PUBLIC SUMMARY DOCUMENT
Product: Dorzolamide hydrochloride with timolol maleate, eye drops 20 mg (base)-5 mg (base) per mL (2%-0.5%), single dose units 0.6 mL, 60, Cosopt® Preservative Free Eye Drops
Sponsor: Merck Sharp and Dohme (Australia) Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application
To request Restricted Benefit listings in the general and optometrical schedules for the reduction of elevated intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension that is not adequately controlled with monotherapy.

2. Background
This was the first submission for dorzolamide with timolol preservative free fixed dose combination eye drops (PF-dorz/tim).

3. Registration Status
Dorzolamide 2 % with timolol 0.5 % preservative free eye drops was registered by the TGA on 7 April 2011 for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma when concominant therapy is appropriate.

4. Listing Requested and PBAC's View
General Schedule:
Restricted Benefit
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.

Optometric Schedule:
Restricted Benefit
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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Glaucoma is a progressive chronic disease characterised by elevated intraocular pressure. The submission stated the current treatment algorithm for glaucoma consists of initial monotherapy with a prostaglandin analogue or a beta-blocker. If the patient requires further IOP lowering, dual therapy, consisting of either a prostaglandin analogue with beta-blocker combination, or a carbonic anhydrase inhibitor with beta-blocker combination is recommended. The submission proposed that dorzolamide with timolol PF will be used in

place of the preservative containing dorzolamide with timolol or brinzolamide with timolol primarily in patients who are intolerant to preservatives.

6. Comparator

The submission nominated the preservative containing dorzolamide with timolol (PC-dorz/tim) formulation as the comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented one randomised double-blinded, single centre study (P081) comparing PF-dorz/tim twice daily with PC-dorz/tim twice daily in 261 patients with ocular hypertension and open angle glaucoma over 14 weeks.

The primary outcome of P081 trial was a reduction in intra-ocular pressure (IOP) from baseline to week 12 at trough (just prior to morning dose) and a change in IOP at peak (2 hours after the morning dose). Variations in visual acuity, visual field defects, visual field global indices, cup to disk ratios and safety were secondary outcomes.

Trial P081 was designed as a non-inferiority trial and the predefined margin for non-inferiority was -1.5 mmHg to 1.5 mmHg. This margin was previously accepted by the PBAC.

The table below details the published trials presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Trial P081/Hutzelmann J.	A Multiple-Dose, double-Masked, parallel, active treatment controlled study of preservative-free 2.0% dorzolamide/0.5% timolol combination and 2.0% dorzolamide/0.5% timolol combination with preservative in patients with elevated IOP	(Protocol 081)
Shedden A, et al. (2010)	Comparison of the efficacy and tolerability of preservative-free and preservative-containing formulations of the dorzolamide/timolol fixed combination (COSOPT) in patients with elevated intraocular pressure in a randomized clinical trial.	Graefes Arch Clin Exp Ophthalmol; 248:1757 – 1764.

8. Results of Trials

The results of the key randomised trial P081 from the primary analysis of all treated patients whose post-baseline intraocular pressure (IOP) data are available (referred to as APT-LOCF analysis) are summarised below.

Trough IOP (mmHg) summary results at Week 12 by treatment and estimated difference between treatments. APT-LOCF - Worse eye

Treatment	N	Baseline mean (SD)	Study value mean (SD)	Change mean (SD)	Difference in mean change (SE)[†]	95% CI	Difference between treatments lies between -1.5 and 1.5[*]
PF-dorz/tim	130	23.7 (1.5)	20.8 (2.6)	-2.9 (2.3)	-0.31 (0.28)	-0.86, 0.23	>0.999

PC-dorz/tim	128	23.7 (1.5)	21.1 (2.5)	-2.6 (2.2)			

IOP= intra-ocular pressure, APT-LOCF = All Patients Treated-Last Observation carried forward.
[†]Difference in mean change of IOP (mmHg) between treatments is based on day -1 baseline and computed as PF-dorz/tim – PC dorz/tim.
[*]The probability that the difference between treatments lies between -1.5 and 1.5 mmHg is 0.950 or more

The baseline IOP measurements were identical between the treatment arms. After 12 weeks of treatment, the trough IOP was reduced by a mean of 2.9 mmHg in the PF-dorz/tim treatment group compared with a reduction of 2.6 mmHg in the PC-dorz/tim treatment group. The between-group differences were -0.31 mmHg (95% CI -0.86, 0.23), in favour of the preservative free formulation, which were within the predefined non-inferiority limits.

The per-protocol (PP) analysis of the primary outcome of trough IOP at Week 12 and both the APT-LOCF and PP analyses of secondary outcomes of trough IOP at Weeks 2 and 6 and peak IOP at Weeks 2, 6 and 12 also confirmed the non-inferiority of PF-dorz/tim to PC-dorz/tim.

The proportions of patients who experienced an adverse event while receiving treatment with PF-dorz/tim or PC-dorz/tim were 26.7% and 33.8% respectively. More patients discontinued from treatment due to drug-related adverse events in the PF-dorz/tim than in the PC-dorz/tim arm.

The submission also presented safety data from the most recent periodic safety update report (PSUR) for dorzolamide/timolol (both PF- and PC-dorz/tim). During this period (19 Feb 2011 to 18 Aug 2011), there was one individual case safety report of a fatal outcome, a myocardial infarction. There had been no safety related updates to the Core Company Data Sheet during this PSUR reporting period.

9. Clinical Claim

The submission described PF-dorz/tim as non-inferior in terms of both comparative effectiveness and comparative safety to PC-dorz/tim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis assuming that the treatment costs with PF-dorz/tim and with PC-dorz/tim over a year of treatment are the same but associated with different levels of wastage for these two formulations.

On the basis of an analysis of Medicare Australia data (concessional patients), different levels of wastage for PF-dorz/tim and PC-dorz/tim were included in the cost minimisation approach.

The equi-effective doses were estimated as PF-dorz/tim (2% dorzolamide, 0.5% timolol) twice daily and PC-dorz/tim (2% dorzolamide, 0.5% timolol) twice daily. The equi-effective doses were estimated based on the key trial P081. The estimation of equi-effective doses was considered reasonable.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission did not provide an estimate for the likely number of patients treated.

The submission estimated a total net cost to the PBS of less than $10 million over the first 5 years, excluding co-payments.

12. Recommendation and Reasons

The PBAC recommended listing dorzolamide hydrochloride with timolol maleate eye drops, preservative free, on the PBS as Restricted Benefit listings in the General and Optometrical Schedules for the reduction of elevated intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension that is not adequately controlled with monotherapy. Listing should be on a cost minimisation basis with dorzolamide hydrochloride with timolol maleate eye drops (preservative containing). The equi-effective doses are one drop of dorzolamide hydrochloride with timolol maleate eye drops preservative free (PF) twice daily and one drop of dorzolamide hydrochloride with timolol maleate eye drops preservative containing (P) twice daily.

The PBAC considered Trial P081 provided a sufficient basis to conclude that dorzolamide hydrochloride with timolol maleate eye drops (PF) are non-inferior for both efficacy and safety to dorzolamide hydrochloride with timolol maleate eye drops with preservative, in terms of lowering intra-ocular pressure and the secondary outcomes assessed in the trial.

The PBAC noted that the submission did not present any evidence regarding efficacy or safety of dorzolamide hydrochloride with timolol maleate eye drops (PF) compared to dorzolamide hydrochloride with timolol maleate eye drops (P) in patients sensitive to preservatives in eye drops. Therefore, no conclusions could be drawn about any differences in efficacy or safety between dorzolamide hydrochloride with timolol maleate eye drops (PF) and dorzolamide hydrochloride with timolol maleate eye drops P in this patient population.

The PBAC did not accept the claims proposed in the submission about different amounts of wastage for dorzolamide hydrochloride with timolol maleate eye drops (PF) compared to dorzolamide hydrochloride with timolol maleate eye drops (P). The PBAC recommended the listing on a cost minimisation basis based on equi-effective doses, excluding any difference in wastage costs. The PBAC considered that the listing should not result in any additional cost to the PBS.

The PBAC recommended that dorzolamide hydrochloride with timolol maleate eye drops (PF) are not suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

The PBAC decided it was not satisfied as required by subsection 101(4AC) of the *National Health Act 1953* and therefore it will not provide advice to the Minister under that section in relation to the following combination item: DORZOLAMIDE HYDROCHLORIDE with TIMOLOL MALEATE, eye drops 20 mg (base)-5 mg (base) per mL (2%-0.5%), single dose units 0.6 mL, 60, Cosopt® Preservative Free Eye Drops. The PBAC noted that as no relevant

evidence was presented in relation to compliance, efficacy or toxicity for this combination item compared to alternative therapies, there was no basis to conclude that this combination item satisfied the requirements specified in Subsection 101(4AC).

Recommendation:
DORZOLAMIDE HYDROCHLORIDE with TIMOLOL MALEATE, eye drops 20 mg (base)-5 mg (base) per mL (2%-0.5%), single dose units 0.6 mL, 60

Restriction:	Restricted Benefit 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.
Max qty:	1
Rpts:	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 has no comments.