Public Summary Document

Product: Cobicistat, tablet (film coated), 150mg, Tybost®
Sponsor: Gilead Sciences
Date of PBAC Consideration: March 2013

1. Purpose of Application

To request Section 100 Highly Specialised Drugs Program Private Hospital Authority Required and Public Hospital Authority Required (STREAMLINED) listings for treatment of an HIV-infected patient as a pharmacokinetic enhancer of atazanavir.

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

The PBAC had not previously considered a submission for cobicistat.

3. Registration Status

The submission was submitted under the TGA/PBAC Parallel Process provisions. At the time of PBAC consideration, no TGA documentation was available.

Cobicistat was TGA registered on 23 October 2013 and is indicated as a pharmacokinetic enhancer of appropriate HIV-1 protease inhibitors in adults.

4. Listing Requested and PBAC's View

Section 100 Highly Specialised Drugs Program
Private Hospital Authority required
Public Hospital Authority required (STREAMLINED)
For use in the treatment of HIV-infected patients as a pharmacokinetic enhancer of atazanavir.

For PBAC's view's, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cobicistat is an inhibitor of cytochrome P450 3A (CYP3A) enzymes. It is also a weak inhibitor of CYP2D6. It has no intrinsic activity against human immunodeficiency virus (HIV) but is intended for use as a pharmacokinetic enhancer of antiretroviral agents that are metabolised by these enzymes.

The submission proposed cobicistat as a pharmacokinetic enhancer of atazanavir, without restriction on the treatment experience of patients.

For PBAC's view's, see Recommendation and Reasons.

6. Comparator

The submission nominated ritonavir as the main comparator. The PBAC considered this may be the appropriate comparator. However, the PBAC noted that ritonavir is PBS listed for its

anti-retroviral activity and is not explicitly listed as a pharmacokinetic enhancer (although this is the accepted primary role of ritonavir in clinical practice).

For PBAC's view's, see Recommendation and Reasons.

7. Clinical Trials

The submission presented two direct head-to-head randomised trials (GS-0105 & GS-0114), comparing cobicistat-boosted atazanavir to ritonavir-boosted atazanavir in combination with emtricitabine/tenofovir in HIV-1 infected antiretroviral treatment naïve adults.

The submission also presented a meta-analysis of the two randomised trials.

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

Trial ID/ First author	Protocol title/ Publication title	Publication citation
GS-0105 Elion et al (2011a)	Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection.	AIDS 2011;25(15):1881-1886
Elion et al (2011b)	The single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate maintains a high rate of viral suppression, and cobicistat is an effective pharmacoenhancer through 48 weeks.	Can J Infect Dis Med Microbiol 2011;22 (S): 58B-59B (Abstract)

8. Results of Trials

The submission presented the proportion of patients achieving and maintaining HIV-1 RNA < 50 copies/mL at Week 48 as the primary outcome for trial GS-0114 and as the secondary outcome for trial GS-0105.

Virological response rates were high in both cobicistat and ritonavir groups. While the pooled response rate was slightly lower for the cobicistat group, the pooled analyses showed that at Week 48, based on the lower bounds of the confidence interval surrounding the treatment difference, the pre-specified non-inferiority margin of 12% was met for all analysed data sets (ITT, modified ITT and per protocol). Similar results were observed in GS-0105, although the non-inferiority criterion was not met. Trial GS-0105 had a small sample size (N=85) with limited power to demonstrate non-inferiority.

The overall incidence of patients with treatment-emergent adverse events was similar in the cobicistat and ritonavir boosted anti-retroviral treatment (ART) groups. However, more cobicistat treated patients had treatment-emergent adverse events at higher severity grades (≥ grade 2) in comparison with ritonavir treated patients.

Patients treated with cobicistat boosted ART were more likely to have hepatobiliary disorders including hyperbilirubinaemia; while ritonavir boosted ART was associated with more diarrhoea. Other event rates appeared comparable between treatment arms.

Post-hoc analyses of pooled data showed no differences between cobicistat and ritonavir groups in treatment emergent adverse events, serious adverse events, discontinuation rates due to adverse events, renal events, and rash events.

The PBAC noted the small increase in the serum creatinine and corresponding decrease in median estimated glomerular filtration rate (eGFR) in both arms of both Trial GS-0105 and GS-0114, which were reversible on cobicistat discontinuation. The PBAC noted the sponsor's Pre-Sub-Committee Response stated that the eGFR reduction was due to inhibition of tubular secretion of creatinine by cobicistat, but that GFR is not affected.

The PBAC also noted renal safety concerns based on the Phase III trials of the fixed-dose combination Stribild, with apparentlymore renal toxicity with the combination of cobicistat with tenofovir than tenofovir alone. However, the PBAC noted comparable renal event rates between arms in the cobicistat trials GS-0105 and GS-0114 where cobicistat and ritonavir were each co-administered with tenofovir in the background therapy.

There were limited long-term safety data on cobicistat.

For PBAC's view's, see Recommendation and Reasons.

9. Clinical Claim

The submission described cobicistat as non-inferior in terms of comparative effectiveness and comparable safety with ritonavir. The clinical claim was not accepted by the PBAC.

For PBAC's view's, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on a claim of non-inferiority for virological outcome. The equi-effective doses were cobicistat 150 mg once daily and ritonavir 100 mg once daily when used as a pharmacokinetic enhancer of atazanavir, based on the dose regimens used in Trials GS-0105 and GS-0114.

11. Estimated PBS Usage and Financial Implications

The submission estimated that cobicistat listing would be cost neutral to the PBS over the first 5 years due to price parity with substituted agents.

12. Recommendation and Reasons

The PBAC rejected the submission on the basis of an unclear clinical need for cobicistat as a single-ingredient product, and inadequate evidence to support a claim of non-inferior comparative effectiveness and safety.

The PBAC considered that as cobicistat has no intrinsic anti-retroviral activity and is only clinically indicated as a component in a combination product for which there is a separate application regimen. The clinical need for cobicistat as a single-ingredient was not established.

Furthermore, the PBAC noted that cobicistat has no current place in published recommended treatment guidelines outside of its use in the combination product Stribild (cobicistat+elvitegravir+emtricitabine+tenofovir).

The PBAC noted that the submission was submitted under TGA/PBAC parallel process, and no TGA documentation was available at the time of PBAC consideration. In the absence of the TGA indication, the PBAC considered that it was not possible to comment on the proposed place in therapy or PBS restriction for cobicistat.

The PBAC noted that ritonavir is listed on the PBS for its anti-retroviral activity and its action as a PK enhancer is not formally part of its PBS listing, although this is the accepted primary role of ritonavir in clinical practice. The PBAC noted that in contrast with the nominated comparator, cobicistat has no intrinsic anti-retroviral activity. The differences in pharmacological and pharmacokinetic properties of the two agents presented challenges in comparing the two drugs, however overall the PBAC considered that ritonavir may be the appropriate comparator.

The PBAC noted that the primary efficacy outcome reported in the submission was viral load. The PBAC considered that as cobicistat has no intrinsic antiretroviral activity, the relevance of this outcome as the only measure in assessing the efficacy of cobicistat was uncertain. The PBAC further considered that pharmacokinetic data demonstrating the effect of cobicistat on the agent being boosted (for instance, whether co-administration of cobicistat allows for reduction in the dose of the active agent) may be a more relevant and informative outcome.

The PBAC also noted that although the trials met the pre-specified non-inferiority margin of 12% for virological response, the trials were of small size and the trial duration was limited to 48 weeks. Moreover, the trial population was not consistent with the proposed PBS population in that all patients in the trials were naive to anti-retroviral treatment. The PBAC therefore considered that the data were not as robust as those in other submissions for anti-retrovirals.

The PBAC considered the claim that cobicistat was non-inferior to ritonavir with respect to comparative safety was only partially supported by the evidence presented, and that the submission did not establish non-inferiority of cobicistat to ritonavir with respect to comparative effectiveness, as viral load may not be the only appropriate outcome.

The PBAC noted that the sponsor's pre-PBAC response indicated that its submission for cobicistat had been primarily to satisfy the requirement in the *Guidelines for preparing submissions to the PBAC (2008)* that the components of a combination product should preferably be listed on the PBS.

The PBAC noted that the Guidelines with respect to the PBS listing of the components contained the qualifier that PBS listing of the components is preferable, but not essential. In addition, the PBAC considered that the Guidelines are necessarily not prescriptive in nature.

The PBAC recalled that it had made a positive recommendation for the fixed dose combination Stribild in the absence of a PBS listing or a positive recommendation for either elvitegravir or cobicistat as single-ingredient products. The PBAC considered that in view of the well-documented direct patient benefits of fixed dose combination products in HIV treatment, the absence of single-ingredient products of cobicistat and elvitegravir on the PBS would not present any barrier to the listing of 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 cobicistat.