi panel of 64 UK clinicians[41], with gaps completed by the company asking one clinical advisor in Wales. Unit costs are from Personal Social Services Research Unit (PSSRU)[42] and the National Schedule of Reference Costs for England[43].

A weighted mean estimate of utility values for each $CD4^+$ cell count category is calculated by pooling values from ART-naive trials[19–21]. Utility values from the literature are applied to patients with infections, AEs and CVD. A minimum method, applying the lowest utility, is used to estimate the utility of patients with comorbid health conditions.

A secondary CMA is suggested by the company to be relevant as evidence from clinical trials are claimed to demonstrate therapeutic equivalence of dolutegravir compared with raltegravir in the ART-naive population[17,21] and superior efficacy and noninferior safety profile compared with raltegravir in the ART-experienced, INI-naive population. The company states that the price of dolutegravir is lower than that for raltegravir, and that there are no differences in the prescribing, administration, monitoring and safety of dolutegravir and raltegravir for the treatment of ART-naive and ART-experienced, INI-naive patients; hence the only difference is drug acquisition cost.

4.1.2 Results

The results of the base case analysis of ART-naive patients are presented in Table 2. [Commercial in confidence data removed].

Table 2. Base case results per patient for dolutegravir compared with efavirenz and darunavir/ritonavir

Medicine	Total costs (£)	Total LYG	Total QALYs	Incremental cost (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Efavirenz	£239,994	17.4	15.2				
Dolutegravir	¶	¶	¶	¶	¶	¶	¶
Darunavir/ ritonavir	£244,053	17.6	15.4				
Dolutegravir	¶	¶	¶	¶	¶	¶	¶

ICER: incremental cost-effectiveness ratio; LYG: life year gain; QALY: quality-adjusted life-year
¶Commercial in confidence figures removed

An analysis comparing dolutegravir with efavirenz, by main cost category, shows that patients on dolutegravir incur marginally higher routine HIV care [Commercial in confidence data removed] and CVD-related costs [Commercial in confidence data removed], similar infection costs [Commercial in confidence data removed] but lower AE [Commercial in confidence data removed] and palliative costs [Commercial in confidence data removed]. [Commercial in confidence data removed

An analysis comparing dolutegravir with darunavir/ritonavir shows that patients receiving dolutegravir incur marginally higher routine care costs [Commercial in confidence data removed], but have lower costs for all other categories [Commercial in confidence data removed]. The biggest saving is ART medication. [Commercial in confidence data removed].

Sensitivity analyses of CUA

Selective results of sensitivity analyses for dolutegravir versus efavirenz are presented in Table 3. The ICER is most sensitive to the price of efavirenz, reflecting the future entry of a generic product to the Welsh market. [Commercial in confidence data removed].

The result is also sensitive to the cost of salvage therapy. In the base case, a monthly cost of £1,571 is used for a combination of raltegravir, darunavir/ritonavir, tenofovir and etravirine. Changing the assumptions on resistance and efficacy of subsequent therapies also has a material impact on results.

For the ranges tested, the results are not sensitive to the efficacy of dolutegravir, routine cost of HIV care, cost of second and third line treatments, utility values, infections, AEs, CVD risk, and provision of counselling.

Table 3. Results of sensitivity analysis for dolutegravir versus efavirenz

Analyses	Range for ICER (£/QALY)	Plausibility
Base case	¶	
Dolutegravir suppression rate at 48 weeks [83.3%; 93.1%]	¶	Plausible ICER is within range using 95% CI
Dolutegravir $CD4^+$ cell count increase at 48 weeks [244.9; 296.6]	¶	Plausible ICER is within range using 95% CI
Dolutegravir late failure probability between 48 and 96 weeks [0.189%; 1.481%]	¶	Plausible ICER is within range using 95% CI
Efficacy of subsequent therapies [−10%; 10%]	¶	Not plausible that efficacy is 10% higher, but plausible that efficacy is 10% less
Cost of routine HIV care [−10%; 10%]	¶	Plausible cost is 10% different from that in study: variances likely to be > 10%.
Cost of salvage therapy [−25%; 25%]	¶	Not plausible that costs 25% greater but plausible savings exceed 25%
No resistance development for any ART beyond SINGLE period (i.e. two year) on first-line therapy	¶	Resistance may decline over time but to nil after year 2 is not plausible
HIV utility by $CD4^+$ cell count based on Kauf et al (2008)[44]	¶	Plausible
Additional adherence counselling cost	¶	Consistent with treatment guidelines[6]
100% generic efavirenz + two NRTIs	¶	Not plausible in short term
60% (generic efavirenz + two NRTIs) + 40% Atripla®	¶	Plausible in short term
No enhancement to late failure rates for subsequent lines	¶	Plausible depending on compliance in clinical practice
With new generic efavirenz price (60% of current price) and market share (40%), salvage therapy cost (tenofovir and etravirine only in lines four to six cost £549 per month versus £1,572 base case) and 10% lower efficacy in subsequent treatments	¶	Price and market share plausible in longer term: current practice regarding salvage therapy unknown but two co-therapies plausible and lower efficacy possible if poor compliance

CI: confidence interval; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
¶Commercial in confidence figures removed

Selective sensitivity analyses for dolutegravir versus darunavir/ritonavir results are presented in Table 4, with dolutegravir being the dominant strategy under all analyses conducted.

Table 4. Results of sensitivity analyses for dolutegravir versus darunavir/ritonavir

Analyses	ICER (£/QALY)	Plausibility
Base case	Dominant	
Dolutegravir suppression rate at 48 weeks [83.5%; 95.8%]	Dominant	Plausible
Dolutegravir CD4+ cell count increase at 48 weeks [244.9; 296.6]	Dominant	Plausible
Dolutegravir late failure probability between 48 and 96 weeks [0.150%; 1.390%]	Dominant	Plausible
Efficacy of subsequent therapies [−10%; 10%]	Dominant	Plausible
Cost of routine HIV care [−10%; 10%]	Dominant	Plausible
Cost of subsequent therapies [−10%; 10%]	Dominant	
Cost of salvage therapy [−25%; 25%]	Dominant	Not plausible that costs 25% greater but plausible savings exceed 25%
No resistance development for any ART beyond FLAMINGO period (i.e. one year) on first-line therapy	Dominant	Resistance may decline over time but to nil after year 1 not plausible
HIV utility by CD4+ cell count based on Kauf et al (2008)[44]	Dominant	Plausible
Additional adherence counselling cost	Dominant	Consistent with treatment guidelines[6]
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year		

Results of the company's CMA

Table 5 reports the results of the CMA comparing dolutegravir price with WPAS to raltegravir. [Commercial in confidence data removed].

Table 5. Unit, daily, annual and 3-year cost of dolutegravir with WPAS and raltegravir

Treatment	Dose	Tablets per pack	Cost per pack	Daily cost	Monthly cost	Annual cost	Cost over 3 years
Raltegravir	400 mg twice daily	60 (400 mg)	£523.79	£17.46	£530.77	£6,369	£19,108
Dolutegravir (with WPAS)	50 mg once daily	30 (50 mg)	¶	¶	¶	¶	¶
Saving with dolutegravir						¶	¶
WPAS: Wales patient access scheme ¶Commercial in confidence figures removed							

4.1.3 AWTTC critique of the economic evidence

Strengths of the economic evidence include:

- The CUA uses a well-validated model, enabling micro-simulation of each patient's progression; this is appropriate as decisions on future management depend on an individual's history and characteristics.
- The first-line comparators are consistent with clinical guidelines[6] and judged appropriate for the Welsh clinical setting.
- Clinical efficacy, safety and utility data for all first-line treatments are from relevant clinical trials; the majority of efficacy data on subsequent treatment lines are also from trials, rather than assumption.

- A systematic literature review was conducted to identify published and unpublished evidence relating to resource use, cost and utilities. Valid sources are used to populate the model.
- The company convened a Welsh Advisory Board to validate model inputs and asked a clinical advisor in Wales for advice when no information was available from the literature.
- A range of sensitivity analyses are conducted to explore the impact of changing key assumptions and parameter values.
- The outputs from the model are compared against the results of the clinical trials[6,19,20], with an explanation provided for the differences.

Limitations of the economic evidence include:

- The CVD cost reported by NICE[39] is for a five-year period, not one year as assumed in the analysis. However, this will not have a material impact on results and the change will favour dolutegravir.
- The cost of managing some AEs seems low; for example, £21.15 to manage depression. The resource use for dizziness, rash and abnormal dreams assume that all are grade 2 events which may also understate costs. However, the sensitivity analyses show the ICER is not sensitive to these costs.
- The validity of the CMA depends on the company demonstrating that dolutegravir and raltegravir are therapeutically equivalent in respect to all dimensions of health outcomes (benefits, harms and patient preferences). Direct comparative efficacy data[21], measuring the achievement of plasma concentrations of HIV-RNA < 50 copies/ml in the ART-naive population, indicate noninferiority of dolutegravir relative to raltegravir at weeks 48 and 96 (adjusted difference in proportions: 2.5% [95% CI: −2.2% to 7.1%] at week 48 and 4.5; [95% CI: −1.1 to 10.0] at week 96). This numerical difference, combined with differences in dosing regimens may impact on the assumption of equivalence, questioning the appropriateness of a CMA. The company acknowledged that CUA would be the usual approach in such circumstances; however, a CMA was carried out as the PAS price for dolutegravir is lower than that raltegravir, and due to computation burden of the ARAMIS-DTG model.
- Clinical data from ART-experienced patients show dolutegravir is superior to raltegravir ($p = 0.03$) in achieving the same endpoint, with similar safety profiles. In this case, CUA is the preferred form of analysis[17]. The CMA underestimates the relative benefits of dolutegravir.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified one economic evaluation comparing the cost-effectiveness of dolutegravir to raltegravir as first-line ART in HIV-infected adults in the United States[45]. The estimated costs for the dolutegravir arm and raltegravir arm at 192 weeks were $100,750 and $96,622 respectively. The ICER for dolutegravir versus raltegravir was estimated to be $412,811 per 1% increase in virological success. The conclusion was the ICER showed favourable cost-effectiveness results for raltegravir compared to dolutegravir when using a 192 week time frame. It is difficult to interpret this result in the Welsh context because of the outcome measure of 1% of virological success.

5.0 ASSESSMENT OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company used Welsh-specific data reported by Public Health England[5] to estimate an annual incidence of 125 patients and prevalent population of 1,660 with HIV at the end of 2013. Of those newly diagnosed with HIV, 85.5% (107 patients)[46] are assumed to start ART therapy. Dolutegravir uptake in the incident group is estimated by the company to rise from 4% in 2014 to 24% in 2018. The discontinuation rate, including mortality, of 11.6% is calculated from trials data involving dolutegravir-naive patients. Only incident patients are assumed to discontinue treatment; patients continuing to the subsequent year remain on treatment for the duration of the model.

Of ART-experienced patients, 91.9% are assumed to be INI-naive and hence eligible for treatment with dolutegravir, with 11.6% switching therapy annually. The market share of dolutegravir is estimated by the company to increase from 8% in 2014 to 24% in 2018. An all-cause mortality rate for a male aged 35–44 years in England and Wales (2012) is also applied.

5.1.2 Results of company's budget impact analyses

Table 6 provides details supporting the company's estimated net savings from adopting dolutegravir in incident patients. [Commercial in confidence data removed]. This is used in combination with fixed-dose NRTI combination tablets costing £4,365 per patient annually (50% 300 mg lamivudine and 600 mg abacavir and 50% 200 mg emtricitabine and 300 mg tenofovir). The displaced medicines comprise 35% Atripla®, 25% raltegravir, 35% darunavir and 5% efavirenz as a single tablet. Prices from the BNF[37] are applied except for the efavirenz single tablet where a 60% discount is made to the branded price. [Commercial in confidence data removed].

Table 7 provides details supporting the company's estimated net savings from adopting dolutegravir in ART-experienced patients. The same additional cost of dolutegravir and fixed-dose NRTI combination tablet is adopted. [Commercial in confidence data removed].

Table 6. Number of ART-naive patients, additional medicine cost (savings) and budget impact for introducing dolutegravir at the WPAS price (per annum)

	2014 (Year 1)	2015 (Year 2)	2016 (Year 3)	2017 (Year 4)	2018 (Year 5)
Incident patients	125	125	125	125	125
Patients commencing treatment (85.5%)	107	107	107	107	107
Dolutegravir uptake rate	4.00%	8.00%	16.00%	20.00%	24.00%
Number of incident patients treated with dolutegravir each year	4	9	17	21	26
Dolutegravir discontinuation rate	11.63%	11.63%	11.63%	11.63%	11.63%
Patients discontinuing dolutegravir	0	1	2	2	3
Patients on dolutegravir each year	4	8	15	19	23
Medicine acquisition cost with WPAS	¶	¶	¶	¶	¶
ADD: Supportive medicines cost	¶	¶	¶	¶	¶
Gross additional medicines cost	¶	¶	¶	¶	¶
LESS: Displaced medicines cost	¶	¶	¶	¶	¶
Net additional medicines saving/cost	¶	¶	¶	¶	¶
Budget impact (ART-naive)	¶	¶	¶	¶	¶
¶Commercial in confidence figures removed					

Table 7. Number of ART-experienced patients, additional medicine cost (savings) and budget impact for introducing of dolutegravir at the WPAS price (per annum)

	2014 (Year 1)	2015 (Year 2)	2016 (Year 3)	2017 (Year 4)	2018 (Year 5)
Prevalent patients	1,785	1,908	2,031	2,154	2,276
Patients commencing treatment (85.5%)	1,526	1,631	1,735	1,840	1,944
Total deaths (all patients)	2	2	2	3	3
Sub-population (INI-naïve)	91.89%	91.89%	91.89%	91.89%	91.89%
Patients switching any line of therapy	11.63%	11.63%	11.63%	11.63%	11.63%
Market uptake for dolutegravir	8.00%	14.00%	21.00%	24.00%	24.00%
Eligible for dolutegravir	13	24	39	47	50
Discontinuing dolutegravir	4	7	11	14	15
Total number of dolutegravir patients	9	27	54	88	123
Medicine acquisition cost with WPAS	¶	¶	¶	¶	¶
ADD: Supportive medicines cost	¶	¶	¶	¶	¶
Gross additional medicines cost	¶	¶	¶	¶	¶
LESS: Displaced medicines cost	¶	¶	¶	¶	¶
Net additional medicines saving/cost	¶	¶	¶	¶	¶
Budget impact (ART-experienced)	¶	¶	¶	¶	¶
¶Commercial in confidence figures removed					

[Commercial in confidence data removed].

5.1.3 AWTTC critique of the budget impact analysis

- The company has used Welsh specific data to characterise the epidemiology of HIV.
- The validity of the anticipated savings is dependent on the validity of the usage levels of the different comparators, given that the comparators' costs are calculated as weighted average cost based on these estimates.
- The budget impact has assumed take-up of generic efavirenz at a 60% discount but only 5% of incident patients are assumed to switch from this therefore the impact of the assumed future price is limited. This differs from the CUA which assumed no use of efavirenz combination therapy.
- The cost estimates are derived from the company's CUA and CMA; therefore, the limitations and uncertainties associated with these costs also apply to the budget impact analysis.

5.2 Table of comparative unit costs

Examples of acquisition costs for dolutegravir and other medicines to treat HIV are shown in Table 8.

Table 8. Examples of acquisition costs for medicines used for the treatment of HIV

Medicine	Example dose*	Example cost per year of treatment†
Tivicay® (dolutegravir) (with WPAS) 50 mg tablet	50 mg once daily	¶
Isentress® (raltegravir) 400 mg tablet	400mg twice daily	£6,373
Sustiva® (efavirenz) 600 mg tablet	600 mg once daily	£2,437
Prezista® (darunavir) 800 mg + Norvir® (ritonavir booster) 100 mg	800 mg once daily + 100 mg once daily	£3,623 + £237

*Doses based on SPCs
Refer to SPCs for full dosing details[2,47–50].
†Costs are based on current Monthly Index of Medical Specialities (MIMS) as of 22 May 2014[51].
¶Commercial in confidence figures removed

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company anticipate that dolutegravir (Tivicay®▼) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted FLAMINGO and SINGLE as ongoing studies from which additional results are likely to be available within 6–12 months. See Section 3.1.1.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 2 May 2014
Date range of evidence search: No date limits were applied to database searches.

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