PUBLIC SUMMARY DOCUMENT
Product: TAFLUPROST, eye drops, 15 micrograms per mL (0.0015%), single dose units, 0.3 mL, 30, Saflutan®
Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission sought an unrestricted benefit listing on the General and Optometrical Schedules, for the treatment of ocular hypertension and primary open-angle glaucoma.

2. Background

This drug had not previously been considered by the PBAC.

A submission to the PBAC was initially lodged for consideration at the July 2011 PBAC meeting but was withdrawn by the sponsor shortly after consideration by the ESC in June 2011 following notification from the TGA that the product had not received registration.

3. Registration Status

Tafluprost was TGA registered on 14 February 2012 for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension, as monotherapy or as adjunctive therapy to beta blockers.

4. Requested Listing and PBAC's View

Section 85 – General Schedule
Unrestricted benefit

Optometrical Schedule
Unrestricted benefit

For PBAC's view, see Recommendation and Reasons.

5. Clinical place for the proposed therapy

Glaucoma is a progressive chronic disease characterised by elevated IOP. Prostaglandin analogue (PGA) therapy is currently first-line therapy for ocular hypertension and open angle glaucoma. Some patients may be prescribed beta-blocker therapy initially.

The submission proposed that the place in therapy of tafluprost is as an alternative first line therapy to existing prostaglandin analogues and as an add-on therapy for patients requiring multiple drugs to lower IOP. As tafluprost is available in single dose units which are preservative free, the submission claimed that it may be of benefit for patients who are intolerant of or hypersensitive to benzalkonium chloride preservative.

6. Comparator

The submission nominated latanoprost 0.005% with preservative (latanoprost-P) as the main comparator. The PBAC agreed that this was the appropriate comparator.

7. Clinical trials

No trials were available that directly compared preservative-free (PF) tafluprost and latanoprost-P. Trials 74458, TFL01 and 74457 compared tafluprost-P one drop, once daily per affected eye with latanoprost-P, at the same dose regimen, in patients with open-

angle glaucoma or ocular hypertension. As Trials 74458, TFL01 and 74457 used tafluprost-P, rather than tafluprost-PF, the submission included a pharmacodynamic crossover trial comparing tafluprost-PF with tafluprost-P (Trial 77550) to support the equivalence of the two formulations (PF and P).

The submission also presented a single arm study (Study 77552) where patients switched from latanoprost-P to tafluprost-PF. Subjects in the study were patients with open-angle glaucoma or ocular hypertension who had been treated with latanoprost-P for at least 6 months but were experiencing ocular signs or symptoms.

The submission did not provide any evidence regarding the use of tafluprost-PF as an adjunct to beta-blockers for the treatment of ocular hypertension and open-angle glaucoma.

Details of the trials published at the time of submission are presented in the table below.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials: tafluprost-P versus latanoprost-P		
Trial 74458 Uusitalo H et al.	Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study.	Acta Ophthalmologica 2010; 88(1): 12-19.
Trial 74457 Papadia M et al. Traverso C et al.	A pilot phase II study on the extent, duration of action and stability of the IOP lowering effect of tafluprost 0.0015%, a novel prostaglandin analogue, as compared to latanoprost 0.005%. A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of tafluprost compared with latanoprost.	Investigative Ophthalmology & Visual Science 2006; 47: conference abstract. Journal of Ocular Pharmacology and Therapeutics 2010; 26(1): 97-104.
Crossover trial: tafluprost-PF versus tafluprost-P		
Trial 77550 Hamacher T et al.	Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from pharmacodynamics analysis.	Acta Ophthalmologica 2008 Supplement; 242: 14-19.
Single-arm study: switching from latanoprost-P to tafluprost-PF		
Study 77552 Uusitalo H et al.	Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication.	Acta Ophthalmologica 2010; 88(3): 329-336.

P = preserved; PF = preservative free

8. Results of trials

Tafluprost-P versus latanoprost-P

The submission specified a minimal clinically important difference (MCID) of 1.5 mmHg for change of IOP from baseline. The PBAC had previously accepted this MCID as the upper confidence interval (CI). This has been used in a number of clinical trials investigating the treatment effect of PGAs in patients with open-angle glaucoma or ocular hypertension.

The primary analysis in Trial 74458 was a repeated measurements (RM) analysis of covariance (ANCOVA). The model included fixed effects for baseline IOP, pooled centre (Trial 74458 was conducted in 8 countries at 49 centres), treatment, visit and time, and all interactions among treatment, visit and time. RM analysis of variance (ANOVA, without baseline IOP as a covariate) was included as a sensitivity analysis. Both the primary analysis and the sensitivity analysis were performed on a modified intention-to-treat (mITT) basis and on a per protocol (PP) basis.

The results of Trial 74458, in terms of change in IOP, are presented in the two tables below.

Difference in absolute change in diurnal IOP from baseline at Month 6 – Trial 74458

	N	Difference in change[a] (mmHg)	95% CI[b] (mmHg)
Primary analyses (RM ANCOVA)			
PP population	467	1.29	[0.89, 1.69]
mITT population	511	1.44	[1.04, 1.84]
Sensitivity analyses (RM ANOVA)			
PP population	467	0.93	**[0.45, 1.41]**
mITT population	511	1.08	[0.60, 1.56]

CI = confidence interval; IOP = intraocular pressure; mITT = modified intention-to-treat; PP = per protocol; RM = repeated measures

Note: Bolded typography indicates that the pre-specified non-inferiority criterion of 1.5 mmHg was satisfied

[a] Tafluprost-P – latanoprost-P. A positive difference indicates a greater reduction in IOP in the latanoprost-P arm than in the tafluprost-P arm.

[b] The lower bounds of the 95% CIs were calculated during the evaluation and revealed that in all analyses tafluprost-P was statistically inferior to latanoprost-P.

Latanoprost-P was statistically superior to tafluprost with preservative (tafluprost-P) in terms of IOP reduction for all analyses at both month 6 and month 24 in Trial 74458. Tafluprost-P failed to meet the non-inferiority criterion of 1.5 mmHg compared with latanoprost-P in terms of IOP reduction in the primary (ANCOVA) analyses of Trial 74458.

In the 24-month analysis of Trial 74458, tafluprost-P met the non-inferiority criterion in both PP and mITT populations in the sensitivity analyses (using the ANOVA model which did not control for baseline IOP); however a non-inferiority claim of tafluprost-P versus latanoprost-P in reducing IOP was not supported by the results from the primary analyses where there was adjustment of baseline IOP.

Difference in absolute change in diurnal IOP from baseline at Month 24 – Trial 74458

	N	Difference in change[a] (mmHg)	95% CI[b] (mmHg)
Primary analyses (RM ANCOVA)			
PP population	377	1.07	[*0.59*, 1.55]

mITT population	409	1.15	[*0.68*, 1.62]
Sensitivity analyses (RM ANOVA)			
PP population	377	0.75	**[*0.18*, 1.32]**
mITT population	409	0.81	**[*0.23*, 1.39]**

CI = confidence interval; IOP = intraocular pressure; mITT = modified intention-to-treat; PP = per protocol; RM = repeated measures

Note: Bolded typography indicates that the pre-specified non-inferiority criterion of 1.5mmHg was satisfied

[a] Tafluprost-P – latanoprost-P. A positive difference indicates a greater reduction in IOP in the latanoprost-P arm than in the tafluprost-P arm.

[b] The lower bounds of the 95% CIs were calculated during the evaluation and revealed that in all analyses tafluprost-P was statistically inferior to latanoprost-P.

In trial TFL01 the decrease in IOP from baseline at the end of treatment (week 4 or discontinuation) was no worse in patients treated with tafluprost-P than those treated with latanoprost-P. The upper bounds of the 95% CIs in the primary analyses were below the specified MCID of 1.5 mmHg for both mITT and PP populations.

For both repeated measurements analysis of variance (RM ANOVA) and repeated measurements analysis of covariance (RM ANCOVA) analyses in Trial 74457, the upper bounds of the 95% CI for the treatment effect of reducing IOP at the end of the 6 week treatment period fell within the non-inferiority limit of 1.5 mmHg.

In terms of drug-related ocular and non-ocular adverse events, there were more incidences of "any" drug-related adverse event, ocular adverse events and non-ocular adverse events in patients treated with tafluprost-P compared to those treated with latanoprost-P in trials 74458 and TFL01. Ocular adverse events, such as eye pain and conjunctival hyperaemia, occurred more frequently in patients treated with tafluprost-P. Inferiority of tafluprost-P versus latanoprost-P was observed in terms of conjunctival hyperaemia at month 12 in Trial 74458 (RR: 2.3 [1.2, 4.2]). Trials 74458 and TFL01 were not sufficiently statistically powered to reliably assess the non-inferiority of tafluprost-P relative to latanoprost-P in terms of other drug-related ocular adverse events, including eye pain. Trial 74457 was too small to reliably assess adverse events between the treatment arms.

Tafluprost-PF versus tafluprost-P

The results of the pharmacodynamic crossover trial comparing tafluprost-PF and tafluprost-P are presented in the following table.

Difference in change from baseline in diurnal IOP at Week 4 – Trial 77550

	N	Difference in change[a] (mmHg)	95% CI (mmHg)
Primary analyses (RM ANCOVA)			
PP population	41	-0.05	**[-0.52, 0.42]**
ITT population	43	0.01	**[-0.46, 0.49]**
Secondary analyses (RM ANOVA)			
PP population	41	-0.14	**[-1.00, 0.73]**
ITT population	43	-0.12	**[-0.95, 0.71]**

CI = confidence interval; IOP = intraocular pressure; ITT = intention-to-treat; PP = per protocol.

Note: Bolded typography indicates that the equivalence range of -1.5 to 1.5mmHg was satisfied.

[a] Tafluprost-PF – tafluprost-P. A negative difference indicates a greater reduction in IOP in the tafluprost-PF arm. A positive difference indicates a greater reduction in IOP in the tafluprost-P arm.

Trial 77550 was a crossover trial in which all patients were treated with tafluprost-PF or tafluprost-P (Treatment phase 1) and then switched to the other treatment (Treatment phase 2). Patients were treated for a period of 4 weeks each, with a wash-out period of at least 4 weeks between treatments. The analysis combined the results of patients on treatment with tafluprost-PF in Treatment phases 1 and 2 and that of tafluprost-P in Treatment phases 1 and 2. The pre-specified equivalence range (from -1.5 mmHg to 1.5 mmHg) in IOP change was satisfied for all analyses. It was unclear whether the selection of patients with a known positive treatment response (a 15% reduction in IOP) to prior PGA therapies at randomisation was appropriate for demonstrating the equivalence treatment effect of the two tafluprost formulations in the PBS target population.

There was a total of 20 ocular adverse events reported by 11 (25.6%) patients for the unpreserved formulation of tafluprost across the two treatment phases. Meanwhile seven ocular adverse events were reported by six (14.3%) patients treated with tafluprost-P. Tafluprost-PF provided no additional safety benefit, relative to tafluprost-P, in terms of ocular adverse events in patients without a known allergy or hypersensitivity to the study medications or their components, including the preservative benzalkonium chloride (BAK), the main preservative in PGA eye drops.

Switching from latanoprost-P to tafluprost-PF

Patients enrolled in Study 77552 had been treated with latanoprost-P for at least 6 months and had a minimum of two ocular symptoms/signs at randomisation. Baseline mean IOP was within the normal range (10 – 21 mmHg). The primary outcomes of this study were changes in ocular symptoms and signs upon non-instillation and change from baseline in conjunctival inflammatory markers at week 6 and 12. The results of the secondary outcome of change in IOP reported in Study 77552 indicated that control of IOP was maintained after switching from latanoprost-P to tafluprost-PF during a 12-month treatment period.

Reductions in both ocular symptoms and signs were observed in Study 77552 after patients switched from treatment with latanoprost-P (baseline) to tafluprost-PF (Weeks 6 and 12). However, all patients switched to treatment with tafluprost-PF from latanoprost-P, so the results did not inform whether the reported ocular symptoms or signs may have resolved if latanoprost-P was continued.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described tafluprost-PF as non-inferior in terms of comparative effectiveness and superior in terms of comparative tolerability over latanoprost-P.

The PBAC did not accept the claim of non-inferiority, noting that the PSCR accepted that the trial 74458 failed to meet the criteria for non-inferiority. The PBAC did not accept the claim of superior tolerability of tafluprost-PF compared to latanoprost-P, *see Recommendations and Reasons*.

10. Economic Analysis

The submission presented a cost analysis. This approach was appropriate only if the PBAC accepted the claim of non-inferiority of tafluprost-PF to latanoprost-P, which it did

not. The PSCR accepted that the relative reduction in IOP is better with latanoprost than tafluprost. In the PSCR this difference was calculated as 8.6% however this was arithmetically incorrect and was recalculated as 13.65% for the ESC Advice.

The submission claimed that tafluprost-PF one drop daily to an affected eye is equi-effective to latanoprost-P one drop daily to an affected eye.

The approach to estimating the proposed price of tafluprost-PF in the submission was not appropriate, given that: 1) the inclusion of PF-artificial tears as a cost off-set associated with tafluprost-PF was based on the assumption that tafluprost-PF had superior safety/tolerability when compared with latanoprost-P, which was not supported by the evidence presented in the submission; 2) the difference in wastage between latanoprost-P and tafluprost-PF remained uncertain, with an assumption of zero wastage of tafluprost-PF being unrealistic; and 3) even if the submission's assumptions regarding PF-artificial tears (10.5% patients treated with latanoprost-P requiring concomitant artificial tears) and drug wastage (12.17 packs of tafluprost-PF vs. 14.86 packs of latanoprost-P per year) were accepted, tafluprost-PF was not cost minimising relative to latanoprost-P when the whole target population was considered.

The PSCR proposed a revised cost analysis resulting in a new dispensed price for maximum quantity (DPMQ) with the following assumptions:

1. A reduced price to compensate for the difference in efficacy of tafluprost-P to latanoprost-P in trial 74458 equivalent to the percentage difference in IOP reduction from baseline;
2. Inclusion of an additional prescription of tafluprost-PF to account for wastage; and
3. A reduction in the cost-offset for PF-artificial tears to take into account those patients sensitive to preservatives who may not benefit from a switch to tafluprost-PF.

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the number of prescriptions dispensed in Year 5 of listing was between 400,000 and 500,000. The net financial cost to the PBS was estimated in the submission to be cost saving. The financial implications are to be further verified.

The PBAC considered that the net costs of listing tafluprost-PF were uncertain. The uptake rate of tafluprost-PF may be higher, and the difference in drug wastage of PGAs relative to tafluprost-PF and the proportion of patients requiring PF-artificial tears for treatment of preservative sensitivity may be lower than those estimated in the submission.

12. Recommendation and Reasons:

The PBAC recommended the listing of tafluprost eye drops (preservative-free), 15 micrograms per mL (0.0015 %), single dose units 0.3 mL, on the PBS as an unrestricted benefit in the general and optometrical schedules at a 13.65% lower price than latanoprost eye drops using reference doses of one drop daily of tafluprost 15 micrograms per mL (0.0015 %) and one drop daily of latanoprost 50 micrograms per mL (0.005 %) for pricing purposes.

The PBAC agreed that latanoprost with preservative (latanoprost-P) is the appropriate comparator. The PBAC noted that latanoprost-P was statistically superior to tafluprost with preservative (tafluprost-P) in terms intra-ocular pressure (IOP) reduction for all analyses at both month 6 and month 24 in Trial 74458 and that tafluprost-P failed to meet

the non-inferiority criterion of 1.5 mmHg compared with latanoprost-P in terms of IOP reduction in the primary (ANCOVA) analyses of Trial 74458. The PBAC also noted that in trial TFL01 the decrease in IOP from baseline at the end of treatment (week 4 or discontinuation) was no worse in patients treated with tafluprost-P than those treated with latanoprost-P. For both repeated measurements analysis of variance (RM ANOVA) and repeated measurements analysis of covariance (RM ANCOVA) analyses in Trial 74457, the upper bounds of the 95% CI for the treatment effect of reducing IOP at the end of the 6 week treatment period fell within the non-inferiority limit of 1.5 mmHg. However, the PBAC noted that the results of Trials TFL01 and 74457 were potentially confounded, and that Trial 74457 was not specifically designed to test non-inferiority. The PBAC concluded that the clinical benefit of the difference in IOP reduction between tafluprost-P and latanoprost-P in Trial 74458 was uncertain.

The PBAC did not accept the claim of superior tolerability of tafluprost preservative-free (tafluprost-PF) compared to latanoprost-P. The PBAC noted that all patients in the single-arm study 77552 switched to treatment with tafluprost-PF from latanoprost-P. Hence the results do not inform whether the reported ocular symptoms or signs may have resolved if latanoprost-P was continued. The PBAC further noted that tafluprost-PF was less tolerable than tafluprost-P in the crossover trial 77550 with a higher number of patients treated with tafluprost-PF experiencing ocular adverse events compared with those in the tafluprost-P arm. There were also more incidences of "any" drug-related adverse event, ocular adverse events and non-ocular adverse events in patients treated with tafluprost-P compared to those treated with latanoprost-P in trials 74458 and TFL01.

The PBAC therefore did not accept the submission's cost-offsets for the use of artificial tears based on the claim of superior tolerability of tafluprost-PF to latanoprost-P. The PBAC further did not accept that there would be less wastage with tafluprost-PF relative to latanoprost-P as the wastage of both products is likely to be for the same reason, such as improper storage and loss or misplacement of medication.

The PBAC considered it was not appropriate to restrict tafluprost-PF to "patients who are intolerant of preservatives in topical eye medications", as proposed in the Pre-PBAC Response, considering this restriction not to be reflective of the likely clinical use of tafluprost-PF. This proposed listing was also not supported by the evidence presented in the submission.

The PBAC accepted the proposal in the Pre-Sub-Committee Response to list tafluprost-PF at a lower price compared to the price of latanoprost-P based on the percentage difference in IOP reduction in Trial 74458 of 8.6 %, and corrected in the ESC Advice to 13.65 %, (based on a 35.9 % reduction in IOP from baseline for latanoprost-P and a 31 % reduction in IOP from baseline for tafluprost-P). The PBAC made this pricing recommendation due to the failure to demonstrate statistical non-inferiority in IOP reduction of tafluprost-P to latanoprost-P in Trial 74458.

The PBAC recommended that the Safety Net 20 Day Rule should not apply.

The PBAC recommended that tafluprost is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as the PBAC has previously recommended that anti-glaucoma drugs are 'out of scope' for nurse practitioner prescribing.

Recommendation:
TAFLUPROST, eye drops (preservative-free), 15 micrograms per mL (0.0015%), single dose units 0.3 mL, 30

Restriction: Unrestricted benefit

Max 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 has no comments.