PUBLIC SUMMARY DOCUMENT

Product: Dolutegravir, tablet, 50 mg, Tivicay®
Sponsor: ViiV Healthcare Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) Authority Required (+/- STREAMLINED) listing for the treatment of the human immunodeficiency virus (HIV) infection in combination with other anti-retrovirals, in a patient with a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease.

The submission was made under TGA/PBAC parallel process provisions. At the time of PBAC consideration, the TGA Clinical Evaluation Report and Delegate's Overview, both with a favourable recommendation, were available.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Dolutegravir was TGA registered on 17th January 2014 for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age and weighing 40 kg or more.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private Hospital Authority required
Public Hospital Authority required (STREAMLINED)

Initial treatment of HIV infection in combination with other antiretroviral agents in a patient with a CD4 count of less than 500 per cubic millimetre or symptomatic HIV disease.

Continuing treatment of HIV infection in combination with other antiretroviral agents where the patient has previously received PBS-subsidised therapy for HIV infection.

Listing was requested on a cost-minimisation basis with raltegravir as the comparator.

5. Clinical Place for the Proposed Therapy

Infection with the human immunodeficiency virus (HIV) causes progressive failure of the immune system. As the disease progresses, HIV infection leads to severe immune deficiency and/or the development of the opportunistic infections and cancers that define the acquired immune deficiency syndrome (AIDS).

The current PBS restriction for the initiation of an antiretroviral therapy (ARV) requires patients to have a CD4+ count less than 500cells/mm^3 or the presence of symptomatic HIV disease.

Dolutegravir would be an alternative integrase inhibitor (INI) to raltegravir to be added to an antiretroviral therapy (ART) regimen for treatment-naïve and treatment-experienced patients with HIV.

6. Comparator

The submission nominated raltegravir as the comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission was based on two randomised controlled trials (SPRING-2 and SAILING) and a single-arm study (VIKING-3). Details are presented in the table below.

Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials		
SPRING-2	A Phase III, randomized, double blind study of the safety and efficacy of GSK1349572 50mg once daily compared to raltegravir 400mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naive adult patients. Week 48 results. Raffi, F., t al. 'Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study'	13 July 2012 The Lancet, 2013, 381 (9868) pp735-743
SAILING	A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults - Week 48 Results	31 May 2013
Supplementary randomised trials		
VIKING-3	A Phase III study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1 infected adult patients with treatment failure on an integrase inhibitor containing regimen (ING112574- Week 24 Results of 114 Patients).	25 September 2012

SPRING-2 is a randomised, double blind trial which compared dolutegravir (GSK1349572) with raltegravir in patients with human immunodeficiency virus (HIV)-1 infection who were ART-naïve. The trial is ongoing, with the results at 48 weeks being available from a planned study period of 96 weeks. 822 patients were recruited, with 411 patients randomised to receive dolutegravir (GSK1349572) 50 mg once daily, with another 411 patients randomised to receive raltegravir 400 mg twice daily.

All patients received a background treatment of either abacavir/lamivudine 600 mg/300 mg fixed dose combination (FDC) or tenofovir/emtricitabine 300 mg/200 mg FDC once daily. The analysis was conducted on the intent-to-treat exposed population.

SAILING was a randomised, double blind trial which compared dolutegravir with raltegravir in patients with human immunodeficiency virus (HIV)-1 infection who were ART-experienced but INI naïve. Patients also must have documented genotypic or phenotypic resistance to at least one member of at least two ART drug classes. The trial is ongoing, with the results at 48 weeks being available from a planned study period of 96 weeks.

The two trials relied on by the submission to support the clinical claim (SPRING-2 and SAILING) both have a low risk of bias. Given that VIKING-3 was an unblinded single arm study, the overall risk of bias is high. The PBAC noted that VIKING-3 trial was included as part of the wider evaluation of the adverse events and comparative harms of dolutegravir. Additionally, VIKING-3 was relied upon by the submission to estimate the use of dolutegravir 50 mg twice daily in treatment experienced patients with INI resistance.

8. Results of Trials

With regard to comparative effectiveness, the submission provided the results of the proportion of patients with HIV RNA level of less than 50 copies/mL, an outcome that has previously been accepted by the PBAC. The non-inferiority margins were nominated to be -10% for SPRING-2 and -12% for SAILING. Both were consistent with non-inferiority trials for HIV treatments that the PBAC has considered previously.

The results from the SPRING-2 study are presented in the table below. The results indicate that dolutegravir was non-inferior to raltegravir based on a non-inferiority margin of -10%, for the outcome of the proportion of patients with a HIV-1 RNA level less than 50 copies/mL at 48 weeks. There was no significant difference in the proportion of patients developing genotypic or phenotypic INI resistance mutations between the two patient groups.

Results of patient-relevant outcome in SPRING-2 (ITT-E population)

Outcome	Dolutegravir n/N (%)	Raltegravir n/N (%)	Mean difference (%) (95% CI)	Relative difference RR (95% CI)
HIV-1 RNA <50 c/mL at Week 48	361/411 (88)	351/411 (85)	2.5 (-2.2, 7.1)	1.03 (0.97, 1.09)
INI resistance	1/411 (0.2)	2/411 (0.5)	-0.2 (-1.1, 0.6)	0.50 (0.05, 5.49)

The results in the SAILING study are presented in the table below. A statistically significantly greater proportion of ART-experienced patients treated with dolutegravir had a HIV-1 RNA level <50 copies/mL at 48 weeks compared with those treated with raltegravir.

However any claims of superiority would not be strongly supported given (i) the relative risk is only marginally significant and (ii) the clinical significance of the difference is uncertain. The data also indicated that fewer patients treated with dolutegravir had genotypic or phenotypic INI resistance mutations detected at 48 weeks compared with raltegravir.

Results of patient-relevant outcome in SAILING (ITT-E population)

Outcome	Dolutegravir n/N (%)	Raltegravir n/N (%)	Mean difference (%) (95% CI)	Relative difference RR (95% CI)*
HIV-1 RNA <50 c/mL at Week 48	251/354 (71)	230/361 (64)	**7.2 (0.3, 14.0)**	**1.11 (1.0,1.23)**
INI resistance	4/354 (1)	17/361 (5)	**-3.6 (-6.0, -1.1)**	**0.24 (0.08, 0.71)**

Text in bold indicate statistically significant results
*post-hoc analysis of the relative risk conducted by the evaluation group/Department of Health

Results from the analysis of the 24 week data cut off of the single-arm VIKING-3 study showed that 63% of patients had a HIV RNA level of <50 copies/mL. The PBAC noted that without a comparator arm it was not possible to say whether dolutegravir is effective in patients who are treatment experienced and INI experienced. Moreover, given the complete ART regimen that patients were on could be optimised in VIKING-3, any observed benefit, if real, might not be entirely attributable to dolutegravir.

With regard to comparative harms, the PBAC noted that the safety profile of dolutegravir was similar to raltegravir in the SPRING-2 and SAILING trials and studies included in the extended assessment of comparative harms.

9. Clinical Claim

For ART naïve patients (SPRING-2), the submission described dolutegravir as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety compared to raltegravir. The PBAC considered that this claim was adequately supported.

For ART experienced but INI naïve patients (SAILING), the submission described dolutegravir as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over raltegravir. The PBAC considered that this claim was not adequately supported as:

- The relative risk of the primary outcome is only marginally statistically significant (1.11; 95% CI: 1.00, 1.23) with the lower bound of the 95% CI being 1.00; and
- It is unclear whether the magnitude of the difference is clinically relevant.

The PBAC considered that the data presented supported non-inferiority of dolutegravir compared to raltegravir for ART experienced but INI naïve patients.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on a non-inferiority claim for HIV RNA less than 50 copies/mL at 48 weeks, not including additional costs/offsets for administration/adverse events. The equi-effective doses were estimated as dolutegravir 50 mg once daily over 48 weeks and raltegravir 400 mg twice daily over 48 weeks, based on the dosages used and outcomes reported in the SPRING-2 and SAILING trials.

The PBAC noted that the VIKING-3 study used a dose of 50 mg dolutegravir twice daily in patients with documented INI resistance mutations. The PBAC considered that this difference in dose would affect the cost-minimisation analysis and should be accounted for in the determination of the appropriate cost-minimised price for dolutegravir.

11. Estimated PBS Usage and Financial Implications

A combination of an epidemiological and market share approach was taken to estimate the cost to the government of dolutegravir for the requested listing for ART naïve and ART experienced HIV patients. The likely number of patients was estimated in the submission to be less than 10,000 in Year 5.

Overall, the PBAC considered that the submission's estimate was an underestimate as there was potential for increased uptake of dolutegravir due to reduced dosing frequency and pill burden, which was desirable in the HIV patient population.

The submission estimated a cost saving to the PBS based on the lower treatment failure rate of dolutegravir (29%) compared with raltegravir (37%), seen in treatment experienced patients without INI resistance in SAILING. This difference was assumed to lead to a reduction in protease inhibitor (PI) use. The PBAC agreed with the Evaluation that the claim of reduced PI use was not adequately supported and the submission's nomination of a reduction only in PI use (as opposed to NNRTIs for example) had not been justified. Thus, it would be more reasonable and conservative to not assume any of the cost savings assumed for protease inhibitors. The net costs to the R/PBS, (without proposed savings from reduced PI use) were estimated to be less than $10 million per year in the first 5 years of listing.

The PBAC noted that the total R/PBS costs included all treatment-naïve, treatment experienced (with no INI resistance) and treatment experienced (with INI resistance) patients. For the former two categories of patients, a reduction in the use of raltegravir completely offsets these costs. Thus the net R/PBS costs refer only to treatment experienced patients with INI resistance who would be treated with 50 mg dolutegravir twice daily. As stated above, given the assumptions used to derive these estimates, it was a likely underestimate.

12. Recommendation and Reasons

The PBAC considered the sponsor's submission, the Commentary, and the ESC advice for the submission and the sponsor's responses to the Commentary, and the ESC advice.

The PBAC recommended the Section 100 (Highly Specialised Drug Program) Authority Required (+/-STREAMLINED) listing of dolutegravir for the treatment of the human immunodeficiency virus (HIV) infection in combination with other anti-retrovirals on the basis of non-inferior efficacy and non-inferior safety to the comparator, raltegravir.

The PBAC made its recommendation based on accepting the cost-minimisation with raltegravir. The equi-effective doses accepted for the purposes of cost-minimisation are dolutegravir 50 mg once a day as equivalent to raltegravir 400 mg twice a day.

In terms of accounting for the difference in dose of dolutegravir between the SPRING and SAILING trials, and the VIKINGS-3 trial in the economic analysis, the PBAC considered all patients that would be considered for treatment with dolutegravir 50 mg twice a day must have demonstrated resistance to raltegravir. This leads to fourth line treatment and beyond as it was expected that the use of dolutegravir at a dosage of 50 mg twice a day would be restricted as an option of salvage therapy. Therefore, the use of raltegravir as a comparator in a cost-minimisation analysis for this sub-set population was methodologically inappropriate as it did not represent a valid alternative treatment option. The most appropriate comparators for use in fourth line treatment to be included in a cost-minimisation analysis include (ritonavir boosted) tipranavir, enfuvirtide and maraviroc.

The PBAC estimated the number of people on 50 mg twice-daily to be approximately 6% of the patient population. The PBAC considered that with increasing rates of HIV detection and treatment, the percentage of the patient population using dolutegravir 50 mg twice daily was likely to increase in the future.

At its November 2013 PBAC meeting, the PBAC also considered a submission from the Australasian Society for HIV Medicine, National Association of People with HIV Australia, and Australian Federation of AIDS Organisations requested removal of the CD4+ threshold to initiate antiretroviral therapy in HIV positive patients. The PBAC considered that the outcome of this consideration would also be applicable to dolutegravir. The sponsor of dolutegravir was advised of this outcome.

The PBAC noted a number of factors which may impact overall utilisation of dolutegravir. These include:

- reduced dosing interval and reduction in pill burden for the majority of dolutegravir patients, potentially leading to an increase in compliance;
- the current recommendations at a government level to increase the coverage of ART amongst people with HIV ;
- restriction change in terms of the removal of CD4+ count greater than 500 cells/ mm3; and
- modest market growth of INI use in ART.

Section 100 medicines are currently considered out of scope for prescribing by nurse practitioners.

In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that dolutegravir should be treated as interchangeable on an individual patient basis with raltegravir.

Outcome:
Recommended

Recommended listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
DOLUTEGRAVIR tablet 50 mg, 30	2	5	Tivicay VI

Condition:	HIV Infection
Treatment phase:	Initial
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have a CD4 count of less than 500 per cubic millimetre; OR Patient must have symptomatic HIV disease. AND The treatment must be in combination with other antiretroviral agents.

Condition:	HIV Infection
Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection. AND The treatment must be in combination with other antiretroviral agents.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

ViiV Healthcare welcomes the PBAC's recommendation to list dolutegravir on the PBS.

However, the Sponsor disagrees with the PBAC that the claim of superiority in terms of comparative effectiveness over raltegravir in treatment experienced but INI naïve patients (SAILING) was not adequately supported. The Sponsor also disagrees with the PBAC's estimation on the number of people on 50 mg twice-daily.