PUBLIC SUMMARY DOCUMENT
Product: Brinzolamide with timolol maleate, eye drops, 10 mg -5 mg (base) per mL, (1%-0.5%), Azarga®
Sponsor: Alcon Laboratories (Australia) Pty Ltd.
Date of PBAC Consideration: March 2010 PBAC

1. Purpose of Application

To request a Restricted Benefit listing, in both the General and the Optometrical Schedules, for the reduction of elevated intraocular pressure in certain patients with open-angle glaucoma or with ocular hypertension.

2. Background

This combination eye drop had not previously been considered by the PBAC.
A similar product, dorzolamide hydrochloride with timolol maleate eye drops (Cosopt®), was recommended for listing at the September 2001 PBAC meeting on a cost-minimisation basis compared with the individual components.

3. Registration Status

TGA registration for Azarga eye drops occurred on 23 December 2009 for the following indication: Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy with either component provides insufficient IOP reduction.

4. Listing Requested and PBAC's View

Restricted Benefit (General and Optometrical)
Reduction of elevated intro-ocular pressure in patients with open-angle glaucoma who are not adequately controlled with timolol maleate 5 mg (base) per mL (0.5 %) eye drops;
Reduction of elevated intra-ocular pressure in patients with ocular hypertension who are not adequately controlled with timolol maleate 5 mg (base) per mL (0.5 %) eye drops.

For PBAC's view see Recommendation and Reasons

5. Clinical Place for the Proposed Therapy

For a patient in whom the first-line therapy is not sufficiently effective, a second topical medication can be added. This fixed combination product provides a therapeutic alternative to two mono-therapies of the respective components. The sponsor claims it has the advantage of improving compliance, less ocular toxicity from preservatives and avoids 'wash out' effect of concomitant treatment if the second drop is administered less than 5 minutes after the first.

6. Comparator

As recommended for a combination product, more than one comparison was presented. The submission nominated (1) the individual components given concomitantly (brinzolamide and timolol) and (2) the combination product that most prescribers would replace in practice – dorzolamide/timolol (Cosopt). The PBAC considered the comparators nominated in the submission were reasonable, however the submission had not presented any evidence comparing Azarga to its components given concomitantly.

7. Clinical Trials

The submission presented three randomised trials of the fixed combination of

brinzolamide 1% and timolol 0.5% in populations with increased intraocular pressure at baseline;

- one three arm trial, versus (vs) brinzolamide 1% vs timolol 0.5% as monotherapies (Trial C-05-24)
- one trial vs timolol 0.5% monotherapy (Trial C-97-22: a 14 day exploratory study)
- one trial vs dorzolamide 2% and timolol 0.5% in fixed dose combination (Trial C-05-10: a non-inferiority trial)

The submission also presented two trials of brinzolamide 1% and timolol 0.5% given concomitantly vs dorzolamide 2% and timolol 0.5% given concomitantly (Michaud 2001, which was a non-inferiority trial, and Martinez 2009), and two studies of self assessed patient comfort of Azarga vs Cosopt (Study C-05-49, Mundorf 2008). As noted, the submission did not present a comparison of the fixed combination of brinzolamide 1% and timolol 0.5% against its components taken concomitantly.

The trials published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Azarga vs monotherapy		
Trial C-05-24 Kaback, Scoper, Arzeno, 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(10): 1728-1734.e2.
Croxtall and Scott	Brinzolamide/timolol: in open-angle glaucoma and ocular hypertension.	Drugs & Aging 2009; 26(5): 437-46
Azarga vs Cosopt (dorzolamide + timolol)		
Trial C-05-10 Manni et al	The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension.	J Glaucoma 2009; 18(4): 293-300
Supplementary evidence		
Timolol + brinzolamide or dorzolamide		
Michaud 2001	Michaud J-E and Friren B. Comparison of topical brinzolamide 1% and dorzolamide 2% eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension.	American Journal of Ophthalmology 2001; 132(2): 235-243.
Martinez 2009	A comparison of the long-term effects of dorzolamide 2% and brinzolamide 1%, each added to timolol 0.5%, on retrobulbar hemodynamics and intraocular pressure in open-angle glaucoma patients.	J Ocul Pharmacol Ther 2009; 25(3): 239-48.
Self assessed ocular discomfort		
Study C-05-49 Vold, Evans, Stewart, et al.	A one-week comfort study of BID-dosed brinzolamide 1%/timolol 0.5% ophthalmic suspension fixed combination compared to BID-dosed dorzolamide 2%/timolol 0.5% ophthalmic solution in patients with open-angle glaucoma or	Journal of Ocular Pharmacology and Therapeutics 2008; 24(6): 601-5.

	ocular hypertension.	
Mundorf 2008	A patient preference comparison of Azarga (brinzolamide/timolol fixed combination) vs Cosopt (dorzolamide/timolol fixed combination) in patients with open-angle glaucoma or ocular hypertension.	Clin Ophthalmol 2008; 2(3): 623-8

8. Results of Trials

There were statistically significantly larger reductions in mean intraocular pressure in patients treated with fixed combination brinzolamide 1% and timolol 0.5% (Azarga) at 6 months compared with brinzolamide 1% or timolol 0.5% monotherapies.

None of the differences in mean IOP between the fixed combination brinzolamide 1% and timolol 0.5% (Azarga) and the fixed combination dorzolamide 2% plus timolol 0.5% (Cosopt) were statistically significant, and at 6 and 12 months the upper bound of the 95% confidence interval (CI) for the mean difference in intraocular pressure was less than the non-inferiority margin of +1.5mmHg, therefore Azarga was demonstrated to be non-inferior to Cosopt. Analysis using the intention to treat population also demonstrated non-inferiority. The participants of both Trials C-05-24 and C-05-10 were not using any intraocular pressure lowering eye-drops at baseline, and therefore were not the population for whom listing was sought (i.e. elevated intraocular pressure not adequately controlled with timolol 0.5%).

In the comparison of concomitant dosing of brinzolamide 1% and timolol 0.5% vs. concomitant dosing of dorzolamide 2% and timolol 0.5% the upper 95% confidence limits to all time points were below +1.5mmHg, thus non-inferiority of brinzolamide compared with dorzolamide when used concomitantly with timolol 0.5% up to 3 months was demonstrated. However, this trial did not use the fixed dose combination, Azarga. Martinez 2009 reported statistically significant decreases in resistance index from baseline in patients treated with dorzolamide in all retrobulbar arteries over 5 years, indicating an improvement in blood flow, thus reduced probability of visual field defect progression. No decrease in resistance index was found in patients treated with brinzolamide.

In Study C-05-49, after two weeks patient assessed discomfort on a 0 to 4 scale was statistically significantly lower in the Azarga group compared with the Cosopt group, the difference -0.77 (95%CI -0.36, -1.17), p = 0.0003. In Mundorf 2008, 84/127 patients (66.1%) expressed a preference for Azarga over Cosopt. These results indicate that patients generally found Azarga more comfortable to use than Cosopt. The adverse event profile of Azarga is comparable to that of brinzolamide 1% and timolol 0.5% given concomitantly, and is similar to Cosopt, except that Azarga produces less burning, stinging, and eye pain, though causes more blurred vision.

For PBAC's view see Recommendation and Reasons

9. Clinical Claim

The submission described Azarga as superior in terms of comparative effectiveness in lowering intraocular pressure compared with brinzolamide 1% or timolol 0.5% given as monotherapies, but with greater toxicity. This description is reasonable. The submission

also described Azarga as "as effective" as Cosopt in reduction of intraocular pressure and as superior in terms of comparative safety.

Although the submission did not present a comparison of the fixed combination of brinzolamide 1 % and timolol 0.5 % against its components taken concomitantly, the PBAC agreed that it is reasonable to describe Azarga as superior in terms of comparative effectiveness in lowering intraocular pressure compared with brinzolamide 1 % or timolol 0.5 % given as monotherapies, but with greater toxicity. The PBAC further agreed that the comparison of the fixed combination Azarga versus the fixed combination Cosopt presented in the submission supported the claim of non-inferiority of Azarga with Cosopt.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses are estimated as one drop of Azarga is equi-effective to one drop of brinzolamide 1% plus one drop of timolol 0.5%. The submission did not present any evidence to support the assumption that Azarga is equi-effective compared to concomitant treatment with its components. One drop of Azarga is also equi-effective to one drop of Cosopt.

For PBAC's view see Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions dispensed per year was estimated to be between 50,000 and 100,000 in Year 3. The financial cost per year to the PBS was < $10 million in Year 3. The submission's estimate is reasonable if the market share estimates are accurate.

12. Recommendation and Reasons

The PBAC recommended the listing of brinzolamide with timolol eye drops in the General and Optometrical Schedules as a restricted benefit for elevated intraocular pressure due to open angle glaucoma/ocular hypertension in a patient in whom this condition is not adequately controlled with monotherapy. Listing was recommended on a cost-minimisation basis against the individual components given concurrently and against the combination product dorzolamide 2 % (base) with timolol 0.5 % (base) eye drops (Cosopt). The equi-effective doses for the purposes of cost-minimisation are one drop of the combination brinzolamide with timolol eye drops is equi-effective to one drop of brinzolamide 1 % eye drops plus one drop of timolol 0.5 % eye drops; and that one drop of the combination brinzolamide with timolol eye drops (Azarga) is equi-effective to one drop of the combination dorzolamide with timolol eye drops (Cosopt).

Although the submission did not present a comparison of the fixed combination of brinzolamide 1 % and timolol 0.5 % against its components taken concomitantly, the PBAC agreed with ESC that it is reasonable to describe Azarga as superior in terms of comparative effectiveness in lowering intraocular pressure compared with brinzolamide 1 % or timolol 0.5 % given as monotherapies, but with greater toxicity.

The PBAC further agreed with the ESC that the comparison of the fixed combination Azarga versus the fixed combination Cosopt presented in the submission supported the claim of non-inferiority of Azarga with Cosopt. In the per protocol analysis, none of the differences in mean IOP between Azarga and Cosopt were statistically significant, and at 6 and 12 months the upper bound of the 95 % CI for the mean difference in intraocular

pressure was less than the non-inferiority margin of +1.5 mmHg, which the PBAC has previously accepted as the appropriate non-inferiority margin.

The Committee also accepted the sponsor's arguments that the results of the Martinez 2009 study which appear to show an advantage for dorzolamide over brinozolamide in terms of progression of visual field deterioration should be discounted as the very large differential drop out rates in this study make the results difficult to interpret. Thus overall the PBAC considered it was reasonable to conclude that non-inferiority had been demonstrated against the individual components given concurrently and against the combination product dorzolamide with timolol eye drops (Cosopt).

The PBAC noted that the dispensed price for maximum quantity (DPMQ) requested in the submission is based on the current PBS prices of the individual component brinzolamide and timolol eye drops, which at $ 29.65 is higher than the current DPMQ of $ 27.49 for the combination dorzolamide with timolol eye drops. The PBAC requested this matter be referred to the Pharmaceutical Benefits Pricing Authority with the advice that the PBAC could see no justification for the higher price for brinzolamide with timolol eye drops compared to dorzolamide with timolol eye drops.

The PBAC also recommended a restriction wording of "*elevated intra-ocular pressure in a patient with open angle glaucoma/ocular hypertension not adequately controlled with monotherapy*" be applied to all restricted benefit listings of all combination eye drops containing an alpha-agonist (brimonidine) with timolol, a carbonic anhydrase inhibitor (brinzolamide, dorzolamide) with timolol or a prostaglandin/prostamide analogue (bimatoprost, latanoprost, travoprost) with timolol. The PBAC considered that the use of a combination product in a patient whose elevated intra-ocular pressure due to open angle glaucoma or ocular hypertension is not adequately controlled on monotherapy is consistent with current guidelines which no longer recommend timolol as the first line therapy for all patients. Comment should be sought from the sponsors prior to this change being implemented.

The PBAC recommended that the Safety Net 20 day rule should not apply.

Recommendation:
BRINZOLAMIDE with TIMOLOL MALEATE, eye drops, 10 mg - 5 mg (base) per mL (1 % - 0.5 %), 5 mL

Restriction:	Restricted Benefit (General and Optometrical) Reduction of elevated intra-ocular pressure in a patient with open-angle glaucoma that is not adequately controlled with monotherapy. Reduction of elevated intra-ocular pressure in a patient with ocular hypertension that is not adequately controlled with monotherapy.
Maximum quantity:	1
Repeats:	5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Alcon agrees to the contents of this PSD.