

**5.05 DARUNAVIR with COBICISTAT with EMTRICITABINE and TENOFOVIR ALAFENAMIDE,
Tablet containing darunavir 800 mg with cobicistat 150 mg with emtricitabine 200 mg and tenofovir alafenamide 10 mg,
Symtuza[®],
Janssen-Cilag Pty Ltd**

For improved readability, tradenames for fixed dose combination (FDC) therapies and other combination therapies for the treatment of human immunodeficiency virus (HIV) are used in Public Summary Document (PSD). In some cases, generic names may be used for clarity.

Table 1 presents a summary of the FDCs, indicating their components, abbreviations for each drug and their associated tradenames.

Table 1: Summary of fixed dose combinations (their components, abbreviations for each drug and their associated tradenames)

Fixed dose combination (FDC) or other combination components	Abbreviations	Tradename
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide	DRV/c/FTC/TAF	Symtuza [®]
Darunavir/cobicistat	DRV/c	Prezcobix [®]
Darunavir + ritonavir	DRV+r	Prezista [®] + Norvir [®]
Emtricitabine/tenofovir disoproxil fumarate	FTC/TDF	Truvada [®]
Emtricitabine/tenofovir alafenamide	FTC/TAF	Descovy [®]
Atazanavir/cobicistat	ATV/c	Evotaz [®]
Atazanavir + ritonavir	ATV+r	Reyataz [®] +Norvir [®]
Lopinavir/ritonavir	LPV/r	Kaletra [®]
Abacavir/lamivudine	ABC/3TC	Kivexa [®]
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	EVG/c/FTC/TAF	Genvoya [®]
Rilpivirine/emtricitabine/tenofovir alafenamide	RPV/FTC/TAF	Odefsey [®]
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	EVG/c/FTC/TDF	Stribild [®]
Efavirenz/emtricitabine/tenofovir disoproxil fumarate	EFV/FTC/TDF	Atripla [®]
Dolutegravir/rilpivirine	DTG/RPV	Juluca [®]
Bictegravir/emtricitabine/tenofovir alafenamide	BFTAF	Biktarvy [®]

The term tenofovir includes both tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF).

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs Program – Community Access), Authority Required (STREAMLINED) listing for darunavir/cobicistat/emtricitabine/ tenofovir alafenamide (DRV/c/FTC/TAF; Symtuza) for the treatment of HIV. This FDC has not previously been considered by the PBAC.

1.2 The requested basis for listing is a cost-minimisation of a weighted average cost of four boosted darunavir and FTC/tenofovir regimens.

Table 2: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults and adolescents ≥ 40 kg with HIV infection
Intervention	Fixed-dose combination (FDC) tablet of darunavir 800mg + cobicistat 150mg + emtricitabine 200mg + tenofovir alafenamide 10mg (Symtuza) taken orally once daily
Comparator	Concomitant administration of cobicistat or ritonavir boosted darunavir (Prezcobix® [DRV/c] or Prezista® + Norvir® [DRV+r]) with emtricitabine/tenofovir alafenamide (FTC/TAF; Descovy®) or emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada®)
Outcomes	Virological suppression (patients with plasma HIV RNA < 50 copies per mL using the FDA snapshot algorithm); change from baseline in CD4+ cell count; proportion of patients with virologic rebound defined as: HIV-1 RNA ≥ 50 copies/mL
Clinical claim	The DRV/c/FTC/TAF FDC is non-inferior in efficacy and safety to concomitant administration of boosted darunavir (DRV/c or DRV+r) co-administered with FTC/tenofovir (TAF or TDF) regimens

Source: Table 1.1, p13 of the submission.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DARUNAVIR WITH COBICISTAT WITH TENOFOVIR ALAFENAMIDE AND EMTRICITABINE Darunavir 800 mg + cobicistat 150 mg + tenofovir alafenamide 10 mg + emtricitabine 200 mg tablet, 30	2	5	\$ [REDACTED]	Symtuza, Janssen-Cilag Pty Ltd

Category/Program	Schedule 100 HSD Community Access
Prescriber type	Medical practitioners
Condition:	Human immunodeficiency virus (HIV) infection
PBS Indication:	Human immunodeficiency virus (HIV) infection
Treatment phase:	Initial treatment
Restriction:	<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"/> Authority Required (Streamlined)
Clinical criteria:	Patient must be antiretroviral treatment naïve AND The treatment must not be in combination with ritonavir.
Note	The cobicistat component of darunavir + cobicistat combination product provides the necessary pharmacokinetic enhancement of darunavir to achieve therapeutic levels of darunavir

Treatment phase:	Continuing treatment
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Public Summary Document – November 2019 PBAC Meeting

Restriction:	<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"/> Authority Required (Streamlined)
Clinical criteria:	Patient must have previously received PBS-listed therapy for HIV infection, AND The treatment must not be in combination with ritonavir
Note:	The cobicistat component of darunavir + cobicistat combination product provides the necessary pharmacokinetic enhancement of darunavir to achieve therapeutic levels of darunavir

Category/Program	Section 100 – Highly Specialised Drugs Program {Community Access}
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
Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Continuing treatment
Restriction Level/ Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection AND The treatment must not be in combination with ritonavir AND Patient must have experienced virological failure or clinical failure or genotypic resistance after at least one antiretroviral regimen
Prescriber Instructions:	<i>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.</i>
Administrative Advice:	The cobicistat component of the darunavir + cobicistat combination product provides the necessary pharmacokinetic enhancement of darunavir to achieve therapeutic levels of darunavir.

2.2 The submission requested a restriction for (i) initial therapy for treatment-naïve patients; (ii) continuing therapy with Symtuza or from an alternative HIV regimen for a non-virologic or clinical failure reason; and (iii) continuing therapy for treatment-experienced patients who experienced virologic or clinical failure after at least one antiretroviral regimen. Although the three proposed restrictions for Symtuza are consistent with those for darunavir/cobicistat (DRV/c; Prezcoibix), it is noted that Descovy and Truvada both have only one initial and one continuing restriction. It is not clear whether the continuing restriction for treatment-experienced patients is superfluous.

2.3 The restriction is consistent with the proposed TGA indication, the trial evidence and the cost-minimisation analysis. It is, however, unlikely that substantial numbers of treatment naïve patients in Australia will access Symtuza due to the recommendation not to initiate treatment with protease inhibitors (PI) in the US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.

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

3 Background

Registration status

- 3.1 TGA status at time of PBAC Consideration: At the time of PBAC advice, the Delegate's Overview was available. The TGA Delegate considered that Symtuza, 'has a robust and sustained virological and immunological profile, similar to that of established boosted PI triple-drug ART' and the safety profile, 'is entirely consistent with the known safety profile of the component drugs'. The Delegate supported registration of Symtuza.

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

4 Population and disease

- 4.1 HIV infection is characterised by a decline in the number of CD4+ T-cells which results in damage to, and deterioration of, immune function. The loss of immune function and regulation increases the risk of opportunistic infections and malignancies (known as Acquired Immune Deficiency Syndrome (AIDS)-defining illnesses), which result in reduced quality of life and death.
- 4.2 Without anti-retroviral therapy (ART), the CD4+ T cell counts in HIV infected patients will continue to decline and eventually result in AIDS-defining illnesses (e.g. malignancies including Kaposi's Sarcoma, various pneumonias, tuberculosis and other infections from opportunistic pathogens) and premature death.
- 4.3 The submission claimed Symtuza will provide patients with a complete darunavir 800 mg containing regimen in a single oral once daily tablet and is suitable for patients already maintained or otherwise appropriate for treatment with cobicistat or ritonavir boosted darunavir (Prezcobix [DRV/c] or Prezista + Norvir [DRV+r]) co administered with FTC/tenofovir.

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

5 Comparator

- 5.1 The submission nominated the following comparators:
- DRV/c (Prezcobix) + FTC/TAF (Descovy);
 - DRV + r (Prezista + Norvir) + FTC/TAF (Descovy);
 - DRV/c (Prezcobix) + FTC/TDF (Truvada); and
 - DRV + r (Prezista + Norvir) + FTC/TDF (Truvada).
- 5.2 The submission justified these treatments as main comparators because they are most likely to be replaced by the PBS listing of Symtuza.

- 5.3 The proposed main comparator includes replacement of the individual components of the Symtuza FDC taken concomitantly (i.e. cobicistat- or ritonavir- boosted darunavir and FTC/tenofovir).
- 5.4 The nominated comparators were appropriate but were not necessarily the only relevant comparators. For the requested population, the following PBS-listed medicines are less costly than Symtuza and are alternative therapies because they could be replaced in practice: (i) Evotaz (atazanavir/cobicistat) + FTC/tenofovir and (ii) Reyataz (atazanavir) + Norvir (ritonavir) + FTC/tenofovir. If treatment with Symtuza is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of Symtuza if it is satisfied that Symtuza provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)). The alternative therapies in this case may include Evotaz + FTC/tenofovir and Reyataz + Norvir + FTC/tenofovir.
- 5.5 The Economics Sub-Committee (ESC) considered it was possible regimens containing other PIs, including atazanavir (ATV), could be replaced and may represent relevant and less costly alternative therapies. The Pre-PBAC Response argued regimens containing other PIs, including ATV, were not relevant comparators because:
- Older PIs including lopinavir, fosamprenavir, saquinavir, indinavir, nelfinavir and tipranavir are used infrequently and few, if any, new patients commence treatment on them, therefore DRV would not replace these in practice;
 - The toxicity profile of ATV has led to a change in US and Australian treatment guidelines to indicate boosted DRV as being generally preferred to ATV. Therefore, while the use of ATV is more common in practice compared with older PIs, it is not a relevant comparator. The Pre-PBAC Response included supplementary evidence of a Phase III randomised study (Lennox *et al* 2014¹) and argued that DRV-based regimens provide a significant reduction in toxicity compare with ATV-based regimens. This supplementary study was not evaluated.

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.

¹ Lennox, J. L., Landovitz, R. J., *et al* (ACTG A5257 Team) (2014). Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Annals of internal medicine*, 161(7), 461–471. doi:10.7326/M14-1084

Consumer comments

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

Clinical trials

6.3 The submission is based on the following key evidence:

- EMERALD (n=1,141): A phase 3 randomised trial in treatment-experienced, virologically suppressed patients, which compared a switch to Symtuza versus the maintenance of the patient’s current anti-retroviral (CAR); this comprised a boosted PI (mostly darunavir) co-administered with FTC/tenofovir disoproxil fumarate (FTC/TDF; Truvada). The submission considered that as the majority of patients who will use PBS-reimbursed Symtuza will be treatment experienced and already maintained on boosted darunavir 800 mg co-administered with FTC/tenofovir, EMERALD is the most relevant trial.
- AMBER (n=725): a phase 3 randomised trial comparing Symtuza to cobicistat boosted darunavir co-administered with FTC/TDF (Prezcobix + Truvada) in treatment-naïve patients.
- Mills 2015 (n=725): a phase 2 randomised trial comparing Symtuza to Prezcobix + Truvada in treatment-naïve patients.
- Bioequivalence study comparing the pharmacokinetics of Symtuza to concomitant administration of its components.

6.4 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EMERALD	A Phase 3, randomised, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects	CSR 1 September 2017
	Orkin C et al., Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial.	Lancet HIV. 2018;5(1):e23-e34
	Eron JJ, Orkin C, Cunningham D, Pulido F, Post F, De Wit S, Lathouwers E, Hufkens V, Petrovic R, Van Landuyt E. Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment experienced, virologically-suppressed, HIV-1-infected adults.	ID Week 2018, San Francisco, CA – October 3-7, 2018. Abstract #1768.

Public Summary Document – November 2019 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
	Molina JM Gallant J, Orkin C, Negredo E, Bhatti L, Gathe J, Van Landuyt E, Lathouwers E, Hufkens V, Vanveggel S, Opsomer M. Efficacy and safety of switching from boosted-protease inhibitor plus emtricitabine/tenofovir disoproxil fumarate regimens to the single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in virologically suppressed, HIV-1-infected adults through 24 weeks: EMERALD study. Presented at 9th IAS Conference on HIV Science 2017. Abstract #: TUAB0101.	9th IAS Conference on HIV Science 2017. Abstract #: TUAB0101
	Orkin C, Eron J, Rockstroh J, Podzamczar D, Esser S, Vandekerckhove L, Van Landuyt E, Lathouwers E, Hufkens V, Jezowski J, Opsomer M. Efficacy and safety of the once-daily, darunavir/cobicistat/ emtricitabine/tenofovir alafenamide (D/C/F/TAF) single tablet regimen (STR) in ART-naive, HIV-1-infected adults: AMBER Week 96 results.	Journal of the International AIDS Society. Conference: 2018 International Congress on Drug Therapy in HIV Infection, HIV Glasgow 2018. United Kingdom. 21 (Supplement 8) (pp 8-10), 2018. Date of Publication: October 2018.
	Orkin C, Molina JM, Gallant J, Negredo E, Gathe J, Eron J, Van Landuyt E, Lathouwers E, Hufkens V, Petrovic V, Opsomer M. Week 48 results of EMERALD: A phase 3, randomized, non-inferiority study evaluating the efficacy and safety of switching from boosted-protease inhibitors (bPI) plus emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) regimens to the once daily (QD), single-tablet regimen (STR) of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in virologically-suppressed, HIV-1-infected adults.	IDWeek 2017. San Diego, October 4-8, 2017. Abstract #: 1689b.
	Orkin, C., Molina, J. M., Gallant, J., Negredo, E., Gathe, J., Eron, J., & Opsomer, M. (2017). Week 48 Results of EMERALD: A Phase 3, Randomized, Non-inferiority Study Evaluating the Efficacy and Safety of Switching from Boosted-protease Inhibitors (bPI) Plus Emtricitabine (FTC)/Tenofovir Disoproxil Fumarate (TDF) Regimens to the Once Daily (QD), Single-tablet Regimen (STR) of Darunavir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (D/C/F/TAF) in Virologically Suppressed, HIV-1-infected Adults.	Open forum infectious diseases (Vol. 4, No. suppl_1, pp. S737-S738). US: Oxford University Press.
	Eron, J.J., Orkin, C., Molina, J.-M., Van Landuyt, E., Lathouwers, E., Petrovic, R., Nettles, R.E., Brown, K. (2018) Analysis of HIV patients switching to D/C/F/TAF by prior ART treatment experience.	Topics in Antiviral Medicine. Conference: 25th Conference on Retroviruses and Opportunistic Infections, CROI 2018. United States. 26 (Supplement 1) (pp 208s-209s)
	Huhn G.D. De Jesus, E., Girard, P.-M., Petrovic, R., Wong, E.Y., Brown, K. (2018) HIV treatment experienced patients switched to D/C/F/TAF: Age, gender, race analyses. Topics in Antiviral Medicine.	25th Conference on Retroviruses and Opportunistic Infections, CROI 2018. United States. 26 (Supplement 1) (pp 207s), 2018
AMBER	A Phase 3, randomised, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects	CSR. 1 September 2017

Trial ID	Protocol title/ Publication title	Publication citation
	Eron JJ, Orkin C, Gallant J, Molina JM, Negredo E, Antinori A, Mills A, Reynes J, Van Landuyt E, Lathouwers E, Hufkens V, Jezorwski J, Vanveggel S, Opsomer M. A week-48 randomized phase-3 trial of darunavir/cobicistat/ emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients.	AIDS, 2018; 32(11):1431-1442.
	Orkin C, Eron JJ, Rockstroh J, et al. Efficacy and safety of the once-daily, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen (STR) in antiretroviral treatment (ART)-naïve, HIV-1-infected adults: AMBER Week 96 results.	HIV Glasgow 2018, Glasgow, October 28-31; abstract O212. Available at: https://vimeo.com/297973536
	Gallant J, Orkin C, Molina J.M, Negredo E, Antinori A, Mills A, Eron J, Reynes J, Van Landuyt E, Hufkens V, Jezorwski J, Opsomer M. Week 48 results of AMBER: a phase 3, randomised, double-blind trial in antiretroviral treatment (ART)-naïve HIV-1-infected adults to evaluate the efficacy and safety of the once-daily, single-tablet regimen (STR) of darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide (D/C/F/TAF) versus darunavir/cobicistat (DRV/c) plus emtricitabine/ tenofovir disoproxil fumarate (FTC/TDF).	The European AIDS Clinical Society Conference 2017. Milan, October 25-27, 2017; abstract PS8/2.
	Spinner CD, Rashbaum B, McDonald C, Mussini C, Luo D, Jezorwski J, Brown K, Wong EY. Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1 Treatment-naïve Patients: Week 48 Results in Subgroups Based on Baseline Viral Load, CD4+ Count, and WHO Clinical Staging.	IDWeek, San Francisco, October 3-7, 2018; poster 541
	Rashbaum, B., McDonald, C., Mussini, C., Spinner, C.D., Jezorwski, J., Wong, E.Y., Brown, K. (2018) Age, gender, and race analyses of D/C/F/TAF in HIV-1 treatment naïve patients.	Topics in Antiviral Medicine. Conference: 25th Conference on Retroviruses and Opportunistic Infections, CROI 2018. United States. 26 (Supplement 1) (pp 203s), 2018.
Mills 2015/ GS-US-299-0102	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naive Adults	CSR. November 2014
	Mills, A., Crofoot Jr, G., McDonald, C., Shalit, P., Flamm, J. A., Gathe Jr, J., & Martin, H. (2015). Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial hiv-1 therapy: a randomized phase 2 study.	JAIDS Journal of Acquired Immune Deficiency Syndromes, 69(4), 439-445.
Bioequivalence trial TMC114FD2HTX1001	A single-dose, open-label, randomized, crossover study to assess the bioequivalence of darunavir 800 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, in the presence of cobicistat 150 mg, administered as either a fixed-dose combination tablet or as separate agents in healthy subjects	CSR. June 2016

Source: Table 2.4, pp38-40 of the submission,

6.5 The key features of the direct randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Symtuza vs. CAR*					
EMERALD	1,141	R, OL, MC, 48 weeks	High	Treatment experienced	Virologic rebound
Symtuza vs. Prezcoibix + Truvada					
AMBER	725	R, DB, MC, 48 weeks	Low	Treatment naïve	Virologic response
MILLS 2015	725	R, DB, MC, 48 weeks	Low	Treatment naïve	Virologic response
Bio-equivalence Symtuza vs DRV + c + FTC + TAF					
TMC114FD2HTX1001	96	b/e, R, 2-way cross-over, SC, OL	NA	Healthy patients	Pharmacokinetics and Bioequivalence

Source: Table ES.3, p.iv of the executive summary of the submission and p1 of 'Phase 1 bioequivalence trial Summary.'

b/e = bioequivalence; CAR = current antiretroviral therapy; DB=double blind; MC=multi-centre; OL=open label; R=randomised.

* For EMERALD: CAR was comprised of a boosted protease inhibitor combined with FTC/TDF (Truvada); 70% of patients were treated with darunavir 800mg

6.6 The EMERALD trial was the only included trial that was consistent with the most likely population of Symtuza patients, treatment experienced patients. The submission specified that all patients in the EMERALD study had at least four prior ART classes (including the booster), but 41.8% of patients had never taken an ART prior to their screening ART regimen (boosted PI + FTC /tenofovir disoproxil fumarate). This seemed to indicate that for these patients, their regimen at screening was their first treatment. If 42% of patients had a less than 30 day treatment with any ART, it appears that they would probably not be reflective of the expected population of patients accessing Symtuza in Australia (i.e. predominantly treatment experienced patients). The Pre-Sub-Committee Response (PSCR) argued this would not impact conclusions of comparative efficacy and safety, which was supported by the TGA Delegate's assessment that the clinical data from the Phase 3 trials was consistent with the known efficacy and safety profile of similar PI based antiretroviral therapy.

6.7 The EMERALD trial was unblinded, and blinding was compromised in the Mills 2015 trial, increasing the potential risk of bias of these trials.

Comparative effectiveness

6.8 Table 5 presents a proportion of virologic rebound through Week 48 of EMERALD.

Table 5: Proportion of protocol-defined virologic rebound (HIV-1 RNA ≥50 Copies/mL) cumulative through Week 48

Population	Symtuza; n/N (%)	CAR; n/N (%)	Difference in Proportions (95% CI)	P value (non-inferiority)
Boosted DRV pop.	11/537 (2.0%)	6/266 (2.3%)	-0.2 (-3.0; 1.9)	<0.01
ITT	19/763 (2.5%)	8/378 (2.1%)	0.4 (-1.5; 2.2)	<0.001

Source: Table 2.24, p 81 of the submission.

bDRV = boosted darunavir; CAR = current antiretroviral; CI = confidence interval; HIV = human immunodeficiency virus; ITT = intention to treat analysis; RNA = ribonucleic acid

p-value based on the relative risk

6.9 The upper bounds of the difference in proportions were less than 4% in both populations presented and thus met the trial's non-inferiority margin.

6.10 Table 6 presents the result of virologic response using the US Food and Drug Authority (FDA) snapshot approach in the three trials.

Table 6: Proportion of Virologic response (<50 copies/mL) through Week 48 using FDA snapshot approach

Trial	Symtuza; n/N (%)	CAR; n/N (%)	Difference in Proportions (95% CI)	P value
Treatment experienced				
EMERALD (DRV patients)	518/537 (96.5)	252/266 (94.7)	1.7 (-1.2, 5.4)	NR
EMERALD (ITT)	724/763 (94.9)	354/378 (93.7)	1.2 (-1.7, 4.2)	NR
	Symtuza; n/N (%)	Prezcobix + Truvada n/N (%)	Difference in Proportions (95% CI)	P value
Treatment naïve				
AMBER	331/362 (91.4)	321/363 (88.4)	2.7 (-1.6, 7.1)	<0.001
Mills 2015	77/103 (74.8)	37/50 (74.0)	3.3 (-11.4, 0.155)	0.64
POOLED AMBER/Mills 2015	408/465 (87.7)	358/413 (86.7)	1.1 (-3.4, 5.5)	0.68

Source: Table 2-25 of the submission.

CAR = current anti-retroviral therapy; CI = confidence interval; DRV = darunavir; FDA = food and drug administration; ITT = intention to treat; NR = not reported

p-value based on the relative risk; Virologic response was not the primary outcome of the EMERALD trial but included here for consistency

6.11 The lower bounds of the 95% CI for the differences in proportions of virologic response were outside the pre-specified non-inferiority margin of -10% to -12% in the EMERALD and AMBER trials, thus the non-inferiority criteria were met. The lower bound of the 95% CI in Mills 2015 was -11.4% which did not meet the -10% non-inferiority criterion but, given the context, is likely due to the smaller sample size.

6.12 Change in CD4 count from baseline showed no statistically significant differences between arms in any of the trials.

Comparative harms

6.13 Overall, the AEs in the trials were similar between the Symtuza and comparator arms.

6.14 A significantly higher incidence of the following any grade treatment emergent adverse events (TEAEs) was observed for Symtuza compared with CAR and Prezcoibix + Truvada:

- diarrhoea (EMERALD: 7.9% vs 4.2%, RR= 1.86 [95% CI: 1.09, 3.18]), and
- headache (EMERALD: 7.6% vs 4.2%, RR=1.80 [95% CI: 1.05, 3.08]).

6.15 A significantly lower incidence of nausea (AMBER: 7.7% vs 12.4%, RR=0.62 [95% CI: 0.40, 0.98]) and vitamin D deficiency (Mills 2015, 1.9% vs 10%, RR=0.19 [95% CI: 0.04, 0.97]) was observed in the Symtuza arm.

6.16 Table 7 presents a summary of adverse events in the randomised trials. Though the trial evidence did indicate small statistical differences in some AEs, the evidence generally supported a claim of non-inferior safety.

Table 7: Summary of key adverse events in the randomised trials

Trial ID	Symtuza n/N (%)	CAR or Prezcobix + Truvada n/N (%)	RR (95% CI)	OR (95% CI)	RD (95% CI)
EMERALD					
Any adverse event	625 (81.9)	311 (82.3)	1.00 (0.94, 1.05)	0.98 (0.71, 1.35)	-0.00 (-0.05, 0.04)
Diarrhoea	60 (7.9)	16 (4.2)	1.86 (1.09, 3.18)	1.93 (1.10, 3.40)	0.04 (0.01, 0.06)
Headache	58 (7.6)	16 (4.2)	1.80 (1.05, 3.08)	1.86 (1.05, 3.28)	0.03 (0.01, 0.06)
AMBER					
Any adverse event	312 (86.2)	307 (84.6)	1.02 (0.96, 1.08)	1.14 (0.75, 1.72)	0.02 (-0.04, 0.07)
Nausea	28 (7.7)	45 (12.4)	0.62 (0.40, 0.98)	0.59 (0.36, 0.97)	-0.05 (-0.09, -0.00)
Mills 2015					
Any adverse event	95 (92.2)	47 (94.0)	0.98 (0.90, 1.07)	0.76 (0.19, 2.99)	-0.02 (-0.10, 0.07)
Vitamin D deficiency	2 (1.9)	5 (10.0)	0.19 (0.04, 0.97)	0.18 (0.03, 0.95)	-0.08 (-0.17, 0.01)
Arthralgia	9 (8.7)	0 (0)	9.32 (0.55, 156.9)	10.15 (0.58, 178.05)	0.09 (0.03, 0.15)

Source: Tables 2.31, and 2.32, p 96-101 of the submission.

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk
Bold statistical values denote statistically significant results.

6.17 The incidence of serious TEAEs was low and similar in the Symtuza and CAR arms in EMERALD: 4.6% v 4.8%, respectively (RR=0.96 [95% CI: 0.55, 1.68]); and between the Symtuza and Prezcoibix + Truvada arms in AMBER=4.7% v 5.8%, (RR: 0.81 [95% CI: 0.44, 1.51]). The incidence of Grade 3 or higher AEs were low and consistent across the treatment groups.

Clinical claim

6.18 The submission claimed that the efficacy of Symtuza is non-inferior to boosted darunavir co-administered with FTC/tenofovir (both TDF and TAF), as assessed by the clinically relevant outcomes of viral rebound, virologic response and change in CD4+ cell count. Additionally, Symtuza is bioequivalent to concomitant administration of its components, and therefore is non-inferior in efficacy and safety.

6.19 The submission stated Symtuza has a non-inferior safety profile compared with boosted darunavir co-administered with FTC/tenofovir (both TDF and TAF).

6.20 The ESC considered that the therapeutic conclusion presented in the submission was adequately supported by the evidence presented in the submission.

6.21 The PBAC considered that the claim of non-inferior comparative effectiveness to boosted darunavir co-administered with FTC/tenofovir (both TDF and TAF) was reasonable.

6.22 The PBAC considered that the claim of non-inferior comparative safety to boosted darunavir co-administered with FTC/tenofovir (both TDF and TAF) was reasonable.

Economic analysis

6.23 Table 8 presents a summary of the submission's approach to the cost minimisation analysis (CMA).

Table 8: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior
Evidence base	Direct comparison of Symtuza and CAR in EMERALD or Prezcobix + Truvada in AMBER and Mills 2015 trials
Equi-effective doses	Symtuza (800mg darunavir/150mg cobicistat/ 200mg emtricitabine and 10mg Tenofovir alafenamide) = <ul style="list-style-type: none"> • 1 x Prezcobix (DRV/c 800mg/150mg) co-administered with 1 x Descovy (FTC/TAF 200mg/10mg) • 1 x Prezcobix (DRV/c 800mg/150mg) co-administered with 1 x Truvada (FTC/TDF 200mg/300mg) • 1x Prezista (DRV 800mg), taken with 1 x ritonavir (100mg) and 1 x Descovy (FTC/TAF 200mg/10mg) • 1x Prezista (DRV 800mg), taken with 1 x ritonavir (100mg) and 1 x Truvada (FTC/TDF 200mg/300mg)
Direct medicine costs	The price of Symtuza is equivalent to a weighted price of the submission's nominated comparators
Other costs or cost offsets	None

Source: Table 3-1, p 114 of the submission.

CAR = current antiretroviral regimen

- 6.24 The submission based its consideration of equi-effective doses on the clinical demonstration of the non-inferiority of Symtuza to boosted DRV 800mg co-administered with FTC/tenofovir after 48 weeks of treatment.
- 6.25 Based on the therapeutic relativity sheets (1 June 2019), the submission considered a single daily tablet of 800mg DRV + 150 mg cobicistat + 200mg FTC + 10mg TAF was equi-effective to the following:
- 1 x Prezcobix (DRV/c 800mg/150mg) co-administered with 1 x Descovy (FTC/TAF 200mg/10mg)
 - 1 x Prezcobix (DRV/c 800mg/150mg) co-administered with 1 x Truvada (FTC/TDF 200mg/300mg)
 - 1 x Prezista (DRV 800mg), taken with 1 x ritonavir (100mg) and 1 x Descovy (FTC/TAF 200mg/10mg)
 - 1 x Prezista (DRV 800mg), taken with 1 x ritonavir (100mg) and 1 x Truvada (FTC/TDF 200mg/300mg)
- 6.26 These equi-effective doses were reasonably supported. However, as noted in paragraph 5.4 above, these are not the only potential relevant alternatives. An approach consistent with the National Health Act 1953, Section 101(3B) could include other, less expensive comparators.
- 6.27 No additional costs or cost offsets were included. Given the non-inferiority of Symtuza and its comparators, and the absence of any notable differences in monitoring requirements, this is reasonable.

6.28 The submission conducted a CMA (see Table 9) based on weighting the total prices of each regimen by relative use based on a 10% PBS sample data from Prospecion Pty Ltd. The weighted analysis is inconsistent with National Health Act 1953, Section 101(3B), which was acknowledged by the Sponsor in its PSCR. Furthermore, the weighted analysis assumes that only the four nominated comparators will be replaced. The submission's financial estimates indicated that only 28.9% of Prezista and 45.2% of Prezcobix prescriptions were in combination with FTC/tenofovir. This indicates that the majority of darunavir-containing regimens prescribed are not used with FTC/tenofovir. Therefore, it is likely that other darunavir based regimens would be replaced in practice. It was unclear from the submission which other regimens would be likely to be replaced.

6.29 Further sensitivity analyses of this CMA conducted during the evaluation, with justification, are also presented in Table 9.

Table 9: Results of the cost-minimisation analysis

Treatment	Drug costs (AEMP) 30 days		Weighting
Submission CMA			
Prezcobix 900mg/150mg	\$606.08	\$1,306.14	0.583
Descovy (200mg/10mg)	\$700.06		
Prezcobix 900mg/150mg	\$606.08	\$1,004.04	0.051
Truvada (300mg/200mg)	\$397.96		
Prezista (800mg)	\$597.76	\$1,331.08	0.233
Ritonavir (100mg)	\$33.26		
Descovy (200mg/10mg)	\$700.06		
Prezista (800mg)	\$597.76	\$1,028.98	0.133
Ritonavir (100mg)	\$33.26		
Truvada (300mg/200mg)	\$397.96		
			\$1259.68
Alternative CMA 1: Excluding ritonavir-based regimens			
Although the total DPMQ for Prezista + Norvir + Descovy/Truvada is greater than Prezcobix + Descovy/Truvada (see above), the therapeutic relativity sheets indicate that cobicistat 150mg and ritonavir 100mg are non-inferior in combination with atazanavir or darunavir. Thus, there is no basis for the price premium associated with ritonavir boosted regimens and these were excluded from the weighting.			
Prezcobix 900mg/150mg	\$606.08	\$1,306.14	0.816
Descovy (200mg/10mg)	\$700.06		
Prezcobix 900mg/150mg	\$606.08	\$1,004.04	0.184
Truvada (300mg/200mg)	\$397.96		
			\$1,250.55
Alternative CMA 2: Excluding ritonavir and 94:6 TDF/TAF weighting			
The PBAC previously noted that Australian data on renal impairment, as defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min, in HIV patients estimated approximately 6% of patients have an eGFR below this level, and would therefore be ineligible to receive TDF-based regimens. Consequently, this analysis selects the least expensive TAF regimen and the least expensive TDF regimen and weights them at a 94:6 ratio (based on the dolutegravir/rilpivirine (Juluca) Public Summary Document, July 2018 PBAC).			
Prezcobix (800mg/150mg)	\$606.08	\$1,306.14	0.06

Treatment	Drug costs (AEMP) 30 days		Weighting
Descovy (200mg/10mg)	\$700.06		
Prezcobix (800mg/150mg)	\$606.08	\$1,004.04	0.94
Truvada (300mg/200mg)	\$397.96		
			\$1,022.17
Alternative CMA 3: Versus atazanavir combinations (excluding ritonavir, 94:6 TDF/TAF weighting)			
Darunavir and atazanavir regimens are included in recommended regimens in 'certain clinical situations' (p22 of submission). This is further supported by the fact that nearly 30% of patients treated with PI's access either atazanavir (Reyataz) or the boosted atazanavir (Evotaz) FDC, suggesting that for a substantial proportion of patients, atazanavir-based regimens are used and thus could be considered a relevant lower cost comparator. The PSCR argued regimens containing atazanavir were not relevant comparators as they were unlikely to be replaced in practice.			
Evotaz (300mg/150mg)	\$373.57		\$771.53
Truvada (300mg/200mg)	\$397.96		
Evotaz (300mg/150mg)	\$373.57		\$1,073.63
Descovy (200mg/10mg)	\$700.06		
			\$789.66

Source: Tables 3-2 and 3-3 of the submission
Evotaz = Atazanavir/ cobicistat FDC

- 6.30 The ESC considered the relative price weighting of TDF with FTC [Truvada] and TAF with FTC [Descovy] of 94:6 (Alternative CMA 2) to account for patients unable to use TDF due to poor renal function (Juluca, PSD, July 2018) remained appropriate.
- 6.31 The ESC considered it was appropriate to consider potential replacement of a range of alternative therapies, including atazanavir to ensure listing Symtuza would be cost-neutral or cost-saving for Government. The Pre-PBAC Response argued alternative CMA 3 was not reasonable as ATV was not a relevant comparator (refer to paragraph 5.5).

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

- 6.32 The drug cost of Symtuza per patient per year is \$ [REDACTED] based on the requested dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] (based on the Sponsor requested price) for two months' supply and six dispensing's per year.
- 6.33 The manner in which all of the regimen costs were calculated was consistent. The CMA was based on ex-manufacturer prices, while the financial estimates were based on DPMQ. The financial estimates did not calculate per patient costs, but rather estimated number of scripts expected, and proportions of individual comparator regimens replaced. This approach was generally consistent with the CMA.

Estimated PBS usage & financial implications

- 6.34 This submission was not considered by DUSC.
- 6.35 The submission used a market share approach to estimate the utilisation and financial impact of listing Symtuza. The evaluation considered this was appropriate.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	■	■	■	■	■	■
Estimated financial implications of Symtuza						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Estimated financial implications for other ART regimens displaced						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Net financial implications						
Net cost to PBS/RPBS	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Net cost to MBS/DHS	None.					

Source: Tables 4.8 - 4.13, p130 -135 of the submission.

- 6.36 The submission assumed that Symtuza will only be used in patients appropriate for, or already maintained on, treatment with 800 mg of darunavir (assuming DRV 800 = 28.9% and DRV/c = 45.2%, based on Prospection analysis of PBS 10% sample data) which is co-administered with an FTC/tenofovir backbone. The submission therefore only considered darunavir-based regimens utilised at this dose as the relevant market.
- 6.37 The submission claimed that the majority of the regimens replaced by Symtuza would be DRV-based regimens with an FTC/tenofovir backbone.
- 6.38 The submission further adjusted the population by applying rates of darunavir and FTC/tenofovir treated patients who will elect to switch to the Symtuza FDC. The evaluation considered that uptake in the first years of listing appeared to have been underestimated.
- 6.39 At Year 6, the estimated number of patients was less than 10,000 and the net save to the PBS would be less than \$10 million.

Quality Use of Medicines

- 6.40 The submission briefly described potential education for patients, prescribers and dispensers.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of the combination drug darunavir with cobicistat with emtricitabine and tenofovir alafenamide (DRV/c/FTC/TAF, Symtuza) for the treatment of HIV infection, on the

basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program – Community Access).

- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Symtuza would be acceptable if it were cost-minimised against the following:
- Prezcobix (DRV/c); with
 - A mixed comparator of Truvada (FTC/TDF) and Descovy (FTC/TAF) at a relative weighting of 94:6, the latter accounting for a small patient population (6% of the total population) who are ineligible to receive a TDF-based regimen due to moderate or severe renal impairment for which TDF-based regimens are not recommended. The PBAC recalled it previously considered this weighting as part of its consideration of Juluca at its July 2018 meeting and reaffirmed these relativities remained appropriate.
- 7.3 The equi-effective doses are one tablet of Symtuza (DRV/c/FTC/TAF 800mg/150mg/200mg/10mg) once daily and either: one tablet of Prezcobix (DRV/c 800mg/150mg) and one tablet of Truvada (FTC/TDF 200mg/300mg) once daily; or, in patients with renal impairment, one tablet of Prezcobix (DRV/c 800 mg/150mg) and one tablet of Descovy (FTC/TAF 200mg/10mg) once daily.
- 7.4 The PBAC considered the requested listing should broadly align with the current listings for Prezcobix, with removal of the criterion, 'The treatment must be in combination with other antiretroviral agents', as Symtuza is a complete regimen for the treatment of HIV infection. The PBAC also advised that maximum quantities and repeats should be aligned with current listings for HIV infection to permit two months' therapy per prescription with five repeats. The PBAC also advised the separate virologic failure restriction could be combined with the initial treatment restriction.
- 7.5 The PBAC considered there was a clinical place for Symtuza as a complete single-tablet PI containing regimen which would reduce the cost to patients currently prescribed the individual components of the FDC; however the clinical need for a new combination therapy containing already listed drugs was low.
- 7.6 The PBAC considered the nominated comparators of the alternative regimens (Prezcobix + Descovy; Prezista + Norvir Descovy; Prezcobix + Truvada; and Prezista + Norvir + Truvada) were appropriate.
- 7.7 The PBAC noted the ESC advised it may be appropriate to consider alternative therapies as potential comparators. The PBAC recalled it has previously considered that tenofovir and non-tenofovir based regimens are generally not comparable when it considered Descovy at its July 2016 meeting and re-affirmed its position that non-tenofovir containing regimens were not likely to be replaced and were therefore not relevant comparators.

- 7.8 The PBAC also noted that the current Australian treatment guidelines from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)² state that in general, PI containing regimens (specifically boosted DRV or ATV) are only recommended as initial regimens in certain clinical situations and integrase strand inhibitor based regimens are preferred initial regimens for most patients. The PBAC further noted the guidelines state that in general, boosted DRV is preferred over boosted ATV and that the use of other PIs was low in the Australian setting. On that basis, the PBAC considered that regimens that do not contain a PI as well as other PI-based regimens, including ATV, were not relevant comparators.
- 7.9 The PBAC noted the Pre-PBAC Response included additional evidence from a Phase III Study of efficacy and tolerability of DRV, ATV and raltegravir (Lennox *et al* 2014). The PBAC noted that while these results were not evaluated, there was a body of evidence available which supported a claim that DRV may offer an improvement in tolerability and reduction in toxicity over ATV. Based on the available evidence, the PBAC considered it was unlikely patients would switch from DRV-containing regimens to ATV-containing regimens, which further supported a conclusion that ATV-based regimens were not a relevant comparator to Symtuza.
- 7.10 The PBAC noted the submission was supported by two randomised controlled Phase III studies in treatment-naïve patients (AMBER) and treatment experienced patients (EMERALD), a Phase II randomised study (Mills 2015) and an open-label bioequivalence study comparing Symtuza with its individual components. The PBAC considered the evidence supported a conclusion of therapeutic equivalence between Symtuza and its component drugs administered concomitantly.
- 7.11 The PBAC considered the clinical evidence in the trials supported a conclusion that the safety profile of Symtuza was similar to the known profiles of its component drugs.
- 7.12 The PBAC noted the submission cost-minimisation proposal was based on expected substitution of the four nominated comparator regimens. The PBAC agreed with the alternative proposal put forward under Alternative CMA 2 (Table 9) and considered an appropriate cost-minimisation should include:
- No weighting for use of a Prezista + Norvir regimen, as Prezcofix represents the least costly boosted DRV regimen and ritonavir does not offer either an improvement in effectiveness or reduction in toxicity over a cobicistat boosted DRV regimen; and
 - A mixed comparator weighting of 94:6 for Truvada and Descovy for reasons outlined in paragraph 7.2.

² Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) (2019). *Antiretroviral Guidelines: US DHHS Guidelines with Australian Commentary*. Current version October 25, 2018. Accessed 6 November 2019.

- 7.13 The PBAC considered the listing was likely to only substitute for the four comparator regimens containing Prezcobix or Prezista + Norvir and either Truvada or Descovy and is not likely to grow the overall market. The PBAC advised the listing was likely to be cost neutral or modestly cost-saving, as there will likely be some limited replacement of more costly regimens containing concomitant Norvir.
- 7.14 The PBAC noted the treatment landscape of HIV had changed substantially in recent years with a proliferation of treatment options and changing treatment guidelines, and recommended the Drug Utilisation Sub-Committee (DUSC) undertake a future review of the utilisation and costs of anti-retroviral therapies used in the treatment of HIV infection.
- 7.15 The PBAC advised Symtuza should be included in the list of medicines eligible for prescribing by Nurse Practitioners when such a recommendation is able to be implemented.
- 7.16 The PBAC recommended that the Early Supply Rule should apply, similar to other antiretroviral listings for the treatment of HIV infection.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.
- 7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Symtuza is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over its component drugs, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
DARUNAVIR WITH COBICISTAT WITH TENOFOVIR ALAFENAMIDE AND EMTRICITABINE Darunavir 800 mg + cobicistat 150 mg + tenofovir alafenamide 10 mg + emtricitabine 200 mg tablet, 30	2	5	Symtuza®	Janssen-Cilag Pty Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program {Community Access}
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Initial treatment
Restriction Level/ Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a medical practitioner or an authorised nurse practitioner in consultation with a medical practitioner.
Clinical criteria:	Patient must be antiretroviral treatment naïve OR <i>Patient must have experienced virological failure or clinical failure or genotypic resistance after at least one antiretroviral regimen</i> AND The treatment must not be in combination with ritonavir
Prescriber Instructions:	<i>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.</i>

Category/Program:	Section 100 – Highly Specialised Drugs Program {Community Access}
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Continuing treatment
Restriction Level/ Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a medical practitioner or an authorised nurse practitioner in consultation with a medical practitioner.
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection AND The treatment must not be in combination with ritonavir
Administrative Advice:	The cobicistat component of the darunavir + cobicistat combination product provides the necessary pharmacokinetic enhancement of darunavir to achieve therapeutic levels of darunavir.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.