PUBLIC SUMMARY DOCUMENT

Product: LATANOPROST with TIMOLOL MALEATE, eye drops, 50 micrograms-5 mg(base) per mL (0.005%-0.5%), 2.5 mL Xalacom®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

To provide the information requested by the PBAC in July 2005 when the Committee deferred an application seeking a Section 85 listing of Xalacom for the reduction of elevated intraocular pressure in certain patients with open-angle glaucoma and ocular hypertension.

2. Background

A submission for Xalacom was rejected by the PBAC its September 2001 meeting due to insufficient evidence of additional benefit of the combination over latanoprost monotherapy.

At the July 2005 meeting, the Committee deferred a decision on the listing of Xalacom as the re-submission to that meeting did not satisfactorily address the PBAC's concern that there was insufficient evidence of a clinically important improvement in effectiveness with this combination by adding timolol maleate to latanoprost administered once daily. The reported point estimates of -1.2mmHg (Trial 004) and -1.0mmHg (Trial 005) reduction in mean diurnal IOP between latanoprost + timolol maleate 0.5% fixed combination eye drops once daily and latanoprost 0.005% monotherapy once daily were less than the accepted non-inferiority margin of 1.5mmHg, and this was considered to suggest that the detected differences were not clinically important. The Pre-PBAC Response provided an abstract of a new small randomised cross-over trial (Konstas) which demonstrated a 2.5mmHg greater reduction in IOP for the combination over latanoprost monotherapy. Listing was deferred to request that the sponsor provide a meta-analysis of Trial 004 and the Konstas trial (accepting that Trial 005 could be excluded because the eye drops were administered at different times in the day, which might confound the extent of the additional effect of timolol maleate, and noting that no argument was presented by the sponsor to suggest that the effect of timolol maleate is similarly influenced by whether it is given in the morning or the evening)

3. Registration Status

Xalacom is registered by the TGA for "The reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins or other intraocular pressure lowering medications. Xalacom should not be used to initiate therapy."

4. Listing Requested and PBAC's View

Restricted Benefit:
Reduction of elevated intraocular pressure in patients with open angle glaucoma who are not adequately controlled with timolol maleate 5mg (base) per mL (0.5%) (bd) eye drops or who are insufficiently responsive to prostaglandins or other intraocular pressure lowering medication;
Reduction of elevated intra-ocular pressure in patients with ocular hypertension, who are not adequately controlled with timolol maleate 5mg (base) per mL (0.5%) eye drops or who are insufficiently responsive to prostaglandins or other intraocular pressure lowering medication.

The PBAC noted that the restriction recommended was not consistent with that for the other PBS-listed combination products, dorzolamide with timolol and brimonidine with timolol, in that with latanoprost and timolol, the PBAC recommended that patients inadequately controlled with either of the constituents may commence therapy with the combination. This broader restriction was recommended in recognition of superiority of latanoprost over timolol. For dorzolamide with timolol and brimonidine with timolol, use of the combination therapy is restricted to patients who fail timolol. Neither dorzolamide nor brimonidine has been shown to be superior to timolol and thus timolol would be the treatment choice over these agents.

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 nominated the unfixed combination of latanoprost and timolol (these two mono-therapies used in combination). This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented results from the Konstas trial and a meta-analysis of this trial and Trial 004. Preliminary results (in the form of a conference abstract) from the Konstas trial were first provided to the Committee as part of the pre-PBAC Response for the July 2005 Xalacom submission. Trial 004 was included in the July 2005 submission.

Thirty-nine patients were randomised in the Konstas trial. Two patients discontinued the trial early prior to the diurnal assessment and were excluded from the analysis.

Both studies had been published at the time of the submission, as follows:

Trial/First author	Protocol title	Publication citation
004/Pfeiffe, N	A comparison of the fixed combination of latanoprost and timolol with the individual components.	Greafes Archive for Clinical and Experimental Ophthalmology 2002; 240(11):893-09.
Konstas	Twenty-four hour control with latanoprost-timolol fixed combination therapy versus latanoprost therapy.	Arch. Ophthalmol 2005; (vol 123), July, 898-902.

As there were differences in the design of the Konstas and Trial 004 studies, only the first period data from Konstas was used in the meta-analysis.

8. Results of Trials

The submission claimed that the fixed effects model demonstrated a treatment difference between the fixed combination and latanoprost monotherapy of –1.51mmHg (-2.05, -0.97), whilst the random effects model demonstrated a treatment difference in favour of the fixed combination of -1.77mmHg (-3.03, 0.50). The submission added that the chi-squared test for heterogeneity result was p=0.04 indicating that the random effects model was the more appropriate result to consider.

The submission concluded that both analyses provided a point estimate greater than the PBAC-defined 'clinically significant difference', of greater than 1.5mmHg, further justifying the efficacy of the fixed combination latanoprost with timolol maleate eye drops.

For the PBAC's view on these results, see Recommendations and Reasons.

9. Clinical Claim

This submission appropriately did not make a clinical claim. However, the previous submission to the PBAC claimed that latanoprost with timolol maleate fixed combination eye drops once daily was no worse than concomitant latanoprost once daily and timolol maleate eye drops twice daily in terms of effectiveness and has similar or less toxicity.

The PBAC accepted this claim. See Recommendations and Reasons.

10. Economic Analysis

A cost-minimisation analysis was presented based on the current prices-to-pharmacist of the single agents.

11. Estimated PBS Usage and Financial Implications

The previous submission estimated the financial cost to the PBS to be < $10 million per year by year four of PBS listing.

12. Recommendation and Reasons

Consistent with its policy on fixed dose combination products, the PBAC recommended listing on a cost-minimisation basis, concluding that the meta-analysis of the Konstas trial and trial 004 provided a point estimate of a greater than 1.5 mmHg reduction in intra ocular pressure. The PBAC recalled that the data previously presented demonstrated that the fixed combination product showed non-inferiority to the comparator when administered in the evening.

The PBAC also acknowledged that there was a potential advantage in terms of patient compliance, though this was not the primary reason for the positive recommendation.

The PBAC's advice to the Pharmaceutical Benefits Pricing Authority (PBPA) is that latanoprost with timolol maleate should be priced on a mg per mg basis compared to the individual components, using half the daily dose of timolol maleate 0.5% to adjust for the once daily administration of the recommended combination product.

Recommendation:
List

Restriction:	<u>Restricted Benefit</u> Reduction of elevated intraocular pressure in patients with open angle glaucoma who are not adequately controlled with timolol maleate 5mg (base) per mL (0.5%) (twice daily) eye drops or who are insufficiently responsive to latanoprost or other intraocular pressure lowering medication; Reduction of elevated intra-ocular pressure in patients with ocular

	hypertension, who are not adequately controlled with timolol maleate 5mg (base) per mL (0.5%) eye drops or who are insufficiently responsive to latanoprost or other intraocular pressure lowering medication.
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