PUBLIC SUMMARY DOCUMENT

Product: Elvitegravir, tablet (film coated), 85 mg and 150 mg, Vitekta®
Sponsor: Gilead Sciences
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested Section 100 Highly Specialised Drugs Program Private Hospital Authority Required and Public Hospital Authority required (STREAMLINED) listings for continuing treatment of HIV infection, in combination with a boosted protease inhibitor and other antiretroviral agents, where the patient has previously received PBS-subsidised therapy for HIV infection.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This product had not been previously considered by PBAC.

3. Registration Status

Elvitegravir was considered under the TGA/PBAC parallel process. At the time of PBAC consideration, there were no TGA documents available.

Elvitegravir was TGA registered on 23 October 2013 and is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults and adolescents when co-administered with a ritonavir-boosted protease inhibitor and other antiretroviral therapy.

4. Listing Requested and PBAC's View

Section 100 Highly Specialised Drugs Program
Private Hospital Authority Required
Public Hospital Authority required (STREAMLINED)
Continuing treatment of HIV infection in combination with a boosted protease inhibitor and other antiretroviral agents, where the patient has previously received PBS-subsidised therapy for HIV infection

For PBAC's view, see Recommendation & Reasons.

5. Clinical Place for the Proposed Therapy

Human immunodeficiency virus (HIV) infection is a chronic, immunosuppressive infection. 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).

Standard medical management of HIV infection consists of combinations of different antiretroviral therapies. There are many PBS-listed antiretroviral agents for the treatment of HIV-infection, which can be classified into six classes based on mechanism of action. Some of these agents are available as fixed-dose combination products.

Elvitegravir is a HIV-1 integrase strand transfer inhibitor (INSTI). Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection.

The submission proposed elvitegravir, with a fully-active boosted protease inhibitor and other antiretroviral agents, as an alternative treatment option in treatment-experienced patients. According to treatment guidelines, any subsequent antiretroviral therapy regimen in treatment experienced patients should contain at least two (preferably three) fully-active agents. The submission proposed that elvitegravir would substitute for some raltegravir use, specifically among treatment experienced patients, with a boosted protease inhibitor in the background therapy.

For PBAC's view, see Recommendation & Reasons.

6. Comparator

The submission nominated raltegravir as the comparator as raltegravir is currently the only other integrase strand transfer inhibitor (INSTI) available in Australia, and would most likely be replaced in practice.

For PBAC's view, see Recommendation & Reasons.

7. Clinical Trials

The submission presented one randomised non-inferiority trial (GS-0145), comparing elvitegravir 150 mg daily (85 mg daily for patients taking atazanavir/ritonavir or lopinavir/ritonavir) with raltegravir 400 mg twice daily administered with background regimen containing a fully-active ritonavir-boosted protease inhibitor and a second agent in 724 treatment-experienced patients with HIV-1 infection. A 144-week open-label extension phase is on-going.

The table below details the published trial presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
GS-0145 Molina JM et al	Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study.	The Lancet Infectious Diseases 2012; 12(1):27-35

8. Results of Trials

The submission presented the proportion of patients achieving and maintaining HIV-1 RNA <50 copies/mL through to Week 48as the primary outcome and through to Week 96 as the secondary outcome, using the time to loss of virologic response (TLOVR) analysis.

The proportions of patients with virological response (HIV-1 RNA <50 copies/mL) through to Week 48 were similar between elvitegravir and raltegravir arms in the modified intention-to-treat (mITT) and the per protocol (PP) populations. The stratum-adjusted differences between arms were 1.1% (95% CI -6.0%, 8.2%) for the mITT analysis and 1.4% (95% CI -5.9%, 8.6%) for the PP analysis. The non-inferiority criterion was met, as the lower bound of the two-sided 95% CI was greater than the pre-specified non-inferiority margin of -10%.

The Week 48 results using the TLOVR analysis in the post-hoc intention-to-treat population, the snapshot algorithm, the missing=failure imputation and the missing=excluded imputation also concured with the results of the primary outcome.

The proportion of patients with virological response (HIV-1 RNA <50 copies/mL) through to Week 96 in both arms were lower compared to the proportions at Week 48 (47.6% vs 59.0% in the elvitegravir arm; 45.0% vs 57.8% in the raltegravir arm). The stratum-adjusted differences between arms was 2.6% (95% CI -4.6%, 9.9%) at 96 weeks. As the lower bound of the 95% CI was greater than the pre-specified non-inferiority margin of -10%, this supported the conclusion of non-inferiority. The results of the snapshot analysis at Week 96 were consistent with the TVOLR analysis.

There were no PP analyses of the Week 96 dataset presented in the submission or the Interim Clinical Study Report.

With regards to adverse events, the most frequently reported adverse events in the elvitegravir group were diarrhoea, upper respiratory tract infection, headache, nausea and back pain. The most frequently reported adverse events in the raltegravir group were diarrhoea, upper respiratory tract infection, cough, nausea, and headache.

Safety issues based on Phase II studies included selected renal events, bone fractures and hepatic events. Renal events and bone fractures were identified as events of special interest for the fixed-dose combination Phase III trials.

For PBAC's view, see Recommendation & Reasons.

9. Clinical Claim

The submission described elvitegravir as non-inferior in terms of comparative efficacy and comparable in terms of comparative safety over raltegravir, on a background of a fully-active protease inhibitor and a second approved agent. This claim was adequately supported and considered reasonable by the PBAC.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the non-inferiority claim of a daily dose of elvitegravir compared to twice daily dose of raltegravir.

The equi-effective doses were elvitegravir 85mg (with atazanavir/ritonavir or lopinavir/ritonavir) once daily and elvitegravir 150mg (with darunavir/ritonavir, fosamprenavir/ritonavir or tipranavir/ritonavir) once daily and raltegravir 400mg twice daily, based on the dose regimens used in Trial GS-0145. The submission also presented additional pharmacokinetic data for elvitegravir to support the proposed equi-effective doses.

For PBAC's view, see Recommendation & Reasons.

11. Estimated PBS Usage and Financial Implications

The total PBS/RPBS cost in Year 5 of listing was estimated in the submission to be between $10 - $30 million, with equivalent cost-offsets for reduced use of raltegravir.
The submission claimed no net financial impact to the PBS of listing elvitegravir based on the following assumptions:

- Elvitegravir will only substitute for raltegravir;
- Elvitegravir is non-inferior in terms of efficacy and has a similar safety profile compared to raltegravir;
- Elvitegravir has an identical price to the weighted price of raltegravir;
- The listing of elvitegravir is not expected to increase the INSTI market.

The PBAC considered that the claim of no net financial cost was unlikely to be realised.

For PBAC's view, see Recommendation & Reasons.

12. Recommendation and Reasons

The PBAC rejected the submission of the basis that, in the absence of the final TGA indication it was not possible to identify the clinical place of elvitegravir outside the context of a fixed dose combination. The PBAC therefore considered that it was not possible to formulate an appropriate PBS restriction, or to construct the appropriate price for elvitegravir.

The PBAC considered that raltegravir was the appropriate primary comparator, however as the TGA process is still ongoing and the indication for elvitegravir was not available at the time of consideration it was not possible to conclude with certainty that raltegravir was the only comparator.

The PBAC noted the results for the primary and secondary outcomes in Trial GS-0145. The PBAC also noted a high proportion of voluntary discontinuations (due to non-compliance, withdrawn consent) and loss to follow-up, and considered that these confounding factors affected the results of the trial. The PBAC considered that the discontinuation rates reflected changes in treatment-experienced patients' behaviour; with more available treatment options, trial patients may be less motivated to adhere to randomised treatment.

Overall, the PBAC concluded that elvitegravir is non-inferior to raltegravir in terms of comparative effectiveness.

The PBAC noted the safety outcomes reported in Trial GS-0145 and considered that the long-term safety of elvitegravir, beyond the 96 weeks of the trial, was uncertain. The PBAC noted that longer term post-marketing surveillance with the comparator raltegravir had identified additional safety issues, and it was unclear whether these events are integrase strand transfer inhibitor class effects. The PBAC also noted there is an on-going open-label extension phase of Trial GS-0145.

Overall, the PBAC concluded that based on the available data elvitegravir is probably non-inferior to raltegravir in terms of comparative safety, albeit with a different adverse event profile.

The submission requested listing on a cost-minimisation basis with raltegravir and proposed that both doses of elvitegravir (85 mg and 150 mg) be priced equivalent to raltegravir. The PBAC noted that elvitegravir requires boosting, with co-administration with a boosted protease inhibitor featured as a requirement of the proposed TGA indication and requested PBS listing. In contrast, raltegravir does not require boosting. The PBAC further noted that elvitegravir does not therefore incur additional costs for a boosting agent, if used as per the requested listing as the booster is available in the background therapy. The cost of the boosting agent was not included in the cost-minimisation analysis.

The PBAC considered the submission's utilisation estimates were uncertain and were underpinned by several unsupported assumptions. The PBAC considered the assumption of identical cost of elvitegravir per patient per year to be unrealistic.

The PBAC considered that in view of the well documented direct patient benefits of fixed dose combination products in treatment of infectious diseases such as HIV, the absence of single-ingredient products of cobicistat and elvitegravir on the PBS would not present any barrier to the listing of the fixed dose combination of cobicistat/elvitegravir/emtricitabine/tenofovir (Stribild).

The PBAC noted that the submission is eligible for an Independent Review.

Recommendation:
Rejected

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

Gilead will continue to work with the PBAC to secure a PBS listing for elvitegravir.