Scottish Medicines Consortium

tafluprost 15 micrograms/ml preservative-free eye drops single-dose container (Saflutan®) No. (581/09)

Merck Sharpe & Dohme Ltd

06 November 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tafluprost preservative-free eye drops (Saflutan®) are accepted for restricted use within NHS Scotland for the reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension - as monotherapy: in patients who would benefit from preservative-free eye-drops, who are insufficiently responsive to first-line therapy, or who are intolerant or contraindicated to first-line therapy - or as adjunctive therapy to beta-blockers.

Tafluprost is restricted to use in patients who cannot tolerate currently available prostaglandin preparations due to proven sensitivity to the preservative benzalkonium chloride.

Preservative-free tafluprost has shown equivalence to a formulation of tafluprost with preservative in lowering intraocular pressure. The adverse event profile was similar for both formulations. The formulation of tafluprost with preservative has shown non-inferiority to a beta-blocker but failed to demonstrate non-inferiority to a prostaglandin comparator in a pre-specified primary analysis. Saflutan is the only preservative-free prostaglandin eye drop available.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension - as monotherapy in patients: who would benefit from preservative-free eye-drops; who are insufficiently responsive to first-line therapy; or who are intolerant or contraindicated to first line therapy – or as adjunctive therapy to beta-blockers.

Dosing information

One drop instilled once daily in the evening.

Product availability date

1 September 2009

Summary of evidence on comparative efficacy

Primary open-angle glaucoma can cause blindness and once diagnosed requires lifelong treatment. Ocular hypertension (OHT) with no visual field loss or optic nerve damage is often the precursor of open-angle glaucoma. Long-term lowering of intraocular pressure (IOP) remains the only effective strategy against sight loss. Tafluprost is a new prostaglandin which reduces intraocular pressure by increasing the aqueous outflow through the trabecular network.

The submitting company have presented an economic case to support the use for preservative-free (PF) tafluprost in a subset of the licensed indication, including only those patients who cannot tolerate the currently available prostaglandin preparations due to toxicities caused by the preservative, benzalkonium chloride. Tafluprost with preservative is not available in the UK.

There are five phase lll studies with tafluprost 0.0015%, including four monotherapy studies (PF tafluprost versus tafluprost with preservative, tafluprost versus latanoprost 0.005%, tafluprost versus timolol 0.5% and a study of patients switched from treatment with latanoprost to PF tafluprost) and one adjunctive therapy study of timolol with or without tafluprost. All patients included in the studies were 18 years or over and had a diagnosis of open-angle glaucoma or OHT. The primary efficacy analysis in all studies, with the exception of the switch study, was the change from baseline in the diurnal IOP in the intention to treat (ITT) and per protocol (PP) populations calculated using a repeated measurements analysis of variance (RM-ANCOVA) model. Equivalence was demonstrated if the 95% confidence interval (CI) for the difference between treatments was within the range -1.5mmHg and +1.5mmHg, and non-inferiority if the upper limit was less than 1.5mmHg.

In a randomised, investigator-blinded, cross-over, equivalence study tafluprost with preservative was compared with PF tafluprost. Patients had an IOP of 22-34 mmHg in at least one eye at baseline and a known positive treatment response to prostaglandins. There were two treatment periods of four weeks, separated by a washout period of at least four weeks.

A total of 43 patients were randomised and stratified by centre. Patients were not blinded to treatment. Reduction in IOP was similar for both formulations at week one and sustained at week 4.

The overall treatment difference at week 4 was 0.01mmHg (95%CI: -0.46 to 0.49) for the ITT efficacy dataset and -0.05mmHg (-0.52 to 0.42) for the PP efficacy dataset. These 95% CIs lay within the pre-specified equivalence range and therefore equivalence was demonstrated.

In an open-label tolerability study, patients who had been treated with latanoprost were switched to PF tafluprost. Over the 12 weeks of treatment with PF tafluprost, IOP was maintained at a similar level to that recorded with latanoprost. Effects on adverse ocular symptoms, signs and markers of irritation were defined as efficacy outcomes but are reported in the safety section of this document.

In the remaining active comparative studies against latanoprost and timolol, formulations with preservative of all products, including tafluprost, were used.

In the randomised, double-blind non-inferiority study of tafluprost versus latanoprost, 533 patients, with an IOP of 22-34mmHg in at least one eye at baseline, were randomised to tafluprost (n=264) one drop instilled daily or latanoprost (n=264) one drop instilled daily for 6 months. Patients could enter an extension period up to 24 months. The initial six month study period was completed by 498 patients, 35 discontinued (23 tafluprost patients and 12 latanoprost patients) and 420 patients continued into the extension period. The estimated overall treatment difference at 6 months from the RM-ANCOVA model was 1.44 mmHg (upper 95% CI:1.84). The upper limit exceeded the predetermined non-inferiority limit of 1.5mmHg and therefore non-inferiority was not demonstrated. The IOP lowering effect was maintained over the 24 months in both groups but non-inferiority of tafluprost to latanoprost, measured using the RM-ANCOVA primary analysis, was not demonstrated at any time point.

In the double-blind non-inferiority study of tafluprost versus timolol, 458 patients with an IOP of 22-34 mmHg in at least one eye at baseline, were randomised to tafluprost, instilled once daily plus vehicle instilled once daily (n=267) or timolol maleate 0.5% instilled twice daily (n=191). Patients with significant cardiac and respiratory conditions were excluded from the study. The difference in IOP between the tafluprost group and the timolol group was -0.28 (upper 95%CI: 0.21) in the ITT population and -0.19 (upper 95%CI: 0.30) in the PP population, thus demonstrating the non-inferiority of tafluprost to timolol.

In a study of adjunctive therapy, tafluprost or placebo was added to the therapy of patients with an IOP of between 22 and 30mmHg despite four weeks open-label treatment with timolol maleate 0.5% twice daily. Patients continued treatment with timolol but were randomised to tafluprost or vehicle once daily for six weeks followed by a six week extension when patients treated with vehicle were switched to tafluprost. Tafluprost was considered to be superior to vehicle if the upper limit of the 95%CI for the difference in IOP did not exceed 0mmHg or if $p<0.05$. At 6 weeks, there was a significant difference in IOP level in favour of tafluprost, -1.49 (upper 95% CI:-0.66) in the ITT population. At 12 weeks patients switched to tafluprost achieved a similar IOP lowering as those treated with tafluprost throughout the study.

Summary of evidence on comparative safety

Most of the evidence for tafluprost is based on the formulation with preservative which is not available in the UK. As the proposed improved tolerability of PF tafluprost is based on the absence of benzalkonium chloride it is not possible to use these studies to assess the adverse event profile of PF tafluprost. In the comparison of PF tafluprost versus tafluprost with preservative, the number of patients reporting adverse events was higher in the PF tafluprost group (11 patients versus 7 patients). Most adverse events were mild and none were severe.

The most common adverse event was ocular/conjunctival hyperaemia with one mild and one moderate report in the tafluprost with preservative group and seven mild and one moderate report in the PF tafluprost group.

An open-label study in 158 patients who had been treated with latanoprost for a minimum of six months and then transferred to treatment with PF tafluprost, measured the change from baseline in adverse ocular symptoms, signs and markers of irritation as the primary outcomes. Patients were required to have at least two ocular symptoms or at least one ocular symptom and one ocular sign of at least mild severity at screening and were assessed at weeks 6 and 12. There was significant improvement from baseline in ocular symptoms and signs at 6 and 12 weeks ($p<0.001$). There was a significant reduction in the number of patients with abnormal values for conjunctival inflammatory markers at 6 weeks but not at 12 weeks. For the combined symptom score, the mean at baseline was between severity grades trace and mild, and improved to between severity grades none and trace at 6 and 12 weeks.

Summary of clinical effectiveness issues

All currently available prostaglandin eye-drops contain benzalkonium chloride as preservative. Benzalkonium chloride is known to cause a number of ocular adverse events. However, prostaglandins themselves are known to cause ocular adverse events.

The clinical evidence for the preservative-free formulation of tafluprost is limited. Although five phase lll studies were evaluated only one study, in which patients treated with latanoprost switched to tafluprost, represents the patient group under consideration as proposed by the company. Even in this study the patients only had mild adverse ocular events before being switched to the preservative-free formulation and were not truly intolerant of the formulation with preservative. The open-label methodology of this study might have introduced bias. In addition, the reduction in patients with abnormal inflammatory markers was only significant at 6 weeks but not at 12 weeks.

There is only one direct comparison using the preservative-free formulation with the formulation with preservative. There was no difference in the lowering of IOP between the formulations. However, the number of adverse events reported in this study was higher in the PF tafluprost group (n=15, 14 were mild and one was moderate) than in the tafluprost with preservative group (n=6, four were mild and one was moderate). The most common adverse event was ocular/conjunctival hyperaemia. This might suggest that tafluprost itself contributes to this adverse event. Due to the short duration of the study, only four weeks, any reduction in the level of conjunctival inflammatory markers would not be demonstrated: the duration of the switch study was 12 weeks in order to show such changes.

In the comparison with latanoprost, non-inferiority was not demonstrated in the pre-specified primary analysis at 6 months, nor at any other time point during the 18-month extension of this study. Both formulations contained preservative and the concentration of benzalkonium chloride was twice as high in the latanoprost eye-drops (0.2mg/ml) as in the tafluprost eye-drops (0.1mg/ml). The adverse event profile of the two formulations was similar but with a trend towards a higher number of adverse events in the tafluprost group, despite the higher concentration of benzalkonium chloride in the comparator formulation. Among the prostaglandins, latanoprost has the highest concentration of benzalkonium chloride.

Tafluprost did demonstrate non-inferiority in the comparison with timolol 0.5%, with a trend to greater IOP reduction in the tafluprost group. Both contained the same concentration of

benzalkonium chloride and the benzalkonium chloride was instilled twice daily in both groups. More adverse events were reported in the tafluprost group but more patients discontinued in the timolol group (9/191 versus 6/267). The presence of preservative in both formulations may have influenced the adverse event profiles and it is not possible from this study to make a comparison of the ocular safety profile of PF tafluprost with PF timolol, one of the proposed comparators in the health economic analysis.

Summary of comparative health economic evidence

The manufacturer presented a simple cost-minimisation analysis comparing PF tafluprost with a weighted average of other PF agents in patients who would benefit from a preservative-free formulation for open-angle glaucoma or ocular hypertension. The comparators included were timolol 0.25% and 0.5%, dorzolamide, betaxolol and metipranolol. The analysis was conducted over a one year time horizon. The assumption of comparable efficacy was supported by a combination of direct trial data and a published meta-analysis all using formulations with preservative. Based on drug costs alone, the manufacturer estimated that tafluprost would be associated with savings of £42 per patient per year compared with a weighted average cost of other PF agents.

Some limitations of the analysis were noted:

- No analysis was provided comparing tafluprost with timolol 0.5% only. This may be more appropriate as direct trial data are available and timolol has the largest PF market share. Based on the data presented, this comparison would result in savings of £23 per patient per year.
- A published meta-analysis was presented to support the assumption of comparable efficacy of tafluprost compared with betaxolol and dorzolamide. However, comparable efficacy of tafluprost compared with metipranolol was based on assumption.
- The meta-analysis included monotherapy studies and as such it was assumed that comparable efficacy can be extrapolated to use of these agents in the adjunctive setting.

Overall, efficacy across the various alternatives is similar, tafluprost has a slightly lower drug acquisition cost than PF timolol 0.5% and is cheaper when compared with a weighted average of other PF agents. The economic case for use has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Glaucoma Society (EGS) issued updated guidelines in 2008. They recommend the use of a preservative-free agent when there are inflammatory conjunctival side-effects or toxicity of the ocular surface, especially in the context of patients with dry eyes or other ocular surface disorders.

The National Institute for Health and Clinical Excellence which provides guidance for England and Wales, issued guidelines in 2009. Clinical Guideline 85. Glaucoma Diagnosis and management of chronic open-angle glaucoma and ocular hypertension. This guideline gives summaries of all treatment options for glaucoma including topical and surgical.

It recommends a preservative-free preparation if there is evidence that the person is allergic to the preservative.

Additional information: comparators

Other prostaglandin eye-drops, although none of these are available without preservative, and other classes of eye-drops - such as beta-blockers and carbonic anhydrase inhibitors which are used in the treatment of glaucoma and which are available preservative-free.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Tafluprost PF	**One drop instilled daily**	**424**
Dorzolamide PF	One drop instilled three times daily	880
Metipranolol PF	One drop instilled twice daily	816
Levobunolol PF	One drop instilled once or twice daily	242 to 484
Timolol PF	One drop 0.25% or 0.5% instilled twice daily	410 to 468
Betaxolol PF	One drop instilled twice daily	409
Latanoprost	One drop instilled daily	324
Bimatoprost	One drop instilled daily	268
Travoprost	One drop instilled daily	264

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26 August 2009. Costs for one years treatment is based on the assumption that two eyes are treated and that a multi-dose eye-drop will be used for 28days for each eye. All PF formulations are unit doses with an assumption of one unit for each eye.

Additional information: budget impact

Based only on newly diagnosed patients eligible for treatment with preservative-free agents, the manufacturer estimated tafluprost would result in savings of £1k in year 1 rising to £5k in year 5. If a small proportion of patients were also switched from non preservative-free treatments, a net cost of £8k in year 1 was estimated rising to £43k in year 5. The gross drug cost of tafluprost was estimated to be £60k in year 1 rising to £311k in year 5. 285 patients were assumed to be eligible in year 1 based on a market share of 1% rising to 1,470 in year 5 based on a 5% market share. These figures included both newly diagnosed patients and patients switching from their current treatment.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 08 October 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission.

Hamacher T, Airaksinen J, Saarela V, Liinamaa MJ, Richter U, Ropo A, Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from a pharmacodynamics analysis. *Acta Ophthalmol.* 2008: 86: S242: 14-19 Clinical Study Report 77550