PUBLIC SUMMARY DOCUMENT
Product: Bimatoprost with timolol maleate, eye drops, 0.3 mg - 5 mg (base) per mL (0.03%-0.5%), 3 mL, Ganfort®
Sponsor: Allergan Australia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application
The submission sought a restricted benefit listing for the reduction of elevated intraocular pressure in certain patients with open-angle glaucoma or ocular hypertension.

2. Background
This combination eye drop had not previously been considered by the PBAC.

3. Registration Status
Ganfort was registered by the TGA on 15 May 2009 for reduction of elevated intraocular pressure in certain patients with open-angle glaucoma or ocular hypertension.

4. Listing Requested and PBAC's View
Restricted Benefit
Reduction of elevated intra-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 or latanoprost eye drops or bimatoprost 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 or latanoprost eye drops or bimatoprost eye drops.

For PBAC's view, see Recommendation and Reasons

5. Clinical Place for the Proposed Therapy
This fixed combination product provides a therapeutic alternative to two mono-therapies of the respective components. Administration of a single product avoids the problem of 'wash out' where the first administered drug is physically 'washed out' of the eye by the second drug.

6. Comparator
The submission appropriately nominated the individual components bimatoprost 0.03% and timolol maleate 0.5%, given concomitantly as the main comparator
The submission also nominated two secondary comparators:
(1) Latanoprost with timolol maleate.
(2) Bimatoprost and timolol maleate each given as monotherapy.

7. Clinical Trials
The submission presented one randomised double-blinded non-inferiority trial (Study 026T) as key evidence in patients with glaucoma or ocular hypertension in which bimatoprost with timolol maleate, administered once daily in the morning, was compared:
(i) with concomitant use of bimatoprost once daily in the evening and timolol maleate twice daily; and
(ii) with bimatoprost alone once daily in the evening.

As supplementary evidence, the submission presented:
(i) one randomised, evaluator (outcome assessor)-blinded trial (Martinez 2007) in patients with glaucoma receiving either bimatoprost with timolol maleate administered once daily in the evening or a once daily evening dose of latanoprost and timolol (Xalacom®); and
(ii) three randomised double-blinded trials (Studies 018T, 021T, and 504T) in patients with glaucoma or ocular hypertension receiving bimatoprost with timolol or its individual components (bimatoprost and timolol maleate) given as monotherapy

The key trials published at the time of submission are shown below:

Trial ID/First Author	Protocol title/Publication title	Publication citation
Key trial (comparing Ganfort with concomitant use of the individual components)		
Study 026T		
Hommer A	A double-masked, randomized, parallel comparison of a fixed combination of bimatoprost 0.03%/timolol 0.5% with non-fixed combination use in patients with glaucoma or ocular hypertension.	European Journal of Ophthalmology 2007; vol 17 no.1:53-62
Hommer A, Wickstrøm J, Friis M M, et al	A cost-effectiveness analysis of fixed-combination therapies in patients with open-angle glaucoma: a European perspective.	Current Medical Research and Opinion 2008; vol. 24, No. 4, 1057–1063.
Katz LJ, Lewis RA, Batoosingh AL, Liu C; for the Ganfort® Investigators' Group II.	Bimatoprost/Timolol Fixed Combination: A one-year, double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension.	Poster presentation ARVO, Fort Lauderdale, May2007
Supplementary trial (comparing Ganfort with Xalacom**)**		
Martinez, A and Sanchez M, 2007	A comparison of the safety and intraocular pressure lowering of bimatoprost/timolol fixed combination versus latanoprost/timolol fixed combination in patients with open-angle glaucoma.	Current Medical Research and Opinion 2007; 23(5): 1025-1032.
Supplementary trials (comparing Ganfort with the individual components given as monotherapy)		
Study 021T		
Brandt JD, Cantor LB, Batoosingh AL, et al ; for the Ganfort® Investigators' Group	A 3-month, randomized study comparing bimatoprost/timolol fixed-combination therapy to monotherapy with bimatoprost or timolol in patients with glaucoma or ocular hypertension.	Poster presentation IGS, Athens, April 2007
Brandt J.D., Cantor L.B., Katz L.J., et al	Bimatoprost/timolol fixed combination: A 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension.	Journal of Glaucoma 2008 17(3): 211-216

8. Results of Trials

In the key trial (Study 026T), the primary endpoint was mean intraocular pressure (IOP) at each time point (Hours 0, 2, and 8) at day 0 and week 3 in the treatment naïve population. The results of the key trial are summarised below:

Mean IOP (mm Hg) at each scheduled time point in Study 026T: ITT

Time point		Ganfort N=178	Concomitant use of bimatoprost and timolol N=177	Ganfort vs Concomitant P-value Difference (95% CI)
Base-Line	Hr 0	26.2	26.4	0.410 -0.18 (-0.62,0.25)
	Hr 2	24.9	25.2	0.300 -0.29 (-0.83,0.26)
	Hr 8	23.7	23.9	0.400 -0.26 (-0.85,0.34)
Week 3	Hr 0	16.5	15.8	0.084 0.60 (-0.08,1.28)
	Hr 2	16.2	15.5	0.077 0.61 (-0.07,1.29)
	Hr 8	15.4	15.5	0.663 -0.15 (-0.80, 0.51)

ITT: Intention to treat (Note: the per-protocol results were consistent with the ITT results), Hr: Hour, CI: Confidence interval.

The table shows that at week 3, there was no statistically significant difference in mean IOP values between the Ganfort and concomitant arms at all time points. The pre-specified non-inferiority criteria in Study 026T stated that to demonstrate non-inferiority, the upper limit of the 95% confidence interval for the difference in mean IOP (fixed minus non fixed) was required to be less than 1.5mmHg for all 3 time points and less than 1.0mmHg for at least 2 time points at week 3.

In the supplementary trial (Martinez 2007), the key endpoint was mean IOP reduction at three time points from baseline to week 4, and the difference in mean diurnal IOP reduction from baseline to week 4. The results of Martinez 2007 are summarised below.

IOP reduction (mmHg) at week 4, unadjusted mean (SD) in Martinez 2007

	Xalacom	Ganfort	Difference (P value)
Week 4			
9.00am	2.2 (0.7)	3.2 (0.7)	1.0 (0.0002)
12.00noon	2.6 (0.8)	3.0 (1.2)	0.4 (0.1983)
3.00pm	1.8 (1.1)	2.2 (1.4)	0.4 (0.2844)
Diurnal	2.1 (0.6)	2.8 (0.9)	0.7 (0.0214)

SD = standard deviation, IOP : intraocular pressure

According to the above table, the unadjusted results illustrate that Ganfort has a superior effect at only one time point (9.00am), and on diurnal IOP over Xalacom.

The results of Study 026T suggested that overall the safety profile of Ganfort showed no notable difference to that of concomitant use of the individual components. The most frequently reported adverse event was conjunctival hyperaemia, reported less in the Ganfort arm (19.3%) compared to the concomitant arm (25.6%). The results of Martinez 2007 suggest that the frequency of most side effects reported was numerically higher in the Ganfort arm compared to the Xalacom arm. In particular, 44% of patients in the Ganfort arm experienced conjunctival hyperaemia compared to 22% in the Xalacom arm.

9. Clinical Claim

Based on the results of Study 026T, the submission claimed that bimatoprost with timolol (with single dosing of timolol) was non-inferior in terms of comparative effectiveness and comparable in terms of safety over concomitant use of the individual components (including two doses of timolol). The PBAC supported this claim.

The submission claimed that according to Martinez 2007, bimatoprost with timolol was superior in terms of comparative effectiveness over latanoprost with timolol. As there are small differences in IOP values between treatment groups at the scheduled time points, the submission claimed that bimatoprost with timolol was considered non-inferior in terms of comparative effectiveness over latanoprost with timolol.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. According to Study 026T, the equi-effective doses were estimated as bimatoprost with timolol one drop instilled once daily and concomitant bimatoprost 0.3mg/mL one drop instilled once daily plus timolol maleate 5mg/mL one drop instilled twice daily.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year were estimated in the submission to be between 10,000 – 50,000 in Year 5.

The submission argued that because the patients who received bimatoprost with timolol would have been treated with two prostaglandin analogue fixed combinations currently listed on the PBS (latanoprost with timolol and travoprost with timolol), there would be no net increase in cost to the PBS/RPBS should bimatoprost with timolol be listed.

12. Recommendation and Reasons

The PBAC recommended the listing of bimatoprost with timolol maleate on the PBS and also for inclusion in the Optometrical Schedule, in accordance with the combination guidelines, on a cost-minimisation basis compared with its constituent components, bimatoprost 0.03% and timolol maleate 0.5% eye drops given concomitantly.

The PBAC agreed that the comparison presented in the submission supported the claim of non-inferiority of bimatoprost with timolol maleate with the concomitant use of the individual components based on an acceptance that the difference in mean intra-ocular pressure (IOP) is less than than 1.5 mmHg.

The PBAC considered that while the pre-specified non-inferiority criteria were not met after adjustment for central corneal thickness, such adjustments have not been a consideration in previous PBAC recommendations for listing other eye drop products and therefore were not considered for this submission. The PBAC has also previously considered the diurnal variation in IOP reduction with different eye drop products but again considered that this issue was not pivotal to the consideration for PBS subsidisation.

The PBAC agreed with the sponsor and recommended changing the wording of the restrictions for all PBS-listed timolol with prostaglandin/prostamide analogue combinations

so that patients who are on a timolol/prostaglandin or prostamide analogue combination do not have to return to monotherapy with timolol prior to a change in the combination eye drop.

Recommendation

BIMATOPROST with TIMOLOL MALEATE, eye drops, 0.3 mg - 5 mg (base) per mL (0.03%-0.5%), 3 mL

Restriction: Restricted Benefit

Reduction of elevated intra-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 or prostaglandin or prostamide analogue monotherapies.

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 or prostaglandin or prostamide analogue monotherapies.

Max. Qty: 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

Allergan Australia welcomes this decision by the PBAC to provide access to a new treatment option for Australian's with ocular hypertension and open angle glaucoma.