PUBLIC SUMMARY DOCUMENT
Product: Travoprost with timolol maleate, eye drops, 40 micrograms-5 mg (base) per mL (0.004%-0.5%), 2.5 mL Extravan®
Sponsor: Alcon Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application
Request for the listing of a new combination product as a Restricted Benefit for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension for whom a single agent therapy provides insufficient intraocular pressure reduction.

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

3. Registration Status
The TGA registered Extravan for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension for whom single agent therapy provides insufficient intraocular pressure reduction on the 15 July 2005.

4. Listing Requested and PBAC's View
Restricted benefit
Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are not adequately controlled with either a beta-blocker or a prostaglandin.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy
This fixed combination product would provide a therapeutic alternative to use of the two drugs separately.

6. Comparator
The submission nominated the individual components, travoprost 0.004% or timolol 0.5% given as monotherapy as the appropriate comparator.

The PBAC did not agree this was the appropriate comparator.

7. Clinical Trials
The submission presented three key trials (C-01-70, C-02-41 and C-01-69) and one supportive trial (C-02-03) in patients with glaucoma or ocular hypertension over three months including:

(i) one non-inferiority trial (C-01-70) comparing Extravan once daily (od) administered in the morning, with concomitant travoprost (od) administered in the evening and timolol maleate (od) administered in the morning;
(ii) one non-inferiority trial (C-02-41) comparing Extravan (od) administered in the morning, with (a) concomitant travoprost (od) administered in the evening and timolol maleate (od) administered in the morning, and (b) timolol maleate monotherapy twice daily (bd); and
(iii) one randomised trial (C-01-69) comparing Extravan (od) administered in the morning,

with (a) travoprost monotherapy (od) administered in the evening, and (b) timolol maleate monotherapy (bd); and

one supporting randomised equivalence trial (C-20-03) comparing Extravan (od) administered in the morning and Extravan (od) administered in the evening in patients with glaucoma or ocular hypertension over six weeks.

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

Trial Author	Protocol Title	Publication
C-01-7002-41 Schuman JS	Efficacy and Safety of a Fixed Combination of Travoprost 0.004%/Timolol 0.5% Ophthalmic Solution Once Daily for Open-Angle Glaucoma or Ocular Hypertension	*Am J Ophthalmol* 2005; 140:242-50.
C-01-69 [a] Barneby HS	The Safety and Efficacy of Travoprost 0.004%/ Timolol 0.5% Fixed Combination Ophthalmic Solutions with open-angle glaucoma or ocular hypertension	*Am J Ophthalmol* 2005; 140:1-7.

8. Results of Trials

The pre-specified non-inferiority criterion of 1.5 mmHg for the combination versus the two components administered separately was not met at all the pre-specified individual time points in trials C-01-70 and C-02-41. The criteria were met at five of the nine time points in trial C-01-70 and four of the nine time points in trial C-02-41, in the per protocol analyses.

There was a statistically significant difference in reduction of intra-ocular pressure (IOP) in trials C-02-41 and C-01-69, favouring Extravan (od) versus timolol maleate monotherapy (bd) at all time points at Month 3, and versus travoprost monotherapy (od) at one of the three time points at Month 3.

Adverse events reported in the randomised trials were mild to moderate in severity. The most common adverse event for patients in the Extravan (od), concomitant travoprost (od) and timolol maleate (od), and travoprost monotherapy (od) trial arms was ocular hyperaemia. The most common adverse event in the timolol maleate trial arms was ocular discomfort.

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

9. Clinical Claim

The submission claimed that Extravan (od) eye drops:

(i) were no worse than concomitant travoprost (od) and timolol maleate eye drops (od) in terms of effectiveness and have similar or less toxicity;

(ii) had significant advantages in effectiveness versus travoprost (od) or timolol maleate (od) monotherapy and had similar or less toxicity.

For PBAC's comments on Clinical Claim, see Recommendations and Reasons.

10. Economic Analysis

The submission did not provide a preliminary economic evaluation based on evidence from the comparative randomised trials. However, the submission did include the comparative cost of Extravan and the constituent therapies, travoprost and timolol maleate.

The choice of the cost-minimisation approach was not appropriate as the PBAC considered that the evidence did not convincingly demonstrate that Extravan was non-inferior to concomitant travoprost and timolol.

The submission did not present a modelled economic evaluation. The costs of possible impacts on other pharmaceutical prescriptions and on other health services were not considered.

11. Estimated PBS Usage and Financial Implications

The submission estimated that if Extravan were listed there would be financial savings to the PBS of up to $100,000 in the third year of listing.

12. Recommendation and Reasons

The PBAC in considering evidence did not accept that the submitted data showed that Extravan has sufficient additive benefit over travoprost, or that it is as effective as the two components given concomitantly.

The PBAC considered that concomitant travoprost 0.004% instilled once daily in the evening (od pm), and timolol maleate 0.5% instilled twice daily (bd), is the therapy which most prescribers will replace in practice with Extravan instilled once daily in the morning (od am) and thus this would have been the most appropriate comparison for the submission. No trial presented assessed this particular comparison.

The PBAC noted that trials C-02-41 and C-01-69 presented comparisons of the combination product with each of its component products administered as monotherapy, which is relevant to the assessment of whether it has an additive effect over these components as provided for in the PBAC's Fixed Combination Product Guidelines. The PBAC noted that there was a statistically significant difference in reduction of intraocular pressure (IOP) in these trials, favouring Extravan (od am) versus timolol maleate monotherapy (bd) at all time points at Month 3, and versus travoprost monotherapy (od pm) at one of the three time points at Month 3. The PBAC has previously agreed that a reduction in IOP of >1.5mmHg is clinically important. Therefore, the improvement in effectiveness of Extravan (od am) over timolol maleate monotherapy (bd) and any improvement in effectiveness of Extravan (od am) over travoprost monotherapy (od pm) may not be clinically important, given the mean IOP reduction at some time points, and given the 95% confidence intervals consistently included unimportant IOP differences.

Although there is likely to be confounding by the difference in timing of the dosing of travoprost (which is consistent with the TGA-recommended dosing which varies depending on whether it is instilled as monotherapy or in the combination product), the PBAC considered there was uncertainty over the submission's claims that Extravan (od am) has statistically significant advantages in effectiveness versus travoprost (od pm) monotherapy, and that it has similar or less toxicity. Extravan (od am) is statistically significantly more effective than timolol maleate monotherapy (bd) at lowering IOP; however the advantage over travoprost (od pm) is of equivocal statistical significance. The PBAC therefore considered there was uncertainty about whether Extravan meets the PBAC Fixed Combination Product Guidelines in terms of demonstration of superiority over travoprost monotherapy.

Trials C-01-70 and C-02-41 provide the closest data to the appropriate comparison for the submission, but compared the combination product to concomitant travoprost (od pm) and timolol maleate (od am) rather than concomitant travoprost (od pm) with timolol maleate (bd). These prospectively designed non-inferiority trials raised similar doubt about the claims that Extravan (od am) is no worse than concomitant travoprost (od pm) and timolol maleate eye drops (od am) in terms of effectiveness, and that it has similar or less toxicity. This is because they did not meet the pre-specified non-inferiority criteria at all time points. Given these doubts about the claim of "non-inferiority" compared with concomitant travoprost (od) and timolol maleate eye drops (od), there was considerable uncertainty as to whether Extravan (od) is no worse than the appropriate comparator, concomitant travoprost (od) and timolol maleate eye drops (bd) in terms of effectiveness and that it has similar or less toxicity.

The PBAC recognised the importance of compliance and that it is likely that Extravan would assist in this regard, particularly in the elderly, who may have poor technique. However, no data were provided to substantiate this claim.

The PBAC therefore decided to reject the submission because the evidence does not convincingly demonstrate that Extravan has additive beneficial effectiveness over the travoprost component, or that it is no worse than its two components given concomitantly.

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