HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French Version

TRANSPARENCY COMMITTEE

OPINION

14 September 2011

SAFLUTAN 15 micrograms/ml, eye drops, single dose container of 0.3 ml B/30 (CIP code: 415 299-4)

Applicant: MSD - CHIBRET

tafluprost

ATC code: S01EE05

List I

Date of Marketing Authorisation (mutual understanding): 28 March 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tafluprost

1.2. Background

SAFLUTAN is a novel preservative free prostaglandin analogue in a single-dose container.

1.3. 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
- insufficiently responsive to first-line therapy
- intolerant or contraindicated to first-line therapy.

As adjunctive therapy to beta-blockers."

1.4. Dosage

"The recommended dose is one drop of SAFLUTAN in the conjunctival sac of the affected eye(s) once daily in the evening.

The dose should not exceed once daily as more frequent administration may lessen the intraocular pressure lowering effect.

For single use only, one container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use.

Use in elderly population:
No dosage alteration in elderly patients is necessary.

Use in children and adolescents:
Tafluprost is not recommended for use in children or adolescents below age 18 due to a lack of data on safety and efficacy.

Use in renal/hepatic impairment:
Tafluprost has not been studied in patients with renal/hepatic impairment and should therefore be used with caution in such patients.

Method of administration
To reduce the risk of darkening of the eyelid skin the patients should wipe off any excess solution from the skin. As with any other eye drops, nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route.

If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

S: Sensory organs
S01: Ophthalmologicals
S01E: Antiglaucoma preparations and miotics
S01EE: Prostaglandin analogues
S01EE05: tafluprost

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparator medicines

There are no preservative-free, prostaglandin analogue based eye drops in single-dose containers with the same indication as SAFLUTAN.

2.2.2. Not-strictly comparator medicines

Medicines in the same prostaglandin category:

- bimatoprost: LUMIGAN 0.1 mg/ml
- travoprost: TRAVATAN 40 µg/ml
- latanoprost: XALATAN 0.005%

These three medicinal products have a different indication to that of SAFLUTAN: decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (AB substantial).

2.3. Medicines with a similar therapeutic aim

2.3.1. Beta blockers as monotherapy:

- betaxolol: BETOPTIC, BENTOS
- carteolol: CARTEOL, CARTEABAC
- levobunolol: BETAGAN, LEVOBUNOLOL ALCON
- timolol: BETANOL, DIGAOL, GAOPTOL, NYOGEL, OPHTIM, TIMABAC, TIMOCOMOD, TIMOLOL CHAUVIN, TIMOPTOL

2.3.2. Carbonic anhydrase inhibitors

- brinzolamide: AZOPT
- dorzolamide: TRUSOPT

2.3.3. Other compounds

- brimodinine: ALPHAGAN, generics
- apraclonidine: IODIPINE
- pilocarpine: PILO, generics

2.3.4. Beta-blockers concomitantly

- With an alpha-blocker :
  - brimodinine/timolol COMBIGAN
- With asymathomimetic:
  - pilocarpine/carteolol CARPILO
  - pilocarpine/timolol PILOBLOQ
- With a prostaglandin analogue :
  - bimatoprost/timolol GANFORT
  - latanoprost/timolol XALACOM
  - travoprost/timolol DUOTRAV
- With a carbonic anhydrase inhibitor:

- dorzolamide/timolol COSOPT
- brinzolamide/timolol AZARGA

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The assessment of the efficacy of tafluprost relies on three randomised, double blind, phase III studies, versus comparator active ingredients or placebo in patients with open-angle glaucoma or ocular hypertension:

- two non-inferiority studies versus:
  - latanoprost: study 74458
  - timolol: study 15-003
- one superiority study compared the combination of timolol/tafluprost with the combination of timolol/placebo: study 74460

In these three studies, a form containing a preservative was used.
Furthermore, the laboratory carried out a phase III cross-over equivalence study (study 77550), between tafluprost with preservative and tafluprost without preservative.

3.1.1. Studies with tafluprost with preservative

➢ Non-inferiority study: tafluprost versus latanoprost[1] (study 74458)

Method: non-inferiority study compared tafluprost 0.0015% with latanoprost 0.005% over 24 months. Each treatment was given daily with one drop per eye at 20:00.

Inclusion criteria : patients ≥ 18 years with intraocular hypertension or open-angle glaucoma with a baseline intraocular pressure (IOP) without treatment of between 22 and 34 mmHg in at least one eye at 8:00 in the morning after a " wash-out" period, and a corrected visual acuity score of at least +0.6 logMAR for each eye.

Primary efficacy endpoint: lowering of the mean diurnal IOP after 6 months of treatment compared with the initial value, calculated by covariance analysis of repeated measurements (RM ANCOVA). Between the two eyes, the highest measurement was used. Non-inferiority was established if the upper limit of the confidence interval of the difference in reduction of IOP was below 1.5 mmHg.

Results: Per protocol analysis (PP) was carried out on 517 patients, 259 in the tafluprost group and 258 in the latanoprost group.
At inclusion, demographic, ocular and history of previous glaucoma treatment characteristics for patients was similar in the two groups.
The mean reduction in IOP at 6 months compared to the initial value was 8.05 mmHg in the tafluprost group and 9.16 mmHg in the latanoprost group, measured at 8:00.
The mean difference in reduction of diurnal IOP between the two groups was 1.29 mmHg, with an upper limit for the confidence interval of 1.69 in the PP population with a non-inferiority threshold value set at 1.5 mmHg. Consequently, the non-inferiority of tafluprost compared with latanoprost was not demonstrated.

[1] H. Uusitalo. 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 Ophthalmol 2010; 88: 12–19

- Non-inferiority study: tafluprost versus timolol (study 15-003)

Method: non-inferiority study compared tafluprost 0.0015% with timolol 0.5% over 12 months. Each treatment was given daily at a dose of one drop per eye at 20:00 for tafluprost and one drop at 8:00 and another at 20:00 for timolol.

Inclusion criteria: patients ≥ 18 years with intraocular hypertension or open-angle glaucoma with a baseline IOP without treatment of between 22 and 34 mmHg in at least one eye at 8:00 in the morning after a "wash-out" period, and a corrected visual acuity score of at least +0.6 logMAR for each eye.

Primary efficacy endpoint: lowering of the mean diurnal IOP after 6 months of treatment compared with the initial value, calculated by covariance analysis of repeated measurements (RM ANCOVA). Between the two eyes, the highest measurement was used. Non-inferiority was established if the upper limit of the confidence interval of the difference in reduction of IOP was below 1.5 mmHg.

Results: PP analysis was carried out on 450 patients, 264 in the tafluprost group and 186 in the timolol group.
The mean reduction in IOP at 6 months compared with the initial value was 6.58 mmHg in the tafluprost group and 6.45 mmHg in the timolol group, measured at 8:00.
The difference in mean reduction of diurnal IOP between the two groups was 0.19 mmHg, with an upper limit for the confidence interval of 0.30 with a non-inferiority threshold value set at 1.5 mmHg. Consequently, the non-inferiority of tafluprost compared with timolol was demonstrated.

- Superiority study: tafluprost/timolol versus timolol/placebo (study 74460)

Method: superiority study compared the combinations of tafluprost 0.0015%/timolol 0.5% and timolol 0.5%/placebo over 12 weeks. Each treatment was given daily at a dose of one drop per eye at 20:10 for tafluprost and one drop at 8:00 and another at 20:00 for timolol.

Inclusion criteria: patients ≥ 18 years with intraocular hypertension or open-angle glaucoma, naive to prostaglandin treatment, with a baseline IOP of between 22 and 30 mmHg in at least one eye, with at least one diurnal measurement taken at the baseline visit, after 4 weeks of treatment with timolol, and a corrected visual acuity score of at least +0.6 logMAR for each eye.

Primary efficacy endpoint: lowering of the mean diurnal IOP after 6 weeks of treatment. Between the two eyes, the highest measurement was used. Superiority of the combination was established if the upper limit of the confidence interval of the difference in reduction of IOP was below 0 mmHg.

Results: intention to treat analysis (ITT)
A total of 191 patients were included, 93 in the tafluprost/timolol group and 88 in the timolol/placebo group.
The mean reduction in IOP at 6 weeks compared with the initial value was 5.49 mmHg in the tafluprost/timolol group and 4.01 mmHg in the timolol/placebo group, measured at 8:00.
The difference in mean reduction of diurnal IOP between the two treatments was -1.49 mmHg, with an upper limit for the confidence interval of -0.66 with a limit set at 0 mmHg. The superiority of the tafluprost/timolol combination compared with timolol alone was demonstrated.

3.1.2. Crossover study comparing tafluprost without preservative with tafluprost with preservative (study 77550)

Method: randomised, equivalence, cross-over, single-blind (clinical investigator) phase III study, compared the efficacy of tafluprost without preservative with tafluprost with preservative over 4 weeks. Treatment was given daily at a dose of one drop per eye at 20:00. A "wash-out" period of at least 4 weeks occurred before each of the two periods of treatment.

Inclusion criteria: patients ≥ 18 years with intraocular hypertension or open-angle glaucoma known to respond (documented) to treatment with prostaglandin eye drops, with a baseline IOP of between 22 and 34 mmHg in at least one eye, at least one diurnal measurement on the visit after the "wash-out " period and a corrected visual acuity score of at least +0.6 logMAR for each eye.

Primary efficacy endpoint: Lowering of the diurnal IOP at 4 weeks of treatment. Between the two eyes, the highest measurement was used. Equivalence was established if the confidence interval of the difference in reduction of IOP fell between the interval [-1.5; 1.5] mmHg.

Results: ITT analysis
A total of 43 patients were included.
At 4 weeks, the difference in reduction of the IOP was 0.01 mmHg with a confidence interval of [-0.46; 0.49] in the ITT population, with a limit found within the following confidence interval [-1.5; 1.5] mmHg. The equivalence of tafluprost without preservative and tafluprost with preservative was established.
With the short duration of this study and the small number of patients included, caution should be taken when interpreting these results.

3.2. Adverse effects

3.2.1. Tolerance during the clinical studies

- Study 74458

Over 24 months, 176/264 (66.7%) patients had an adverse event in the tafluprost with preservative group and 162/264 (61.4%) in the latanoprost with preservative group. A total of 400 ocular adverse events were reported by 127 (48.1%) patients in the tafluprost group and 286 by 117 (44.3%) patients in the latanoprost group
The most common adverse ocular events were (tafluprost vs. latanoprost):

- growth of eyelashes : 6.4% vs. 4.2%
- ocular irritation : 5.3% vs. 5.3%
- eyelash discolouration: 4.8% vs. 3.8%
- eye pain: 5.6% vs. 2.7%
- ocular hyperaemia: 5.3% vs. 2.7%

Non-ocular adverse events were reported in 50.4% of patients in the tafluprost group and 43.2% of patients in the latanoprost group and were linked to treatment in 8 and 7% of cases respectively. No information concerning the details of these adverse events is available.

- Study 15-003

At 6 months, 192/267 (71.9%) patients had had an adverse event in the tafluprost with preservative group and 122/191 (63.9%) in the timolol with preservative group:
- ocular: 45.3% versus 40.8%
- non-ocular: 58.4% versus 49.7%

The most common ocular adverse events linked to tafluprost vs. timolol treatment were:
- ocular hyperaemia: 11.6% vs. 5.2%
- ocular irritation: 6.4% vs. 7.3%
- eye pain: 5.6% vs. 7.3%
- eye pruritus: 6.4% vs. 2.1%

Headaches were the most common non-ocular adverse event linked to treatment: 4.1% in the tafluprost group and 1% in the timolol group.

➢ Study 74460

Over 6 weeks, 78 adverse events were reported for 43/96 (44.8%) patients in the tafluprost/timolol group and 31/89 (34.8%) in the timolol/placebo group. Both tafluprost and timolol contained a preservative. Practically all adverse events (71) were ocular and occurred in 40/96 (41.7%) patients in the timolol/tafluprost group and 26/89 (29.2%) in the timolol/placebo group.
The most common ocular adverse event was conjunctive hyperaemia and eye pruritus in 14.6% of patients in the timolol/tafluprost group for each of the symptoms and 9% and 0% respectively in the timolol/placebo group.

➢ Study 77550

Over 4 weeks, 21 adverse events were reported for 11/43 (25.6%) patients in the tafluprost without preservative group and for 7/42 (16.7%) patients in the tafluprost with preservative group. Practically all of these adverse events (20) were ocular.
The most common ocular adverse event linked to tafluprost was conjunctive hyperaemia in 6/43 (14%) of patients in the tafluprost without preservative group and 2/42 (4.8%) in with the preservative group.
Due to the short duration of this study, caution should be taken when interpreting these results.

➢ Study of tafluprost after latanoprost[2]

The primary aim of this study was the assessment of the tolerance of tafluprost 0.0015% without preservative over 12 weeks in patients with an intolerance to latanoprost with preservative.
This was a non-comparative study.
Inclusion criteria were: patients with glaucoma or ocular hypertension, treated with latanoprost for at least 6 months, with at least two eye symptoms or one symptom and signs of irritation/inflammation of the surface of the eye. The ocular signs and symptoms were measured by the clinical investigator or reported by the patient

In this study, after 12 weeks of treatment with tafluprost without preservative, all ocular signs and symptoms of poor tolerance reduced significantly, in particular ocular hyperaemia, the most commonly reported symptom of intolerance to prostaglandins.

The initial IOP with latanoprost was 16.8 ± 2.5 mmHg. After 12 weeks of treatment with tafluprost after latanoprost, it was 16.4 ± 2.7 mmHg (secondary efficacy endpoint).

[2] H.Uusitalo et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. Acta Ophthalmol 2010; 88: 329–336

Table 1: signs and symptoms of eye intolerance on latanoprost and after 12 weeks on tafluprost

Ocular signs and symptoms **n (%)**	**Baseline value** **On latanoprost** **(with preservative)** **N=158**	**Week 12** **On tafluprost** **(without preservative)** **N=155**
Irritation, burning, stinging	89 (56.3)	44 (28.4)*
Foreign body sensation in eyes	78 (49.4)	42 (27.1)*
Lachrymation	87 (55.1)	42 (27.1)*
Itching	74 (46.8)	41 (26.5)*
Dry-eye	102 (64.6)	61 (39.4)*
Tear film break-up time (fBUT)***	150 (94.9)	111 (71.6)*
Fluorescein staining of cornea	129 (81.6)	63 (40.6)*
Fluorescein staining of conjunctiva	133 (84.2)	67 (43.2)*
Blepharitis	95 (60.1)	63 (40.6)*
Conjunctival hyperaemia	133 (84.2)	93 (60.0)*
Schirmer test – lachrymal secretion	113 (71.5)	92 (59.4)**

* $p < 0.001$
** $p = 0.003$
*** "fluorescein break up time"

These results are to be interpreted with caution, as they are from a non-comparative study with no clear primary efficacy endpoint.

- Study of tafluprost after prostaglandin analogues[3]

This study was a sub-group analysis of an open-label, non-comparative study with very heterogeneous patients recruited, with no criteria for changing treatment. Due to the poor methodology, the results are not presented.

3.2.2. SPC

The SPC specifies other common adverse effects (≥ 1/100, ≤ 1/10) than those stated above: erythema of eye lid, blurred vision, eyelid pigmentation, eye discharge, reduced visual acuity, photophobia, eyelid oedema and increased iris pigmentation.

3.2.3. Pharmacovigilance data

Pharmacovigilance data available (four PSURs) covering the period from 30 April 2008 to 29 April 2009 does not highlight any particular issue. These PSURs combine the adverse effects of tafluprost, with or without preservative.

[3] Hommer A, Kimmich F. Switching patients from a preserved prostaglandin-analog monotherapy to preservative-free tafluprost. Clin Ophthalmol. 2011; 5: 623–31

3.3. Conclusion

The efficacy in terms of IOP reduction and the tolerance of tafluprost were assessed in four randomised studies, in patients with open-angle glaucoma or ocular hypertension.

As monotherapy:

- In a study that included 517 patients, after 6 months of treatment, the non-inferiority of tafluprost with preservative compared with latanoprost with preservative was not demonstrated to reduce IOP.
- In a study that included 450 patients, after 12 months of treatment, tafluprost with preservative was non-inferior to timolol with preservative in reducing IOP.
- In a cross-over study that included 43 patients, the equivalence in reducing the IOP was demonstrated between tafluprost with and without preservative. However, this result is to be qualified due to the very short assessment period (4 weeks).

As a concomitant therapy, in a superiority study that included 191 patients, tafluprost with preservative combined with timolol was superior to timolol associated with a tafluprost placebo in reducing IOP.

The monotherapy studies did not allow the tolerance of SAFLUTAN, which is a preservative-free formulation, to be assessed. Indeed the two initial studies studied tafluprost with preservative and the third was carried out over two periods of 4 weeks, which was too short. The adverse effects observed during these studies were in agreement with those found in the SPC.

In one study in patients with latanoprost intolerance, the evidence of intolerance was reduced after 12 weeks of tafluprost without preservative. However, the short duration of the study (12 weeks), the absence of a main efficacy endpoint and the non-comparative nature of the study limits the use of the results.

No methodologically valid study was carried out on a patient population identified as being intolerant to preservatives.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Glaucoma is a serious condition that can lead to blindness.

This proprietary medicinal product is intended as curative treatment.

Public health benefit:
Glaucoma, in its terminal state, is the primary cause of "total" blindness in France (Groupe technique National de Définition des Objectifs de santé publique - a national group of experts defining French public health objectives, April 2003).
Due to its impact on activity related to visual disability and on quality of life, the public health burden represented by glaucoma is considered as moderate.

To reduce the frequency of blurred vision, ensure early diagnosis and management, and preventing functional limitations and restrictions in associated activities and their consequences are public health needs that are already an established priority (Objective 68 of the Law of 9 August 2004 on public health policy).

However, due to limited data available on the tolerance of tafluprost without preservative, and in the absence of a demonstration of improved compliance, it is difficult to specify the additional impact that SAFLUTAN has in terms of morbidity and quality of life.

Consequently, it is not expected that SAFLUTAN will benefit public health.

No methodologically valid study for tafluprost without preservative (formulation of SAFLUTAN) in patients corresponding to the indications in the Marketing Authorisation was presented, in particular in patients with an intolerance to preservatives. Tafluprost with preservative did not show non-inferiority over another prostaglandin analogue, latanoprost, but did compared with a beta-blocker, timolol. Due to the poor study methodologies available, the improvement in ocular tolerance for SAFLUTAN was not demonstrated, either compared with other prostaglandin analogues or compared with tafluprost with preservative.
Consequently, the efficacy/adverse effects ratio for this product in this indication is not established.

At the current time, the therapeutic use of this proprietary medicinal product cannot be defined.

There are treatment alternatives.

The actual benefit of this proprietary medicinal product is **insufficient** to justify its reimbursement by National Health Insurance.

4.2. Target population

Not applicable

4.3. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.