

**5.02 ATAZANAVIR/COBICISTAT
fixed dose combination tablets, atazanavir 300 mg + cobicistat
150 mg
Evotaz®, Bristol Myers Squibb Pty Ltd.**

1 Purpose of Application

1.1 Section 100, Authority required listing for atazanavir/cobicistat fixed-dose combination (FDC) for the treatment of human immunodeficiency virus, type 1 (HIV-1) infection.

2 Requested listing

2.1 The wording of clinical criteria in the requested listing was the same as in the PBS listing of atazanavir 300 mg.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ATAZANAVIR 300 MG/ COBICISTAT 150 MG FIXED DOSE COMBINATION Oral tablet (30)	2	Not specified	\$ [REDACTED] (Community Access)	Evotaz® Bristol Myers Squibb Pty Ltd
Restriction type	S100 HSD Public: Authority Required (STREAMLINED) S100 HSD Private: Authority Required (STREAMLINED) S100 HSD Community Access, Authority Required (STREAMLINED)			
Condition/indication	HIV infection			
Treatment phase	Initial			
Clinical criteria	Patient must be antiretroviral treatment naive, AND The treatment must be in combination with other antiretroviral agents.			
Treatment phase	Continuing			
Clinical criteria (2)	Patient must have previously received PBS-subsidised therapy for HIV infection, AND The treatment must be in combination with other antiretroviral agents.			

2.2 The requested listing was based on a cost-minimisation analysis against the comparator atazanavir plus ritonavir provided concomitantly.

For more detail on PBAC's view, see section 7 "PBAC outcome".

3 Background

- 3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation the draft Product Information was available. The ESC noted that atazanavir/cobicistat FDC received TGA approval and was registered on the ARTG on 23 September 2015 for the following indication:

“EVOTAZ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults”.

- 3.2 Atazanavir/cobicistat FDC had not been previously considered by the PBAC.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

4 Clinical place for the proposed therapy

- 4.1 Atazanavir/cobicistat FDC was proposed for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced patients.

- 4.2 The place in therapy for atazanavir/cobicistat FDC was suggested to be the same as that of its comparator atazanavir plus ritonavir taken concomitantly. The 2015 Australian Commentary to the U.S. guidelines (Australian Commentary to the US Department of Health and Human Services Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents) recommended that atazanavir plus ritonavir should be used as an alternative treatment and not in the first-line due to the toxicity profile of atazanavir. The ESC noted that the Australian Commentary lists atazanavir plus ritonavir as an acceptable alternative to darunavir plus ritonavir as protease inhibitor-based therapy in naïve patients in the context of the current PBS restriction of darunavir plus ritonavir to treatment experienced patients only.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

5 Comparator

- 5.1 Atazanavir plus ritonavir taken concomitantly was nominated as a comparator. This was appropriate.

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 PBAC consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission presented evidence of bioequivalence from a crossover study in healthy volunteers where atazanavir/cobicistat FDC was compared to atazanavir plus cobicistat taken concomitantly (Study 511, n=64).
- 6.4 The submission also presented two head-to-head trials comparing atazanavir plus cobicistat taken concomitantly to atazanavir plus ritonavir taken concomitantly (Study 114, n=698; Study 105, n=85).
- 6.5 The evidence of bioequivalence was used to establish a link between atazanavir plus cobicistat taken concomitantly used in the clinical trials and atazanavir/cobicistat FDC for which the listing was requested.
- 6.6 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Bioequivalence study		
Study 511	<p>A randomized, 5-period, crossover study in healthy subjects to assess the bioequivalence of atazanavir when co-administered with cobicistat as a fixed dose combination relative to the single agents following a light meal, the relative bioavailability of atazanavir when co-administered with cobicistat as a fixed dose combination relative to the single agents under fasted conditions, and the effect of food on the bioavailability of atazanavir in the fixed dose combination. Clinical Study Report: AI424511. Clinicaltrials.gov ID: NCT01837719</p> <p>Tao X, Sevinsky H, Wang R <i>et al.</i> Atazanavir/cobicistat fixed-dose combination is bioequivalent to the individual components. [abstract]</p>	<p>22 November 2013</p> <p><i>HIV Medicine</i> 15 (Supplement 3): 116</p>
Direct randomised trials		
Study 114	<p>A phase 3, randomized, double-blind study to evaluate the safety and efficacy of GS-9350-boosted atazanavir versus ritonavir-boosted atazanavir each administered with emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected, antiretroviral treatment-naïve adults. Interim Week 48 Clinical Study Report: GS-US-216-0114. Clinicaltrials.gov ID: NCT01108510</p> <p>Gallant JE, Koenig E, Andrade-Villanueva J <i>et al.</i> Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: Week 48 results.</p>	<p>23 January 2012</p> <p><i>Journal of Infectious Diseases</i> 208 (1): 32-39</p>
Study 105	<p>A phase 2, randomized, double-blinded study of the safety and efficacy of GS-9350-boosted atazanavir (ATV/GS-9350) compared to ritonavir-boosted atazanavir (ATV/r) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in HIV-1 infected, antiretroviral treatment-naïve adults. Clinical Study Report: GS-US-216-0105. Clinicaltrials.gov ID: NCT00892437</p> <p>Elion R, Cohen C, Gathe J <i>et al.</i> 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.</p>	<p>31 August 2011</p> <p><i>AIDS</i> 25 (15): 1881-1886</p>

Source: Table B.2.2, p39 of the submission

6.7 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Bioequivalence crossover study					
Study 511	64	R, OL, CO, 31 days	Low	Healthy, ages 18 to 49 years, BMI 18 to 32 kg/m ²	Plasma concentration parameters
Randomised controlled trials					
Study 114	698	R, DB, 96 wks ^a	Low	HIV infection, adult, treatment-naïve	% patients with virologic success ^b
Study 105	85	R, DB, 60 wks	Low	HIV infection, adult, treatment-naïve	% patients with virologic success

Source: *compiled during the evaluation*

R = randomised; DB = double blind; OL = open-label; CO = crossover; BMI = body mass index; HIV = human immunodeficiency virus

^a Study 114 was designed for 96 weeks of treatment, however, the interim clinical study report provided data at the 48 week time point, which was when the primary efficacy analysis took place. The 96-week CSR was not yet available.

^b Virologic success was defined as HIV-1 RNA < 50 copies/mL at 48 weeks.

Comparative effectiveness

- 6.8 Study 511 compared the pharmacokinetic profile of atazanavir/cobicistat FDC with atazanavir plus cobicistat. The two formulations were considered bioequivalent because the 90% interval of geometric least square means ratios for all analysed parameters fell within the pre-defined range of 0.80 to 1.25. Based on these results, it might have been reasonable to consider the efficacy and safety results for atazanavir plus cobicistat taken concomitantly as representative of the efficacy and safety results of atazanavir/cobicistat FDC.
- 6.9 The clinically relevant outcome for benefits was the proportion of patients with HIV-1 ribonucleic acid (RNA) less than 50 copies/mL. This outcome was measured as the primary outcome in Study 114 and Study 105. The submission noted that, following the U.S. Food and Drug Administration (FDA) recommendation, virologic success was assessed using the snapshot algorithm rather than the time to loss of virologic response.
- 6.10 In the pooled analysis, virologic success was achieved in 84.8% of participants in the atazanavir plus cobicistat arm and 87.3% in the atazanavir plus ritonavir arm. The adjusted mean difference was -2.5% and was not statistically significant. The lower bound of the 95% confidence interval (-7.5%) was above the assumed non-inferiority margin of -12%. Therefore, the submission considered that atazanavir plus cobicistat taken concomitantly was non-inferior to atazanavir plus ritonavir taken concomitantly.

Table 3: Percent of patients with virologic success^a at Week 48 using the snapshot algorithm

Trial ID	ATV + c + TVD n/N (%)	ATV + r + TVD n/N (%)	RD (95% CI) ^b
Study 114	293/344 (85.2%)	304/348 (87.4%)	-2.2% (-7.4% to 3.0%)
Study 105 ^c	41/50 (82.0%)	25/29 (86.2%)	-5.4% (-23.8% to 13.1%)
Pooled analysis	334/394 (84.8%)	329/377 (87.3%)	-2.5% (-7.5% to 2.5%)

Source: Table B.6.2, p73 of the submission

Italics calculated during evaluation

ATV = atazanavir; c = cobicistat; r = ritonavir; RD = risk difference; CI = confidence interval; HIV = human immunodeficiency virus; NNT = number needed to treat; RNA = ribonucleic acid; TVD = single tablet emtricitabine/tenofovir disoproxil fumarate

^a Virologic success was defined as HIV-1 RNA < 50 copies/mL at 48 weeks.

^b Calculated based on baseline HIV-1 RNA stratum adjusted Mantel-Haenszel proportion; *reported for Study 114 was a 95.2% confidence interval.*

^c *Modified* intention-to-treat analysis, including those patients who received at least one dose and with missing data or switching to alternative antiretroviral therapy considered as failure

Comparative harms

- 6.11 There was a higher proportion of Grade 3 to 4 adverse events (17.8% vs. 13.3%) and a higher proportion of serious adverse events (9.6% vs. 6.6%) in the atazanavir plus cobicistat taken concomitantly compared to atazanavir plus ritonavir; however, the differences were not statistically significant. There was a greater percentage of patients with renal events (acquired Fanconi syndrome, renal failure and acute renal failure) in the atazanavir plus ritonavir arm than in the atazanavir plus cobicistat arm. One renal event in the atazanavir plus cobicistat arm and four events in the atazanavir plus ritonavir arm were treatment-related. However, these were most likely associated with tenofovir disoproxil fumarate treatment.

Table 4: Summary of key adverse events in the pooled dataset

Adverse event	ATV + c + TVD n (%)	ATV + r + TVD n (%)	RD (95% CI)	RR (95% CI)
N	394	377		
Treatment emergent				
Any AE	361 (91.6%)	347 (92.0%)	0% (-4%, 3%)	1.00 (0.95, 1.04)
Grade 3 or 4 AEs	70 (17.8%)	50 (13.3%)	5% (-1%, 10%)	1.34 (0.96, 1.87)
Serious AEs	38 (9.6%)	25 (6.6%)	3% (-1%, 7%)	1.45 (0.90, 2.36)
AEs leading to discontinuation	27 (6.9%)	27 (7.2%)	0% (-4%, 3%)	0.96 (0.57, 1.60)
Serious AEs related to study drug	5 (1.3%)	6 (1.6%)	0% (-2%, 1%)	0.80 (0.25, 2.59)
Death	0	0	0	NA
Special interest				
Renal events (all)	1 (0.3%)	7 (1.9%)	-2% (-3%, 0%)	<i>0.14 (0.02, 1.11)</i>

Source: Table B.6.6, p82; Table B.6.9, p90 of the submission

Italics value calculated during evaluation; **Bold** indicates statistical significance

ATV = atazanavir; c = cobicistat; r = ritonavir; CI = confidence interval; AE = adverse event; RD = risk difference; RR = relative risk; NA = not applicable; TVD = single tablet emtricitabine/tenofovir disoproxil fumarate

Clinical claim

- 6.12 The submission described atazanavir/cobicistat FDC as bioequivalent to atazanavir plus cobicistat and described atazanavir plus cobicistat as non-inferior in terms of comparative effectiveness to atazanavir plus ritonavir taken concomitantly. The submission also claimed that although the safety profile of atazanavir plus cobicistat was different to that of atazanavir plus ritonavir, it was unlikely to result in worse outcomes for patients with HIV-1 infection.
- 6.13 The submission did not provide direct clinical evidence comparing atazanavir/cobicistat FDC and atazanavir plus ritonavir taken concomitantly, rather it provided bridging evidence:
- A bio-equivalence study comparing atazanavir/cobicistat FDC to atazanavir plus cobicistat. This evidence demonstrated bio-equivalence.
 - Two efficacy and safety trials comparing atazanavir plus cobicistat to atazanavir plus ritonavir. This evidence appeared to demonstrate non-inferior efficacy and safety.
- 6.14 The ESC considered the stepped approach was reasonable to demonstrate non-inferior efficacy and safety of atazanavir/cobicistat FDC and atazanavir plus ritonavir taken concomitantly.
- 6.15 The Pre-Sub-Committee Response (PSCR) indicated that TGA has agreed that atazanavir/cobicistat FDC is bioequivalent to atazanavir plus cobicistat taken concomitantly.
- 6.16 The PBAC considered that the claim of non-inferior comparative effectiveness and comparative safety was reasonable.

Economic analysis

- 6.17 The submission presented a cost-minimisation analysis. The submission did not provide the equi-effective dose of atazanavir/cobicistat FDC and atazanavir plus ritonavir taken concomitantly. Rather it provided the equi-effective doses for atazanavir plus cobicistat taken concomitantly and atazanavir plus ritonavir taken concomitantly, derived from the efficacy and safety trials 114 and 105.
- 6.18 The equi-effective doses were estimated as:
- Atazanavir 300 mg (one capsule) plus cobicistat 150 mg (one tablet) once daily over 48 weeks,
 - Atazanavir 300 mg (one capsule) plus ritonavir 100 mg (one tablet) once daily over 48 weeks.
- 6.19 The cost-minimisation analysis only included the cost of drug acquisition. The submission considered there would be no additional cost consequences of listing atazanavir/cobicistat FDC. This was reasonable.
- 6.20 The ESC noted that atazanavir/cobicistat FDC would likely replace atazanavir plus ritonavir.

Table 5: Cost-minimisation analysis (price for 60 days of treatment)

		Calculation	ATV	RTV
	PBS item code		10321F	10273Q
A	Approved ex-manufacturer price	PBS Schedule	\$521.91	\$40.95
B	Cost per unit	A / 30	\$17.40	\$1.37
C	Price per unit of ATV/c FDC	Sum of B		\$18.76
D	Price per pack of ATV/c FDC	C x 30		\$
E	Mark-up (Private) ^a	PBS Schedule		\$40
F	Dispensing fee			\$6.93
G	Community access DPMQ	(D x 2) + E + F	\$	

Source: compiled during evaluation based on Table D.2.2, p140 of the submission

Italics calculated during evaluation

ATV = atazanavir; c = cobicistat; RTV = ritonavir; FDC = fixed-dose combination; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme

^a For ex-manufacturer price over \$1,000

Drug cost/patient/year: \$ [REDACTED].

6.21 Atazanavir/cobicistat FDC is an ongoing treatment. The annual drug cost was calculated for the community access dispensed price for maximum quantity (\$ [REDACTED]) assuming an average of 9.9 packs per patient per year. The annual cost for the comparator was \$5,832 based on the dispensed price for maximum quantity of atazanavir (\$1,090.75) and ritonavir (\$1,029.09) and assuming the same compliance. Drug prices were updated with the higher dispensing fee of \$6.93 effective from 1 July 2015.

Estimated PBS usage & financial implications

6.22 This submission was not considered by DUSC. The submission used a market share approach to calculate the numbers of prescriptions, patients and packs. In the base case the submission assumed that atazanavir/cobicistat FDC would only replace atazanavir plus ritonavir taken concomitantly.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	70%	75%	80%	85%	90%
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost reduction in other drugs	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to MBS	\$0	\$0	\$0	\$0	\$0
Estimated total net cost					
Net cost to government	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

Source: Section E Excel spreadsheet attachment to the submission

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule

^a Assuming 9.9 per year as estimated by the submission

6.23 At year 5, the estimated number of patients was [REDACTED] less than 10,000 and the net save to the PBS would be \$ [REDACTED]. At year 1, the estimated number of patients was [REDACTED] less than 10,000 and the net save to the PBS would be \$ [REDACTED].

- 6.24 The market size estimates presented in the submission might not have been reasonable because:
- The market for atazanavir/cobicistat FDC was projected based on two data points representing atazanavir use and an assumption regarding the change in market size that was not well justified.
 - The assumed rates of market uptake for the proposed therapy were not justified.
 - Atazanavir/cobicistat FDC could substitute in clinical practice therapies other than atazanavir plus ritonavir. The submission explored the substitution of darunavir plus ritonavir, lopinavir/ritonavir FDC, and atazanavir monotherapy in sensitivity analyses. Substitution of these therapies by atazanavir/cobicistat FDC would likely generate cost-savings to the government. This was reasonable.
 - Replacing public hospital access with Community Access would result in a loss of patient co-payment revenue by the PBS because for every two scripts (for atazanavir and ritonavir) atazanavir/cobicistat FDC would only require one script. This was reasonable. The effects of the Community Access Program on treatment were shown as a sensitivity analysis and were not included in the base case.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC recommended Section 100 Highly Specialised Drugs Program (HSD) listing of atazanavir/cobicistat fixed dose combination for the treatment of HIV. The PBAC recommended the special arrangements under the HSD Community Access Program, Authority Required (STREAMLINED).
- 7.2 The PBAC recommended the listing of atazanavir/cobicistat on a cost-minimisation basis with atazanavir plus ritonavir provided concomitantly. The equi-effective doses are atazanavir 300 mg (one capsule) plus cobicistat 150 mg (one tablet) once daily over 48 weeks is equal to atazanavir 300 mg (one capsule) plus ritonavir 100 mg (one tablet) once daily over 48 weeks.
- 7.3 The PBAC considered that the price of atazanavir/cobicistat should be no higher than the sum of atazanavir and ritonavir, as established by the equi-effective doses above, but taking into account the pricing of other HIV combination drugs.
- 7.4 The PBAC considered that the listing of atazanavir/cobicistat particularly the restriction, maximum quantity and repeats should align with the current listing of atazanavir 300 mg.
- 7.5 The PBAC accepted the proposed clinical place for atazanavir/cobicistat as for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced patients.
- 7.6 The PBAC accepted atazanavir plus ritonavir taken concomitantly as appropriate comparator.
- 7.7 The PBAC acknowledged that the TGA has accepted the bioequivalence of atazanavir/cobicistat to atazanavir and cobicistat taken concomitantly (Study 511). The PBAC also noted that additional two efficacy and safety trials (Study 114 and

Study 105) comparing atazanavir plus cobicistat to atazanavir plus ritonavir also demonstrated non-inferior efficacy and safety. Based on the evidence presented, the PBAC agreed there appears to be no difference in benefits and harms between atazanavir/cobicistat and atazanavir plus cobicistat or ritonavir.

- 7.8 The PBAC agreed that atazanavir/cobicistat was non-inferior to atazanavir plus ritonavir in treatment naïve patients. The PBAC considered that the comparative effectiveness and safety of atazanavir/cobicistat may be reasonably extrapolated to a treatment-experienced population.
- 7.9 The PBAC noted the submission’s utilisation estimates and claim on a small saving.
- 7.10 The PBAC advised that Section 100 medicines are currently considered out of scope by prescribing by nurse practitioners.
- 7.11 The PBAC recommended that the Safety Net 20 Day Rule should apply to atazanavir with cobicistat. The PBAC also recommended that the Safety Net rule should flow-on to all HIV treatment currently listed on the PBS.
- 7.12 In accordance with subsection 101(3BA) of the Act, the PBAC advised that it is of the opinion that atazanavir with cobicistat should not be treated as interchangeable on an individual patient basis with other antiretroviral therapies.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item. Safety Net 20 Day rule to flow-on to all HIV treatment currently listed on the PBS.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ATAZANAVIR 300MG + COBICISTAT 150MG Tablet	60	5	Evotaz	Bristol Myers Squibb Pty Ltd

Category / Program	S100 HSD Community Access: Authority Required (STREAMLINED)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	HIV Infection
PBS Indication:	HIV Infection
Treatment phase:	Initial

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must be antiretroviral treatment naive, AND The treatment must be in combination with other antiretroviral agents.

Category / Program	S100 HSD Community Access: Authority Required (STREAMLINED)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	HIV Infection
PBS Indication:	HIV Infection
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> 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.

9 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.

10 Sponsor's Comment

Bristol-Myers Squibb welcomes the PBAC's recommendation to list atazanavir/cobicistat fixed dose combination tablets on the PBS.