PUBLIC SUMMARY DOCUMENT

Product: Travoprost with Timolol Maleate, eye drops, 40 micrograms-5 mg (base) per mL (0.004%-0.5%), 2.5 mL, DuoTrav®.

Sponsor: Alcon Laboratories (Australia) Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought a restricted benefit PBS listing 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.

2. Background

A submission for Extravan® (previous brand name for DuoTrav®) was previously rejected by the PBAC at the November 2005 meeting because the PBAC did not accept that the evidence convincingly demonstrated that DuoTrav has additive beneficial effectiveness over the travoprost component, or that it is no worse than its two components given concomitantly.

3. Registration Statusb

DuoTrav was registered with TGA on 8 September 2006 (the product was originally registered as Extravan® in July 2005) 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.

4. Listing Requested and PBAC's View

Restricted benefit
Reduction of elevated intraocular pressure in patients with ocular hypertension, who are not adequately controlled with timolol maleate 5 mg (base) per mL (0.5%) eye drops or who are insufficiently responsive to prostaglandins or other intraocular pressure lowering medication.

For the PBAC's view, see Recommendations 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 nominated as the comparator:

(1) the fixed dose combination of latanoprost with timolol maleate (Xalacom®); and
(2) concomitant administration of travoprost and timolol maleate.

7. Clinical Trials

The submission provided:

(1) A comparison of DuoTrav with Xalacom. A new head-to-head non-inferiority trial (C-02-28) data was presented in the re-submission, comparing DuoTrav with the fixed dose combination of latanoprost and timolol maleate in patients with open angle glaucoma or ocular hypertension over 12 months.
(2) A comparison of DuoTrav with concomitant administration of travoprost and timolol maleate. A re-analysis of trial data in the previous submission by averaging the three diurnal IOP measurements at 08:00, 10.00 and 16:00 to obtain a mean diurnal IOP.

The trials published at the time of the submission were:

Trial/First author	Protocol/Publication title	Publication citation
C-01-70/ Schuman, JS et al	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.	American Journal of Ophthalmology 2005 140(2): 242-50.
C-02-41/ Hughes, BA et al	A three-month, multicenter, double-masked study of the safety and efficacy of travoprost 0.004%/timolol 0.5% ophthalmic solution compared to travoprost 0.004% ophthalmic solution and timolol 0.5% dosed concomitantly in subjects with open angle glaucoma or ocular hypertension.	Journal of Glaucoma 2005; 14(5): 392-399.
C-01-69/ Barnebey, HSS et al	The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution.	Am J Ophthalmol 2005 140(1): 1-7.

8. Results of Trials

In the comparison of DuoTrav with Xalacom the mean IOP was lower in the DuoTrav treatment group than in the Xalacom treatment group for all study visits. The per-protocol results demonstrated that DuoTrav was non-inferior to Xalacom – all upper 95% CI were within 1.5mmHg at 10 of 10 study visits and times. The ITT results were consistent with that from the per-protocol analysis.

The re-analyses of the trials C-01-70 and C-02-41 showed that the pre-specified non-inferiority criteria were met at all study visits, for the comparison between DuoTrav and concomitant administration of travoprost and timolol.

In the comparison of DuoTrav with Xalacom, a total of 205 of the 407 patients (50.4%) participating in the study reported adverse events, which included 114 of the 207 patients (55.1%) with exposure to DuoTrav and 91 of the 200 patients (45.5%) with exposure to Xalacom. This difference was not statistically significant.

The most frequently reported treatment-related adverse event in those patients randomised to receive DuoTrav was ocular hyperaemia occurring with an incidence of 15.0% (versus 2.5% in the Xalacom group).

In the comparison of DuoTrav with concomitant administration of travoprost and timolol maleate, no new toxicity data were presented in the re-submission.

9. Clinical Claim

The re-submission described DuoTrav as being no worse than either the concomitant administration of travoprost and timolol or the fixed dose combination of latanoprost and timolol in terms of effectiveness and toxicity.

10. Economic Analysis

The cost-minimisation approach was valid given the assumption of non-inferiority.

The equi-effective doses were the fixed dose combination of travoprost 40µg/mL (0.004%) and timolol 5mg/mL (0.5%), one drop instilled once daily and the fixed dose combination of latanoprost 50µg/mL (0.005%) and timolol 5mg/mL (0.5%), one drop instilled once daily. This relativity was based on one non-inferiority trial with a pre-specified non-inferiority margin of <1.5mmHg.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was in the range of 10,000 – 50,000 in Year 3, while the financial cost per year to the PBS was < $10 million in Year 3.

12. Recommendation and Reasons

The PBAC recommended listing on a cost minimisation basis with Xalacom® (latanoprost 0.005% with timolol 0.5%). The equi-effective doses are the fixed dose combination of travoprost 40µg/mL (0.004%) with timolol 5mg/mL (0.5%), one drop instilled once daily and the fixed dose combination of latanoprost 50µg/mL (0.005%) and timolol 5mg/mL (0.5%), one drop instilled once daily. This recommendation is based on the results of one head to head non-inferiority trial (C-02-28) with a pre-specified non-inferiority margin of <1.5mmHg. The per-protocol results of this trial demonstrated that travoprost 40µg/mL (0.004%) with timolol 5mg/mL (0.5%) is non-inferior to Xalacom® – all upper 95% CI were within 1.5mmHg at 10 of 10 study visits and times. The ITT results were consistent with that from the per-protocol analysis.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation

Travoprost with Timolol Maleate, eye drops, 40 micrograms-5 mg (base) per mL (0.004%-0.5%), 2.5 mL

Restriction: Restricted Benefit

Reduction of elevated intraocular 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 travoprost 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 travoprost eye drops.

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

The sponsor had no comment.