

5.02 BRINZOLOMIDE / BRIMONIDINE TARTRATE 1%/0.2%, suspension 5 mL, Simbrinza[®], Alcon Laboratories (Australia) Pty Ltd.

1 Purpose of Application

1.1 Restricted Benefit listing for brinzolamide + brimonidine fixed dose combination (FDC) for treatment of elevated intra ocular pressure.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing 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
BRINZOLOMIDE/BRIMONIDINE TARTRATE fixed-dose combination, Suspension, 10mg/mL/2mg/mL	1	5	\$ [REDACTED]	Simbrinza [®] Alcon

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	
Condition:	Elevated intra-ocular pressure
PBS Indication:	Elevated intra-ocular pressure
Treatment phase:	N/A
Restriction Level / Method:	<input checked="" 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 type="checkbox"/> Streamlined
Treatment criteria:	N/A
Clinical criteria:	The condition must have been inadequately controlled with monotherapy, AND Patient must have open-angle glaucoma; OR Patient must have ocular hypertension.

Population criteria:	N/A
Prescriber Instructions	N/A
Administrative Advice	<i>For prescribing in accordance with Optometry Board of Australia guidelines. For prescribing by optometrists where care of a patient is shared between an optometrist and ophthalmologist in a formalised arrangement with an agreed management plan. Further information can be found in the Guidelines for Shared Care of Glaucoma Patients</i>

- 2.1 The requested listing of brinzolamide + brimonidine FDC is based on cost-minimisation analysis compared with brinzolamide 1% (Azopt®) and brimonidine tartrate 0.2% (Alphagan®) administered concomitantly.
- 2.2 The Pre-Sub-Committee Response (PSCR) clarified that the 5 mL pack only is intended for PBS listing. The 2.5 mL pack is a physician sample.

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

3 Background

- 3.1 Brinzolamide + brimonidine FDC was TGA registered on 20 November 2014 for decrease of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.
- 3.2 Brinzolamide + brimonidine FDC has not been considered by the PBAC previously.

4 Clinical place for the proposed therapy

- 4.1 Glaucoma is a progressive chronic disease characterised by elevated IOP. Open angle glaucoma (OAG) is a disease of the optic nerve with characteristic changes in the optic nerve head (optic disc) and typical defects in the visual field, usually with raised intraocular pressure, and without the angle of the anterior chamber of the eye being blocked by the root of the iris, as occurs in angle closure glaucoma. Ocular hypertension (OH) is consistently or recurrently elevated intraocular pressure greater than 21 mmHg, in the absence of clinical evidence of optic nerve damage or visual field defect.
- 4.2 For patients presenting with elevated IOP and a diagnosis of OAG or OH, the preferred first-line monotherapy is a prostaglandin analogue (PGA) or beta-blocker monotherapy. Patients inadequately controlled on these monotherapies may switch within the same drug class, or uncommonly, to an agent within one of the other two main classes of anti-glaucoma medication; alpha-2 adrenergic agonist (AA) or carbonic anhydrase inhibitor (CAI). Alternatively, a second active agent may be added to the regimen e.g. timolol is added to a PGA. Simbrinza provides a therapeutic alternative to two monotherapies of the respective components.

5 Comparator

- 5.1 The submission nominated brinzolamide 1% and brimonidine tartrate 0.2% administered concomitantly as the comparator. The main argument provided in support of this nomination are that brinzolamide + brimonidine FDC simplifies the dosing regimen, and offers a reduction in the dosing burden and preservative load by decreasing the number of eye drops administered in one sitting. The ESC noted that concomitant use of the individual components is an appropriate comparator.
- 5.2 The submission also acknowledged that brinzolamide + timolol (Azarga®), dorzolamide + timolol (Cosopt®) or brimonidine + timolol (Combigan®) FDCs could potentially be replaced by brinzolamide + brimonidine FDC in patients currently treated with timolol-based FDCs, but with health concerns related to beta-blocker use. The ESC considered that these FDCs should be considered as relevant secondary comparators. The potential alternative therapies in this case are listed in Table 1.
- 5.3 The ESC noted the PSCR argued that that the prostaglandin-containing FDCs (namely with bimatoprost, latanoprost and travoprost) should not be considered potential comparators.

Table 1: Simbrinza compared to Timolol based FDC therapies

Drug	Form	MoA	Type of FDC	Formulary	DPMQ	AEMP
Brinzolamide with brimonidine tartrate, Simbrinza®		Application to the eye	CAI/AA		\$36.83	\$24.32
Bimatoprost with timolol	Eye drops 300 micrograms bimatoprost with timolol 5 mg (as maleate) per mL, 3 mL	Application to the eye	PGA/BB	CDL	\$46.94	\$33.18
Latanoprost with timolol	Eye drops 50 micrograms latanoprost with timolol 5 mg (as maleate) per mL, 2.5 mL	Application to the eye	PGA/BB	F2	\$41.21	\$27.86
Travoprost with timolol	Eye drops 40 micrograms travoprost with timolol 5 mg (as maleate) per mL, 2.5 mL	Application to the eye	PGA/BB	CDL	\$46.94	\$33.18
Brimonidine with timolol, Combigan®	Eye drops containing brimonidine tartrate 2 mg with timolol 5 mg (as maleate) per mL, 5 mL	Application to the eye	AA/BB	CDL	\$26.37	\$15.86
Brinzolamide with timolol, Azarga®	Eye drops 10 mg brinzolamide with timolol 5 mg (as maleate) per mL, 5 mL	Application to the eye	CAI/BB	CDL	\$27.22	\$16.55
Dorzolamide with timolol, Cosopt®	Eye drops containing dorzolamide 20 mg (as hydrochloride) with timolol 5 mg (as maleate) per mL, 5 mL	Application to the eye	CAI/BB	F2	\$24.19	\$14.10

PGA = prostaglandin analogue; BB = beta-blocker, CAI = carbonic anhydrase inhibitor; AA = alpha-2 adrenergic agonist.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item.
- 6.2 The clinician addressed the clinical positioning of brinzolamide + brimonidine FDC in the treatment algorithm to lower IOP to a safe level thereby eliminating the risk of glaucoma progression. The clinician's view was that FDCs are clinically important as they facilitate adherence and persistence, simplify dosing regimen, exclude wash-out and reduce ocular surface exposure to preservatives. All currently available FDCs contain a beta-blocker which is contraindicated in some patients as described in the NHMRC Guidelines (2010). The clinician emphasised that PBS listing of brinzolamide + brimonidine FDC would benefit this sub group of patients. In clinical practice brinzolamide + brimonidine FDC replaces separate bottles of brinzolamide and brimonidine reducing the daily dosage from four to two drops for patients using brinzolamide and brimonidine consecutively.
- 6.3 The PBAC considered the hearing was moderately informative.

Consumer comments

- 6.4 There were no consumer comments received for this item.

Clinical trials

- 6.5 The submission is based on one phase III non-inferiority head-to-head trial comparing brinzolamide + brimonidine FDC to brinzolamide and brimonidine administered concomitantly (Trial C-10-041) (n=831) and one supportive phase III superiority randomised trial comparing brinzolamide + brimonidine FDC to brinzolamide and brimonidine administered as monotherapy (Trial C-10-040) (n=559). The ESC noted that the C-10-041 trial used a per protocol approach to the comparative effectiveness analysis whilst the C-10-040 study employed an intention to treat (ITT) analysis, which are considered appropriate for non-inferiority and superiority designs respectively. The submission also presented an informal, qualitative comparison of brinzolamide + brimonidine FDC and brinzolamide + timolol FDC using brinzolamide administered as monotherapy as the common reference based on one randomised trial (Kaback 2008) (n=523), where brinzolamide + timolol FDC is used as a proxy for all timolol-containing FDCs containing either brinzolamide, brimonidine or dorzolamide. The ESC considered that the inclusion of this trial is justified on the grounds that brinzolamide + timolol FDC is more widely used than brimonidine + timolol FDC and more relevant than dorzolamide + timolol FDC secondary to the common brinzolamide component.
- 6.6 Details of the trials presented in the submission are provided in below.

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Trial C-10-041	Efficacy and safety of brinzolamide 10mg/mL / brimonidine 2mg/mL eye drops, suspension compared to brinzolamide 10/mL eye drops, suspension plus brimonidine 2mg/mL eye drops, solution in patients with open-angle glaucoma or ocular hypertension, Alcon Research. 29 January 2013.	2013.
	Gandolfi S et al. Randomized trial of brinzolamide/brimonidine versus brinzolamide plus brimonidine for open-angle glaucoma or ocular hypertension.	Adv Ther, 2014; 31: 1213-1227.
Supportive randomised trial		
Trial C-10-040	Safety and IOP-lowering efficacy of brinzolamide 10mg/mL / brimonidine 2mg/mL fixed combination eye drops, suspension compared to brinzolamide 10/mL eye drops, suspension and brimonidine 2mg/mL eye drops, solution in patients with open-angle glaucoma or ocular hypertension, Alcon Research. 18 January 2013.	2013.
	Aung T et al. Twice daily brinzolamide/brimonidine fixed combination versus brinzolamide or brimonidine for open-angle glaucoma or ocular hypertension.	Ophthalmology, 2014; 121: 2348-2355.
Supplementary comparison (Azarga)		
Kaback 2008	Kaback M et al. Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%.	Ophthalmology, 2008; 115: 1728-1734.

Source: Tables 21-22, 63; pp.70-71, 155 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome
Simbrinza vs. Azopt+ Alphagan administered concomitantly					
Trial C-10-041	890	R, DB 6 mths	Low	OAG or OH; Insufficiently controlled on monotherapy	Diurnal IOP at 3 months
Simbrinza vs. Azopt and Alphagan monotherapy					
Trial C-10-040	560	R, DB 6 mths	Low	OAG or OH; Insufficiently controlled on monotherapy	Diurnal IOP at 3 months
Azarga vs Azopt and timolol monotherapy					
Kaback 2008	523	R, DB 6 mths	Low	OAG or OH	IOP at 6 months

DB=double blind; IOP = intra-ocular pressure; MC=multi-centre; OAG=open-angle glaucoma; OH=ocular hypertension; R=randomised.

Source: compiled during the evaluation

6.8 The ESC noted that both the C-10-041 non-inferiority and C-10-040 superiority trials were well balanced at baseline with respect to age, gender, diagnosis and baseline IOP.

Comparative effectiveness

- 6.9 The results of the primary outcome mean change from baseline to 3 months in diurnal IOP, in Trial C-10-041, are presented in the following table.

Table 4: Results of mean change from baseline to 3 months in diurnal IOPa in Trial C-10-041

	Simbrinza N=384	BRINZ+BRIM N=373	Mean Difference ^b (95% CI)	p-value ^c
Mean change from baseline to 3 months, mmHg (SD)(per protocol)	-8.5 (3.14)	-8.3 (3.09)	-0.1 (-0.5, 0.2)	0.38

Abbreviations: BRIM = brimonidine tartrate 0.2%; BRINZ = brinzolamide 1%; CI = confidence interval; IOP = intra-ocular pressure; PP = per protocol; SD = standard deviation.

Source: Table 31, p95 of the submission.

^a Diurnal IOP change averaged for time points 9am and +2 hours.

^b Estimates based on the least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 9 AM baseline IOP stratum are in the model.

^c The submission calculated this post-hoc. This is an unadjusted value.

- 6.10 The mean difference between brinzolamide + brimonidine FDC and brinzolamide + brimonidine used concomitantly, was -0.1 mmHg (95% CI: -0.5, 0.2), thus the non-inferiority criterion of +1.5 mmHg (previously accepted by the PBAC) was met. Efficacy was maintained over 6 months.
- 6.11 An ITT comparison of brinzolamide + brimonidine FDC and its constituent products used as monotherapy indicated statistically significant differences between treatments, which for the most part, favoured brinzolamide + brimonidine FDC. The ESC noted that mean diurnal reduction in IOP from baseline at 3 months was greater in the brinzolamide + brimonidine FDC arm compared with either brinzolamide (-1.4mmHg, p<0.0001) or brimonidine monotherapy (-1.5mmHg, p<0.0001) based on a prior specified clinical relevance cut-off of >1mmHg difference.
- 6.12 The submission did not present an indirect comparison of brinzolamide + brimonidine FDC and brinzolamide + timolol FDC; citing exchangeability issues (differences observed in the trial populations and differences in the mean reduction in IOP observed for patients treated with brinzolamide monotherapy) between the trials as precluding the conduct of an informative indirect comparison. Whilst the sponsor interpreted the provided supplementary comparison as implying that brinzolamide + brimonidine FDC is at least as efficacious as brinzolamide + timolol FDC, the ESC considered that this was not justified as this comparison was entirely qualitative. The results of the indirect comparison conducted during the evaluation indicate that there were no statistically significant differences between the treatments (however brinzolamide + brimonidine FDC consistently failed to meet the non-inferiority criterion when compared with brinzolamide + timolol FDC as the upper confidence limits exceed +1.5 mmHg at all timepoints assessed). The ESC noted that unadjusted confounding (systematic differences in prognostic factors between trials) makes it difficult to separate genuine non-inferiority from the non-significance secondary to confounder imbalance.

Comparative harms

- 6.13 The adverse events reported in Trial C-10-041 up to month 6 are summarised below.

Table 5: Summary of adverse events in Trial C-10-041

Trial ID	Simbrinza n with event/N (%)	BRINZ + BRIM n with event/N (%)	RD (95% CI)	RR (95% CI)
All TEAEs	176/452 (38.9)	181/436 (41.5)	-0.03 (-0.09, 0.04)	0.94 (0.80, 1.10)
All TEAEs related to treatment	106/452 (23.5)	117/436 (26.8)	-0.03 (-0.09, 0.02)	0.87 (0.70, 1.10)
Nonfatal SAE	11/452 (2.4)	7/436 (1.6)	0.01 (-0.01, 0.03)	1.52 (0.59, 3.87)
Nonfatal SAE related to treatment	2/452 (0.4)	0	0.00 (0.00, 0.01)	4.82 (0.23, 100.18)
Number discontinued due to AEs	48/452 (10.6)	58/436 (13.3)	-0.03 (-0.07, 0.02)	0.80 (0.56, 1.14)
Number discontinued due to AEs which are related to treatment	45/452 (10.0)	51/436 (11.7)	-0.02 (-0.06, 0.02)	0.85 (0.58, 1.24)
Number died	0	1/436 (0.2)	0.00 (-0.01, 0.00)	0.32 (0.01, 7.87)

Abbreviations: AE = adverse event; BRIM = brimonidine tartrate 0.2%; BRINZ = brinzolamide 1%; NE = not estimable; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Source: Tables 36, 48, pp. 102, 118 of the submission.

- 6.14 The ESC noted that whilst TEAEs and related discontinuations were numerically higher in the concomitant brinzolamide + brimonidine comparator arm, there were no statistically significant differences in any key adverse events between brinzolamide + brimonidine FDC and brinzolamide plus brimonidine administered concomitantly in Trial C-10-041.
- 6.15 In the supportive Trial C-10-040, all key adverse events were similar between brinzolamide + brimonidine FDC and brinzolamide monotherapy. Although the proportion of patients with adverse events was slightly higher for brinzolamide + brimonidine FDC compared to brimonidine, there were no statistically significant differences. However, compared with brinzolamide monotherapy, significantly greater TEAEs, treatment-related TEAEs, and treatment-related discontinuations were experienced by brinzolamide + brimonidine FDC patients.

Clinical claim

- 6.16 The submission described brinzolamide + brimonidine FDC as non-inferior in terms of comparative effectiveness (as measured by change from baseline IOP) and non-inferior in terms of comparative safety compared with brinzolamide + brimonidine used concomitantly (primary comparator). This ESC considered that this claim was reasonable in terms of the effectiveness and safety data presented, in a population that is not entirely consistent with those for whom listing is sought (the brinzolamide + brimonidine FDC phase III trials included both patients insufficiently controlled on monotherapy and those on multiple IOP-lowering agents).
- 6.17 The submission claims that the supportive Trial C-10-040 showed that brinzolamide + brimonidine FDC was superior in terms of comparative effectiveness over its individual components used as monotherapy. The submission also claimed that brinzolamide + brimonidine FDC was inferior in terms of comparative safety over brinzolamide monotherapy and non-inferior in terms of comparative safety over brimonidine monotherapy. These claims appear to be reasonable in terms of the effectiveness and safety data presented, in a population that was not entirely consistent with those for whom listing was sought (as above, the brinzolamide +

brimonidine FDC phase III trials included both patients insufficiently controlled on monotherapy and those on multiple IOP-lowering agents).

- 6.18 The submission made no claim regarding the comparative efficacy and safety of brinzolamide + brimonidine FDC compared with brinzolamide + timolol FDC; citing exchangeability issues (differences observed in the trial populations and differences in the mean reduction in IOP observed for patients treated with brinzolamide monotherapy) between the trials as precluding the conduct of an informative indirect comparison. While this was acknowledged, the results of the indirect comparison indicate that there were no statistically significant differences between the treatments (where brinzolamide + brimonidine FDC consistently failed to meet the non-inferiority criterion when compared with brinzolamide + timolol FDC as the upper confidence limits exceed +1.5 mmHg at all timepoints assessed).
- 6.19 The PSCR argued that a comparison to establish superiority of brinzolamide + brimonidine FDC over brinzolamide + timolol FDC was neither appropriate nor required as alternate FDCs are not the main comparators. Whilst the sponsor acknowledged that substitution was possible, the PSCR argued that it does not constitute the therapy that would most likely be replaced in practice.
- 6.20 The ESC noted that no formal indirect comparison was provided to establish the comparative efficacy of brinzolamide + brimonidine FDC to brinzolamide + timolol FDC, brimonidine + timolol FDC and dorzolamide + timolol FDC, which the Committee considered to be appropriate comparators.

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

Economic analysis

- 6.21 The submission presented a cost-minimisation analysis comparing brinzolamide + brimonidine FDC with brinzolamide plus brimonidine used concomitantly.
- 6.22 One drop twice daily of brinzolamide 1% and brimonidine 0.2% used as a fixed dose combination was equivalent to use of one drop twice daily of brinzolamide 1% and one drop twice daily of brimonidine 0.2% used concomitantly, based on the dosing in Trial C-10-041.
- 6.23 The submission’s initial proposed price for brinzolamide + brimonidine FDC was based on the sum of individual equivalent dose components, DPMQ \$ [REDACTED] (AEMP \$ [REDACTED]). This compares to a total DPMQ of \$43.59 when the two agents are dispensed individually.

Table 6: Simbrinza price based on components

Brand	Drug	DPMQ	PTP	ExMan
Azopt®	brinzolamide	\$23.11	\$14.22	\$13.23
Alphagan®	brimonidine	\$20.48	\$11.93	\$11.10
Simbrinza®	brinzolamide/brimonidine	\$ [REDACTED] ^a	\$ [REDACTED]	\$ [REDACTED]

^a SIMBRINZA price = [(BRINZ PTP price + BRIM PTP price) * 1.15] + \$6.76 (pharmacy mark-up)

Abbreviations: DPMQ = dispensed price for maximum quantity; PTP = price to pharmacist; ExMan = ex manufacture price

- 6.24 In the pre-PBAC response the sponsor revised its pricing proposal by cost-minimising brinzolamide + brimonidine to a mixed comparator comprising █████% of the sum of the components and █████% of a weighted brinzolamide + timolol and brimonidine + timolol FDC price.

Table 7: Weighted average price of timolol based FDCs

Price methodology	PTP	ExMan	Weighting
Constituent parts price	\$26.15	\$24.32	█████%
Timolol based FDC price	\$█████ ^a	\$█████	█████%
Weighted price	\$█████	\$█████	100.0%

^a Weighted average price of brinzolamide+timolol (█████%) and brimonidine+timolol (█████%) FDCs on the PBS.

- 6.25 The PBAC noted the sponsors new pricing proposal, but considered that the appropriate basis for recommending brinzolamide + brimonidine was on a cost-minimisation basis against the proportion of patients who could use a timolol based FDC rather than the proportions of patients who are using a timolol based FDC. The PBAC further noted that the pre-PBAC approach to weighting the price of the timolol based FDCs was not appropriate (see paragraph 7.9).

Drug cost/patient/year

- 6.26 \$█████ year based on the requested DPMQ and assuming 12 scripts per year. This compared with a cost of \$523.08/year for brinzolamide plus brimonidine used concomitantly, assuming 12 scripts of brinzolamide plus 12 scripts of brimonidine. This also compared with \$290.28, assuming 12 scripts per year of dorzolamide + timolol FDC (dorzolamide/timolol FDC), which is the cheapest of the currently PBS-listed FDCs for the treatment of elevated intra-ocular pressure (and acknowledged by the submission to be a relevant comparator in the sub-population of patients on a timolol-based FDC with specific health concerns related to beta-blockers).

Estimated PBS usage & financial implications

- 6.27 This submission was not considered by DUSC.
- 6.28 The submission reasonably used a market share approach to estimate the extent of use and financial implications of the requested listing for brinzolamide + brimonidine FDC.
- 6.29 The base case identified five patient groups who would potentially use brinzolamide + brimonidine FDC where the extent of brinzolamide + brimonidine FDC substitution would be expected to be different across the five groups.
1. Patients prescribed a CAI and AA as concomitant monotherapy.
 2. Patients using either a CAI or AA FDC in a four-agent, three drop regimen who can reduce the drop burden.
 3. Patients on three active therapies including both a CAI and AA but no change in drop burden.
 4. Patients who require careful consideration and caution prior to being prescribed a beta-blocker.
 5. Patients currently uncontrolled on three or more active therapies.

- 6.30 The ESC noted the sponsor’s claim that brinzolamide + brimonidine FDC was cost-saving to patients accessing through PBS (i.e. patient group previously on concomitant brinzolamide and brimonidine) via reducing the numbers of pharmacy dispensing fees.
- 6.31 The redacted table below shows that the submission estimated the cost to Government in Year 5 to be less than \$10 million.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total prescriptions (all classes)					
Expected Simbrinza uptake	%	%	%	%	%
Scripts					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

Source: Tables 73-76, 89; pp.171-175, 191 of the submission.

Key sensitivity analyses are presented in the following table.

Table 9: Sensitivity analysis of the total net cost to the PBS/RPBS (after copayments) for listing Simbrinza

	Year 1	Year 2	Year 3	Year 4	Year 5
Base Case	\$	\$	\$	\$	\$
Simbrinza uptake					
5.0% by Year 5	\$	\$	\$	\$	\$
Uptake from clinical need groups					
100% Simbrinza uptake from clinical need groups 3, 4, 5*	\$	\$	\$	\$	\$
Use of latest April 2015 DPMQs for substituted drugs (latanoprost, dorzolamide)	\$	\$	\$	\$	\$
DPMQ of Simbrinza = DPMQ of Cosopt (\$24.19)	-\$	-\$	-\$	-\$	-\$

Source: Tables 90-91, pp.192-193 of the submission

Clinical need Group 3 = patients on three active therapies including both a CAI and AA; Group 4 = patients currently treated with a beta-blocker despite special health concerns related to beta blocker treatment; Group 5 = Patients currently uncontrolled on three or more active therapies

- 6.32 The ESC considered that the sensitivity analysis for the financial estimates assuming 100% uptake from clinical need groups was considered unlikely.
- 6.33 The PBAC noted that the financial estimates presented in the submission would need to be revised to take into account the basis upon which the PBAC had recommended listing.

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

Quality Use of Medicines

- 6.34 The submission acknowledged ongoing monitoring is an important aspect of anti-glaucoma care, particularly following the initiation of a new active agent, and brinzolamide + brimonidine FDC is not likely to increase this monitoring burden.

7 PBAC Outcome

- 7.1 The PBAC recommended the Restricted Benefit listing of brinzolamide + brimonidine FDC on a cost-minimisation basis against the mixed comparator of dorzolamide + timolol FDC, which is the least expensive of the currently PBS listed CAI/timolol or AA/timolol FDCs; and the individual components of brinzolamide and brimonidine, with the latter contributing 12.7% of the patient population.
- 7.2 In making this recommendation, the PBAC accepted that concomitant use of the individual components and timolol-based FDCs dorzolamide+timolol FDC, brinzolamide+timolol FDC and brimonidine+timolol FDC were appropriate comparators. The PBAC acknowledged the sponsor's argument in the PSCR that that the prostaglandin-containing FDCs (namely with bimatoprost, latanoprost and travoprost) should not be considered potential comparators.
- 7.3 The PBAC noted it could not recommend the brinzolamide + brimonidine FDC for listing on the PBS at a higher price than alternative therapies, unless it was satisfied that brinzolamide + brimonidine FDC, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapies [Section 101(3B) of the *National Health Act 1953*]. Except for patients who cannot tolerate timolol (a beta blocker), the alternative therapies in this case include the CAI/timolol and AA/timolol FDC's. For the subgroup of patients who cannot tolerate timolol, the alternative therapy is the individual components of brinzolamide and brimonidine given concomitantly. The PBAC noted the estimate, based on the publication [abstract only] by Spooner et al (2002), that 12.7% of the population may have a contraindication to ophthalmic beta-blocker use.
- 7.4 The PBAC considered the results from the randomised trials demonstrated a mean difference of -0.1 mmHg (95% CI: -0.5, 0.2) between brinzolamide + brimonidine FDC and brinzolamide and brimonidine used concomitantly. The PBAC noted that the non-inferiority criterion of +1.5 mmHg was met, and recalled that this criterion had previously been accepted by the Committee.
- 7.5 The PBAC considered the claim of brinzolamide + brimonidine FDC's non-inferior comparative safety and efficacy over the concomitant use of individual components was reasonable.
- 7.6 The PBAC noted the claim of brinzolamide + brimonidine FDC's superior comparative efficacy over individual components used as monotherapy was reasonable. The PBAC noted that brinzolamide + brimonidine FDC was inferior in safety to brinzolamide monotherapy and non-inferior in safety to brimonidine.

- 7.7 The PBAC noted the submission did not present an indirect comparison of brinzolamide + brimonidine FDC and brinzolamide + timolol FDC; citing exchangeability issues (differences observed in the trial populations and differences in the mean reduction in IOP observed for patients treated with brinzolamide monotherapy) between the trials as precluding the conduct of an informative indirect comparison.
- 7.8 The PBAC also noted the results of the indirect comparison conducted during the evaluation which indicate that there were no statistically significant differences between the treatments. Brinzolamide + brimonidine FDC consistently failed to meet the non-inferiority criterion when compared with brinzolamide + timolol FDC as the upper confidence limits exceed +1.5 mmHg at all time points assessed.
- 7.9 The PBAC noted the ESC advice that no formal indirect comparison was provided to establish the superiority of brinzolamide + brimonidine FDC over other CAI/timolol or AA/timolol FDCs (brinzolamide + timolol FDC, brimonidine + timolol FDC and dorzolamide + timolol FDC). Thus the price of brinzolamide + brimonidine FDC can only justifiably be higher than the least expensive of these FDCs if there is a distinct groups of patients with elevated IOP who cannot use them. In this case, such a distinct group does exist in patients who cannot tolerate timolol.
- 7.10 The PBAC noted the submission's estimate of the changes in prescriptions was based on regimens substituted within and across the five clinical need groups identified, and the relative rate of substitution or uptake from each clinical need group. Whether this was an over or underestimate is unknown because there was no evidence to substantiate the assumption of the rate of substitution from clinical need groups 3-5.
- 7.11 The PBAC noted the sponsor's claim that brinzolamide + brimonidine FDC was cost-saving to patients accessing through PBS (i.e. patient group previously on concomitant brinzolamide and brimonidine) via reducing the number of dispensing fees. The PBAC also noted that the financial estimates presented in the submission would need to be revised to take into account the basis upon which the PBAC had recommended listing.
- 7.12 Advice to the Minister under section 101 (3BA) of the Act
The PBAC advised the Minister that there are no drugs or medicinal preparations that should be treated as interchangeable with brinzolamide + brimonidine FDC on an individual patient basis.
- 7.13 The PBAC advised that brinzolamide + brimonidine FDC is not suitable for prescribing by nurse practitioners in line with other anti-glaucoma preparations.
- 7.14 The PBAC recommended that the Safety Net 20 Day rule should not apply in line with the current listing for its active components.
- 7.15 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
BRINZOLAMIDE/BRIMONIDINE TARTRATE fixed-dose combination, Suspension, 10mg/mL/2mg/mL	1	5	Simbrinza® Alcon

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	N/A
Severity:	N/A
Condition:	Elevated intra-ocular pressure
PBS Indication:	Elevated intra-ocular pressure
Treatment phase:	N/A
Restriction Level / Method:	<input checked="" 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 type="checkbox"/> Streamlined
Treatment criteria:	N/A
Clinical criteria:	The condition must have been inadequately controlled with monotherapy, AND Patient must have open-angle glaucoma; OR Patient must have ocular hypertension.
Population criteria:	N/A
Prescriber Instructions	N/A
Administrative Advice	<i>For prescribing in accordance with Optometry Board of Australia guidelines.</i>
Cautions	N/A

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

Alcon welcomes the PBAC's recommendation for the fixed dose combination eye drop, Simbrinza (brinzolamide/brimonidine), to be made available on the PBS for the treatment of elevated intra-ocular pressure in adult patients with primary open-angle glaucoma and ocular hypertension. The listing of a timolol-free fixed dosed combination on the PBS offers a reduction in the dosing burden and preservative load by decreasing the number of drops administered in one sitting.