5.04 DARUNAVIR/COBICISTAT
fixed-dose combination tablet, 30, darunavir 800 mg + cobicstat 150mg,
Prezcobix®, Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 The submission requested Section 100, Authority Required listing for darunavir/cobicistat fixed-dose combination (FDC) for treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in patients who have experienced virological failure (viral load > 400 copies/mL) or clinical failure or genotypic resistance after at least one antiretroviral regimen and have no darunavir resistance associated mutations.

2 Requested listing

2.1 The requested PBS listing for darunavir/cobicistat FDC was the same as PBS listing for darunavir 800 mg.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
DARUNAVIR 800 MG/ COBICISTAT 150 MG FIXED DOSE COMBINATION, ORAL TABLET (30)	2	5	$[redacted] (Public) $[redacted] (Private and Community Pharmacy)	Prezcobix®	Janssen-Cilag Pty Ltd
Section 100 (Highly Specialised Drugs Program), Private Hospital Authority required, Public Hospital Authority required (STREAMLINED) Human immunodeficiency virus (HIV) infection **Clinical criteria:** The treatment must be in addition to optimised background therapy **AND** The treatment must be in combination with other antiretroviral agents, **AND** Patient must have experienced virological failure or clinical failure or genotypic resistance after at least one antiretroviral regimen Virological failure is defined as a viral load greater than 400 copies per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity. **Note:** The cobicistat component of the darunavir + cobicistat combination product provides the necessary pharmacokinetic enhancement of darunavir to achieve therapeutic levels of darunavir. The darunavir + cobicistat combination product must not be administered with ritonavir.					

2.2 The requested listing was based on a cost-minimisation analysis against the comparator, darunavir and ritonavir provided concomitantly.

3 Background

3.1 The submission was made under the TGA/PBAC Parallel Process. The ESC noted that darunavir/cobicistat FDC received TGA approval and was registered on the ARTG on 24 September 2015.

3.2 The TGA approved indications for the darunavir/cobicistat FDC in combination with other antiretroviral agents is for the treatment of HIV-1 infection in:

- antiretroviral treatment-naïve adult patients;
- antiretroviral treatment-experienced adult patients with no darunavir resistance associated mutation and who have plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL; and
- antiretroviral treatment-experienced but HIV-1 protease inhibitor-naïve adult patients for whom HIV-1 genotype testing is unavailable.

3.3 The submission did not seek listing for the antiretroviral treatment-naïve patients.

3.4 This item had not been considered by the PBAC previously.

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

4 Clinical place for the proposed therapy

4.1 Darunavir/cobicistat FDC was proposed as a second-line treatment for patients with HIV infection who have experienced virological or clinical failure (treatment experienced). Darunavir is a protease inhibitor (PI), while cobicistat is a pharmacokinetic enhancer of protease inhibitors, with no detectable antiretroviral activity.

4.2 The place in therapy for darunavir/cobicistat FDC was proposed to be the same as its main comparator, darunavir and ritonavir taken concomitantly. The ESC noted an apparent inconsistency between the proposed clinical place in therapy for darunavir/cobicistat and the main comparator darunavir/ritonavir as therapy for treatment experienced patients only and the most recent US DHHS HIV treatment guidelines which lists darunavir/ritonavir (with TDF/FTC) as a recommended regimen and darunavir/cobicistat (with TDF/FTC or ABC/3TC) as an alternative option in first line therapy for treatment naïve patients.

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

5 Comparator

5.1 The submission nominated two main comparators:

- Darunavir and ritonavir taken concomitantly. This was appropriate.
- Darunavir and cobicistat taken concomitantly. Cobicistat is not listed on the PBS.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with darunavir/cobicistat including improvement in adherence, some savings on co-payment and possibility of fewer side-effects compared to ritonavir boosted darunavir.

Clinical trials

6.3 The submission presented evidence from two pharmacokinetic studies in healthy volunteers, where darunavir/cobicistat FDC was compared to darunavir and ritonavir (Study 1001), and to its components taken concomitantly (Study 1003).

6.4 The submission also presented a naïve indirect comparison of one non-randomised study with darunavir and cobicistat (Study 0130), to single arms of four randomised trials with darunavir and ritonavir (ARTEMIS; ODIN; FLAMINGO and 2LADY).

6.5 The submission used the pharmacokinetics evidence for darunavir/cobicistat FDC as a link to the clinical evidence provided on efficacy and safety on darunavir and cobicistat versus darunavir and ritonavir, the main comparator. Table 1 summarises the evidence provided in the submission.

Table 1: Evidence provided in the submission

Studies	Proposed drug	Common reference [a]	Main comparator	Other arms	Population
Pharmacokinetics evidence					
Study 1001	DRV/c FDC	—	DRV + r	—	Healthy volunteers
Study 1003	DRV/c FDC	DRV + c	—	—	
Efficacy and Safety evidence					HIV patients
Study 0130	—	DRV + c [b]	—	—	Naïve/experienced
ARTEMIS	—	—	DRV + r + TDF + FTC	LPV/r FDC + TDF + FTC	Tx-naïve
ODIN	—	—	DRV + r + ≥ 2 NRTIs [c]	DRV (600 mg) + r + NRTIs	Tx-experienced
FLAMINGO	—	—	DRV + r + 2 NRTIs [d]	DTG + 2 NRTIs	Tx-naïve
2LADY	—	—	DRV + r + TDF + FTC	LPV/r FDC + TDF + FTC	Tx-experienced

Source: *compiled during the evaluation*

FDC = fixed-dose combination; HIV = human immunodeficiency virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; ABC = abacavir; c = cobicistat; DRV = darunavir; DTG = dolutegravir; FTC = emtricitabine; LPV = lopinavir; r = ritonavir; TDF = tenofovir disoproxil fumarate; Tx = treatment; 3TC = lamivudine

[a] The common reference was also the supportive comparator

[b] Plus 2 NRTIs

[c] Emtricitabine and tenofovir disoproxil fumarate took up nearly all NRTI usage

[d] 66.9% was TDF + FTC and 33.1% was ABC/3TC

6.6 Details of the studies presented in the submission are provided in Table 2 below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Pharmacokinetics evidence		
Study 1001	A Phase I open-label, randomised, 3-way crossover study in healthy individuals to evaluate under fed and steady-state conditions the pharmacokinetics and relative bioavailability of two fixed dose formulations (G003 and G004) of darunavir/cobicistat 800/150 mg versus darunavir/ritonavir 800/100 mg coadministered as single agents.	CSR, 22 Feb 2012
	Kakuda TN, Opsomer M, Timmers M, *et al* (2014). Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers.	*J Clin Pharmacol,* 54:949-57.
Study 1003	Single-dose, open-label, 3-panel, randomised, pivotal crossover study to assess the bioequivalence of darunavir 800 mg when administered with cobicistat 150 mg as either a fixed dose combination tablet or as single agents under fed and fasted conditions in healthy individuals.	CSR, 25 Jan 2013
	Kakuda TN, Van De Casteele T, Petrovic R, *et al* (2014). Bioequivalence of a darunavir/cobicistat fixed-dose combination tablet versus single agents and food effect in healthy volunteers.	*Antivir Ther*, 19:597-606.
Efficacy and safety evidence		
Darunavir + cobicistat		
Study 0130	A phase 3b, open-label, single arm study to evaluate the safety and efficacy of cobicistat-boosted darunavir plus two fully active nucleoside reverse transcriptase inhibitors in HIV-1 infected, antiretroviral treatment-naïve and -experienced adults with no darunavir resistance associated mutations.	CSR, 26 Nov 2012 (Week 24)
	Tashima K, Crofoot G, Tomaka FL, *et al* (2014). Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a phase IIIb, open-label single-arm trial.	*AIDS Res Ther*, 11: 1-27
Darunavir + ritonavir		
ARTEMIS	A randomised, controlled open-label, active-controlled trial to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected patients.	CSR, 15 Oct 2007 (Week 48) primary analysis
	Ortiz R, DeJesus E, Khanlou H, *et al* (2008). Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected patients at week 48.	*AIDS,* 22(12):1389-97.
ODIN	A randomised, open-label, non-inferiority trial to compare the efficacy, safety and tolerability of darunavir/ritonavir 800/100 mg q.d versus darunavir/ritonavir 600/100 mg bid in early treatment experienced HIV-1 infected patients.	CSR, 23 Dec 2009 (Week 48) primary analysis
	Cahn P, Fourie J, Grinsztejn B, *et al* (2011). Week 48 analysis of once-daily vs twice-daily darunavir/ritonavir in treatment-experienced HIV-1 infected patients.	*AIDS,* 25:929-39.
FLAMINGO	Clotet B, Feinberg J, Lunzen JA, *et al* (2014). Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study.	*Lancet*, 383:2222-31.

Trial ID	Protocol title/ Publication title	Publication citation
2LADY	Koulla-Shiro S, Ciaffi L, Ndour CT, *et al* (2014). Randomised comparison of three second line ART regimens in Africa: the 2LADY study.	Poster 5411-B Conference on Retroviruses and Opportunistic Infections (CROI).

Source: Table B.7, pp8-10 of Section B of the submission
ART = antiretroviral therapy; CSR = clinical study report; HIV = human immunodeficiency virus

6.7 The key features of the pharmacokinetics evidence and the clinical evidence used for efficacy and safety are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient pop	Key outcomes
Pharmacokinetics evidence for darunavir/cobicistat FDC					
Study 1001	36	R, CO, OL, 10 days	Low	HIV –ve.	PK measurements
Study 1003	40	R, CO, OL, 5 days	Low	HIV –ve.	PK measurements
Efficacy and safety studies for darunavir and cobicistat comparison with darunavir and ritonavir					
Study 0130	313 [a]	R, OL, 48 weeks [b]	High	Tx naïve + exp	VR , VF, Δ CD4 cell count
ARTEMIS	343	R, OL, 48 weeks	High	Tx naïve	VR [c], VF, Δ CD4 cell count
ODIN	294	R, OL, 48 weeks	High	Tx exp	VR [c], VF, Δ CD4 cell count
FLAMINGO	242	R, OL, 48 weeks	High	Tx naïve	VR [c], VF, Δ CD4 cell count
2LADY	154	R, OL, 48 weeks	High	Tx exp	VR [c], VF, Δ CD4 cell count

Source: *compiled during the evaluation*
CD4 = cluster of differentiation 4; CO = crossover; HIV = human immunodeficiency virus; PK = pharmacokinetics; OL = open-label; R = randomised; VF = virologic failure; VR = virologic response; exp = experienced; Tx = treatment; -ve. = negative; Δ = change; pop = population; FDC = fixed-dose combination
[a] Of 313 total patients, 18 were treatment experienced
[b] *The primary outcome, treatment emergent grade 3 or 4 adverse events was performed over 24 weeks*
[c] Primary outcome

Comparative effectiveness

6.8 Study 1001 compared the pharmacokinetic profile of darunavir/cobicistat FDC with darunavir and ritonavir. The two formulations resulted in a similar bioavailability of darunavir (the active component), because the 90% confidence interval (CI) for the least squares means ratio for the key pharmacokinetics parameters fell within the pre-defined criterion of 80% to 125%. Using the same critical values, bioequivalence was also established for darunavir/cobicistat FDC and darunavir and cobicistat taken concomitantly (Study 1003).

6.9 The clinically relevant outcome for benefits was the proportion of patients with virologic response (HIV RNA < 50 copies/mL) at Week 48. Except for Study 0130, this outcome was measured as the primary outcome. The submission stated that virologic response is a surrogate outcome for final HIV outcomes.

6.10 Virologic response at Week 48 was assessed using two statistical methods, the FDA snapshot analysis (Study 0130, FLAMINGO and 2LADY) and the FDA time to loss of virologic response algorithm (ARTEMIS and ODIN). The submission noted that based on the FDA snapshot analysis, the PBAC has previously recommended elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate FDC (March 2013, Public Summary).

6.11 The submission presented a qualitative comparison of the virologic response point estimates (Table 4) and 95% CIs. Due to the lack of a common comparator, the submission appropriately did not attempt to provide a quantitative assessment of the comparative benefits for darunavir/cobicistat FDC and darunavir and ritonavir taken concomitantly.

Table 4: Results of virologic response (viral load < 50 copies/mL) at week 48 (mITT population)

Trial ID	FDA snapshot		FDA TLOVR algorithm	
	DRV + c + 2 NRTIs [a]	DRV + r + 2 NRTIs [a]	DRV + c + 2 NRTIs [a]	DRV + r + 2 NRTIs [a]
All patients; n/N (%)				
Study 0130	253/313 (80.8%)	—	[redacted]	—
Pooled	—	[redacted] [b]	—	[redacted] [c]
Treatment experienced; n/N (%)				
Study 0130	[redacted]	—	8/18 (44.4%)	—
ODIN	—	[redacted]	—	212/294 (72.1%)
2LADY	—	97/154 (63.0%)	—	—
Pooled	—	[redacted]	—	—
Treatment naïve; n/N (%)				
Study 0130	244/295 (82.7%)	—	245/295 (83.1%)	—
ARTEMIS	—	[redacted]	—	287/343 (83.7%)
FLAMINGO	—	200/242 (82.6%)	—	—
Pooled	—	[redacted]	—	—

Source: Table B.25, p54 of Section B of the submission

FDA = Food and Drug Administration; mITT = modified intention-to-treat; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; TLOVR = time to loss of virologic response; c = cobicistat; DRV = darunavir; r = ritonavir

[a] Emtricitabine and tenofovir disoproxil fumarate took up nearly all NRTI usage

[b] Pooled trials: ARTEMIS, FLAMINGO, ODIN and 2LADY

[c] Pooled trials: ARTEMIS, ODIN

6.12 Based on the FDA snapshot analysis, the submission stated that virologic response for darunavir and cobicistat taken concomitantly was similar to darunavir and ritonavir taken concomitantly for the pooled analysis and the treatment-naïve population. The submission's pooled analysis of all patients was potentially biased due to the heterogeneity in treatment experience across the two groups. To provide a more appropriate comparison, separate pooled analyses were performed for both treatment naïve and treatment experienced. This showed that virologic response was likely to depend on treatment experience.

6.13 The submission noted that for treatment-experienced patients, the virologic response was lower compared to the virologic response in treatment-naïve patients. Further, the response for darunavir and cobicistat in treatment experienced patients was numerically lower than for darunavir and ritonavir. According to the submission, this difference was due to worse prognostic factors, as well due to small sample size. This analysis was difficult to interpret, as only 18 treatment-experienced patients were included in Study 0130.

6.14 Due to likely small sample bias and heterogeneity of key patient characteristics in the PBS relevant, treatment-experienced population, the submission used the evidence from a mixed population of treatment-naïve and treatment-experienced patients. This might not be appropriate. The efficacy data was difficult to interpret due the heterogeneity between the studies and the naïve indirect comparison.

Comparative harms

6.15 Results of the key safety outcomes are presented in Table 5.

Table 5: Summary of key adverse events of the safety studies over 48 weeks (mITT analysis set)

Number of patients with: n (%)	DRV + c + 2 NRTIs [a]	DRV + r + 2 NRTIs [a]			
		Treatment naive		Treatment experienced	
	Study 0130-All	ARTEMIS	FLAMINGO	ODIN	2LADY
	(n=313)	(n=343)	(n=242)	(n=294)	(n=154)
Any AE	286 (91.4%)	309 (90.1%)	205 (84.7%)	224 (76.2%)	NR
Treatment related AE [b]	128 (40.9%)	172 (50.1%)	NR	90 (30.6%)	NR
Grade 3-4	24 (7.7%)	64 (18.7%)	NR	23 (7.8%)	NR
SAE (any)	26 (8.3%)	25 (7.3%)	13 (5.4%)	16 (5.4%)	19 (12.3%)
Death (TE)	0	1 (0.3%)	0	2 (0.7%)	3 (1.9%)
AE; discontinued	16 (5.1%)	17 (5.0%)	10 (4%)	10 (3.4%)	NR
AIDS defining illness	NR	10 (2.9%)	NR	NR	30 (19.5%)

Source: Table B.27, p58 of Section B of the submission

AE = adverse event; AIDS = acquired immune deficiency syndrome; mITT = modified intention-to-treat; NR = not reported; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; SAE = serious adverse event; TE = treatment emergent; c = cobicistat; DRV = darunavir; r = ritonavir

[a] Emtricitabine and tenofovir disoproxil fumarate took up nearly all NRTI usage

[b] Related = possibly, probably or very likely related to study drug

6.16 Overall, the submission stated that darunavir and cobicistat taken concomitantly and darunavir and ritonavir taken concomitantly were similarly well tolerated, with the number of adverse events well balanced. The safety data was difficult to interpret, due to the lack of comparability between the studies and the naïve indirect comparison.

Clinical claim

Comparator: darunavir and cobicistat taken concomitantly

6.17 For the pharmacokinetic evidence, darunavir/cobicistat FDC was bioequivalent to darunavir and cobicistat taken concomitantly, and therefore supports non-inferiority of efficacy and safety of darunavir/cobicistat FDC and its individual components. This claim appeared reasonable.

Comparator: darunavir and ritonavir taken concomitantly

6.18 For the pharmacokinetic evidence, darunavir/cobicistat FDC resulted in similar bioavailability of darunavir (active component) compared with darunavir and ritonavir taken concomitantly. This claim appeared reasonable.

6.19 For the clinical evidence of efficacy and safety, the submission concluded non-inferiority of darunavir and cobicistat taken concomitantly to darunavir and ritonavir taken concomitantly. For this claim, there were certain issues for the PBAC consideration:

- The clinical evidence for efficacy and safety consisted of a naïve indirect comparison of a non-randomised study (Study 0130) with darunavir and cobicistat taken concomitantly, to single arms of four randomised trials that used darunavir and ritonavir. There was significant heterogeneity across study design and patient characteristics which limited this qualitative comparison;
- This clinical evidence used predominantly treatment-naïve patients, which was not relevant to the proposed PBS restriction for treatment-experienced patients. Notably, only 18/313 (5.8%) of the patients in Study 0130 were treatment experienced, limiting the applicability of this study to the proposed PBS restriction; and
- The submission considered that the data from treatment-naïve patients could be extrapolated to treatment-experienced patients. The submission cited the PBAC decision that considered the comparative effectiveness and safety in treatment-naïve patients may be reasonably extrapolated to a treatment-experienced population (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate FDC, March 2013 Public Summary Document). However, the PBS listed restriction for elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate FDC is for both treatment naïve and treatment-experienced patients, while the requested listing for darunavir/ritonavir FDC is for treatment-experienced patients only. The ESC considered that notwithstanding the limited clinical data for treatment experienced patients and the limitations of the naïve indirect comparison, the similar efficacy of darunavir/cobicistat to darunavir/ritonavir in treatment naïve patients together with the demonstrated similar bioavailability of darunavir gave confidence that the efficacy in treatment experienced patients would be similar.

6.20 Based from the pharmacokinetic evidence presented above, the PBAC considered that the claim of non-inferior comparative effectiveness and safety against darunavir and cobicistat taken concomitantly was reasonable.

6.21 Based from the pharmacokinetic evidence presented above, the PBAC considered that the claim of non-inferior comparative effectiveness and safety against darunavir and ritonavir taken concomitantly was reasonable.

Economic analysis

6.22 The submission presented a cost-minimisation analysis of darunavir/cobicistat FDC versus darunavir and ritonavir taken concomitantly. This was in line with the clinical evidence of non-inferior efficacy and safety for treatment-naïve patients presented. However, the submission did not resolve the main applicability issue of extending clinical evidence from treatment-naïve to treatment-experienced patients.

6.23 The equi-effective doses were estimated as:
- darunavir 800 mg (with cobicistat 150 mg in the FDC) once daily is equivalent to darunavir 800 mg (with ritonavir 100 mg taken concomitantly) once daily; and
- cobicistat 150 mg (in the FDC) once daily is equivalent to ritonavir 100 mg (with darunavir 800 mg) once daily.

6.24 The equi-effective doses were based on the bioavailability study which compared the pharmacokinetics of darunavir/cobicistat FDC to darunavir and ritonavir taken concomitantly.

6.25 The cost-minimisation analysis (Table 6) was based on the assumption that all costs would be related to the cost of HIV drugs only. This was reasonable.

Table 6: Cost-minimisation analysis for darunavir/cobicistat FDC (priced for 60 days of treatment)

-	Item		Method	DRV 800 mg	r 100 mg
-	PBS item code		—	10367P	10273Q
A	Approved ex-manufacturer price (AEMP)		PBS Schedule	$699.14	$[redacted]
B	Pack size		PBS Schedule	30	30
C	AEMP price per day		A/B	$23.20	$[redacted]
Darunavir/cobicistat FDC					
D	AEMP price per day		Sum C (DRV + r)	$[redacted]	
E	AEMP		D * 30	$[redacted]	
F	Maximum quantity; packs		—	2	
G	HSD mark-up (Private)		PBS Schedule	$40 [a]	
H	Dispensing fee		PBS Schedule	$6.93 [b]	
I	Public hospital for DPMQ	Per unit	E * F	$[redacted]	
J	Private hospital/Community Access for DPMQ	Per unit	I + (G + H)	$[redacted]	

Source: Table D.1, p3 of Section D of the submission

DPMQ = dispensed price for maximum quantity; FDC = fixed-dose combination; HSD = highly specialised drug; PBS = Pharmaceutical Benefits Scheme; DRV = darunavir; r = ritonavir

[a] For drugs with AEMP > $1,000.00

[b] As of 1 July 2015, the ready-prepared dispensing fee is $6.93

Drug cost/patient/year: $[redacted].

6.26 Darunavir/cobicistat FDC is an ongoing treatment. The annual drug cost was calculated for the Community Access dispensed price for the maximum quantity ($[redacted]) assuming 6.1 prescriptions (i.e. 12.2 packs) per year. The annual cost for the comparator was also $[redacted] based on the dispensed price for maximum quantity of darunavir ($[redacted]) and ritonavir ($[redacted]), and assuming the same use.

Estimated PBS usage & financial implications

6.27 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and cost of darunavir/cobicistat FDC over a five year time horizon (Table 7). For the base case, the submission assumed that darunavir/cobicistat FDC would only replace darunavir and ritonavir taken concomitantly.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total DRV 800 mg scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS/MBS	**$** [redacted]	**$** [redacted]	**$** [redacted]	**$** [redacted]	**$** [redacted]

Source: Section E Excel spreadsheet to the submission
DRV = darunavir; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Assuming 6.1 scripts per year as estimated by the submission

6.28 At year 5, the estimated number of scripts was [redacted] and the net cost to the PBS would be $[redacted] *less than $10 million*. At year 1, the estimated number of scripts was [redacted] and the net cost to the PBS would be $[redacted] less than $10 million.

6.29 Overall the submission concluded that there was minimal financial impact of the PBS listing of darunavir/cobicistat FDC to the Commonwealth Government Health Budget. The small increase would be due to a reduction in co-payments for ritonavir, i.e. darunavir/cobicistat FDC would attract one co-payment, compared to two co-payments when darunavir and ritonavir is taken concomitantly. This appeared reasonable.

6.30 The ESC noted that in the context of the most recent US Department of Health and Human Services HIV treatment guidelines there was a risk of leakage to first-line treatment in naïve patients, this would mostly involve ritonavir (or cobicistat) boosted atazanavir being replaced by darunavir/cobicistat or darunavir/ritonavir in those for whom PI-based therapy is preferred. Replacement of atazanavir (with cobicistat or ritonavir) would have a financial impact as atazanavir is cheaper than darunavir.

Quality Use of Medicines

6.31 The submission outlined the importance of the patients, nurses, prescribers and dispensers in assuring the appropriate use of darunavir/cobicistat FDC. The submission stated that these groups would be provided with education, resources and support from the sponsor in the appropriate use of darunavir/cobicistat FDC.

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

7 PBAC Outcome

7.1 The PBAC rejected the request to list darunavir/cobicistat fixed-dose combination (FDC) tablets for the treatment of human immunodeficiency virus (HIV) on the basis that the submission incorrectly proposed treatment in treatment-experienced patients while the evidence presented for clinical efficacy and safety also supported use in treatment naïve patients. The PBAC noted that the submission's proposed listing was not consistent with the current 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 (August 2015), which lists darunavir/ritonavir (with tenofovir disoproxil fumarate/emtricitabine) as a recommended regimen and darunavir/cobicistat (with tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudine) as an alternative option in first line therapy for treatment naïve patients.

7.2 The PBAC noted the submission requested a listing under the Section 100 (Highly Specialised Drugs Program) for Private and Public Hospitals. The PBAC considered that the new HSD Community Access arrangements (commenced 1 July 2015) would be the appropriate listing arrangement for darunavir/cobicistat.

7.3 The PBAC accepted the two nominated comparators, darunavir and ritonavir, taken concomitantly and darunavir and cobicistat, taken concomitantly.

7.4 The PBAC noted the pharmacokinetic studies presented in the submission reported similar bioavailability of darunavir/cobicistat FDC and darunavir and ritonavir (Study 1001) and darunavir/cobicistat FDC and darunavir and cobicistat taken concomitantly (Study 1003).

7.5 The PBAC also noted the results of a naïve indirect comparison of a non-randomised study (Study 0130) with darunavir and cobicistat taken concomitantly, to single arms of four randomised trials (FLAMINGO, 2LADY, ARTEMIS and ODIN) that included darunavir and ritonavir. The PBAC agreed with the evaluation that there was significant heterogeneity across study design and patient characteristics which limited the qualitative comparison.

7.6 The PBAC acknowledged that the TGA has accepted the bioequivalence of darunavir/cobicistat FDC to darunavir and ritonavir taken concomitantly (Study 1001) and also to darunavir and cobicistat taken concomitantly (Study 1003). Based on the evidence presented, the PBAC agreed there appears to be no difference in benefits and harms between darunavir/cobicistat FDC and darunavir plus cobicistat or ritonavir.

7.7 The PBAC agreed with ESC that darunavir/cobicistat could be used in place of other protease inhibitors (PI) such as lopinavir/ritonavir FDC and atazanavir plus ritonavir (or cobicistat) taken concomitantly in those whom PI-based therapy is preferred and that this could potentially increase the estimated net cost. The sponsor's Pre-PBAC Response maintained that it is unlikely to happen, as use in treatment naïve patients is minimal in Australian clinical practice and that there is a clinical preference to use darunavir in patients who have previously failed an antiretroviral therapy regimen or patients who prefer a single tablet regimen.

7.8 The PBAC considered that a minor resubmission would be required to request further consideration of recommending listing of darunavir/cobicistat in the treatment of HIV-1 infection. The PBAC further considered that the resubmission should nominate a listing for darunavir/cobicistat which reflects the status of darunavir as the preferred protease inhibitor for use in treatment naïve patients in the most recent US Department of Health and Human Services Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (August 2015), providing a comparison between darunavir/cobicistat FDC and alternative FDCs in the first line setting

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

Outcome:
Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.