HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

29 May 2013

MONOPROST 50 µg/mL eye drops solution in single-dose container

B/30 single-dose containers of 0.2 mL (CIP: 34009 267 382 6 6)

Applicant: THEA

INN	Latanoprost
ATC code (year)	S01EE01 (antiglaucoma preparations)
Reason for the request	**Inclusion**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension."**

Actual Benefit	**Substantial actual benefit**
Improvement in Actual Benefit	MONOPROST 50 µg/mL eye drops solution in a single-dose container does not provide an improvement in actual benefit (IAB V) when compared with XALATAN 0.005% eye drops solution.
Therapeutic use	First-line treatment of open angle glaucoma and ocular hypertension.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Initial date (decentralised procedure): 14 February 2013
Prescribing and dispensing conditions/ special status	List I

ATC Classification	2012	
	S	Sensory organs
	S01	Ophthalmologicals
	S01E	Antiglaucoma preparations and miotics
	S01EE	Prostaglandin analogues
	S01EE01	Latanoprost

02 BACKGROUND

MONOPROST 50 µg/mL is the first latanoprost-based eye drops solution available in a single-dose container without preservatives. Currently, in the class of prostaglandin analogue eye drops, only SAFLUTAN (tafluprost, a non-refundable medicine) is available in a single-dose container without preservatives.

03 THERAPEUTIC INDICATIONS

“Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.”

04 DOSAGE

“Recommended dosage for adults (including the elderly):

Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if MONOPROST is administered in the evening.

The dosage of MONOPROST should not exceed once daily since it has been shown that more frequent administration decreases the intraocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as normal.

Paediatric population:
No data are available with the MONOPROST formulation.”

05 THERAPEUTIC NEED

Glaucoma is a localised neuropathy of the optic disc, the place where the retinal nerve fibres come together. It has a clinicopathologic definition: it is characterised by a combination of atrophy of the optic nerve (with excavation of the optic nerve being the first visible sign) and an impaired field of vision, with elevated or normal intraocular pressure (IOP). Although elevated intraocular pressure is a major risk factor, someone with ocular hypertension is not considered as having glaucoma if the other two pathognomonic signs are not present.

Normal intraocular pressure is defined as a value of 15 ± 6 mmHg, based on a statistical study of the distribution of intraocular pressure values in a population presumed to be healthy. Ocular hypertension is defined as a pressure > 21 mmHg. This threshold has been arbitrarily defined.

In most cases, the treatment of glaucoma with elevated intraocular pressure or of ocular hypertension is medical, prescribed "for life" and must not be stopped unexpectedly. The choice of medicinal product is essentially made according to the contraindications and adverse effects of each class of drug.

A number of medicinal products are available in local or systemic forms and acting through different mechanisms:

- reduced secretion of aqueous humour:
  - beta-blockers
  - alpha-2 adrenergic agonists
  - carbonic anhydrase inhibitors
- increased elimination of aqueous humour:
  - adrenaline and adrenaline compounds
  - miotics and parasympathomimetics
  - prostaglandin analogues

Beta-blocker eye drops and prostaglandin analogues are prescribed as first-line therapy.

Several pressure-lowering eye drops may be combined, without exceeding triple therapy as a general rule.
For dual therapy, a prostaglandin analogue and a beta-blocker may be combined if one of these has proved to be insufficiently effective or ineffective as first-line monotherapy.
The other classes of pressure-lowering eye drops are prescribed:

- as first-line monotherapy in cases where beta-blockers and prostaglandin analogues are contraindicated
- as a second-line treatment, either as monotherapy or in combination with beta-blockers or prostaglandin analogues, where these are insufficiently effective

In some cases that cannot be controlled by topical treatment, this may be combined with systemic acetazolamide, a carbonic anhydrase inhibitor. However, the frequent and disabling adverse effects of acetazolamide (metabolic acidosis, hypokalaemia, kidney stones) limit its use.

During long-term administration, the preservatives present in multi-dose eye drops can cause adverse effects in the form of conjunctivitis and ocular surface toxicity. There are currently few preservative-free antiglaucoma eye drops available. In 2009, the EMA published a guideline encouraging pharmaceutical companies to develop preservative-free ophthalmic treatments, due to their poor ocular tolerance.[1] The European Glaucoma Society[2] recommends preservative-free eye drops more particularly for patients with dry eye syndrome or another ocular surface disease.

[1] EMEA public statement on antimicrobial preservatives in ophthalmic preparations for human use. 8 Dec 2009
[2] European Glaucoma Society. Guidelines for glaucoma. 3rd edition 2009. Dogma.

However, it states that the most important factor to take into account is the drug's overall safety profile.

In the most serious cases, surgery may be required at the time of diagnosis, but surgical treatment is generally reserved for patients in whom medical treatment has failed. Surgery is the preferred option when the glaucoma is advanced or the patient is young. Laser trabeculoplasty may be used after the failure of medical treatment and before considering surgery.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The closest comparators (from the same pharmacotherapeutic group) are the other prostaglandin analogues indicated in the treatment of glaucoma and ocular hypertension:

Active ingredient	Name *Company*	Indication	Date of opinion	AB	IAB (wording)	Refunded yes/no
Latanoprost	**XALATAN 0.005%** Eye drops solution (and generics)	Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension. Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure.	06/04/2011	Substantial	19/03/2003: The new use as first-line therapy does not change the IAB (**level II**) obtained previously in comparison with beta-blockers (opinion of 8 October 1997).	yes
Bimatoprost	**LUMIGAN 0.3 mg/mL** Eye drops solution	Reduction of elevated intraocular pressure in open-angle glaucoma and ocular hypertension in adults.	06/06/2012	Substantial	01/09/2004: The data submitted for the new use as first-line therapy do not change the IAB (**level III**) previously attributed to LUMIGAN (opinion of 24 April 2002).	yes
	LUMIGAN 0.1 mg/mL Eye drops solution		31/03/2010	Substantial	LUMIGAN 0.1 mg/mL is an addition to the range that does not provide an improvement in actual benefit (**IAB level V**) in comparison with LUMIGAN 0.3 mg/mL.	yes
Travoprost	**TRAVATAN 40 µg/mL** Eye drops solution	Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.	09/05/2012	Substantial	26/11/2003: The new use as first-line therapy does not change the IAB (**level III**) attributed previously (opinion of 23 January 2002).	yes
Tafluprost	**SAFLUTAN 15 µg/mL** Eye drops in single-dose container of 0.3 mL	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.	14/09/2011	Insufficient	Not applicable	no

The other treatments for glaucoma and ocular hypertension are:

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

Carbonic anhydrase inhibitors
- brinzolamide: AZOPT
- dorzolamide: TRUSOPT

Other substances
- brimonidine: ALPHAGAN, generics
- apraclonidine: IODIPINE
- pilocarpine: PILO, generics

Beta-blockers in combination
- with an alpha-blocker:
  - brimonidine/timolol COMBIGAN
- with a sympathomimetic:
  - 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

The actual benefit of all these medicinal products is substantial.

06.2 Other health technologies

Not applicable.

◗ Conclusion

Prostaglandin analogue-based eye drops, particularly XALATAN, which contains latanoprost, are clinically relevant comparators.

None of the currently refunded prostaglandin-based eye drops are available in a preservative-free form.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Reimbursement		
	Date reimbursement started	Yes/No/Assessment in progress	Scope (indications) and special condition(s)
Austria	Assessment in progress		
Belgium	Assessment for reimbursement in progress (Price obtained)		
Bulgaria	Assessment in progress		
Cyprus	MA not obtained		
Czech Republic	Assessment in progress		
Germany	01/01/2013	Yes	MA indication
Denmark	14/11/2012	Yes	MA indication
Estonia	Assessment in progress		
Greece	Assessment in progress		
Spain	19/01/2013	Yes	
Finland	12/11/2012	Yes	MA indication
Iceland	Assessment in progress	Yes	MA indication
Ireland	Assessment in progress		
Italy	MA not obtained		
Latvia	Assessment in progress		
Lithuania	MA not obtained		
Luxembourg	Assessment in progress		
Netherlands	18/01/2013	Yes	MA indication
Norway	21/03/2013	Yes	MA indication
Poland	04/03/2013	Yes	MA indication
Portugal	Assessment in progress		
Romania	Assessment in progress		
Slovenia	Assessment in progress		
Slovakia	Assessment in progress		
Sweden	07/03/2013	Yes	Restricted to patients with an intolerance to preservatives
Switzerland	01/03/2013	Yes	MA indication
United Kingdom	12/12/2012	Yes	MA indication

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

This assessment of the efficacy of MONOPROST is based primarily on a phase III study (study LT2345-PIII-12/08) which aimed to demonstrate the non-inferiority of MONOPROST compared with XALATAN, another latanoprost-based eye drops solution which is available in a multi-dose bottle and formulated with a preservative, in patients with open angle glaucoma or ocular hypertension.

This was a single-blind randomised study: only the investigator was blinded, due to the different immediate packaging of the two medicinal products, namely a single-dose container for MONOPROST and a multi-dose bottle for XALATAN.

Study design:
Patients had to stop their usual treatment for 6 weeks (42 days ± 3 days) before D0, in order to determine their eligibility for inclusion in terms of the IOP criterion.
Patients were treated with AZOPT alone (brinzolamide 0.15 mg/mL, a formulation containing benzalkonium chloride) with one drop in the affected eye(s) twice daily, morning and evening, for 5 weeks (from D-42 to D-5). The brinzolamide treatment was then stopped 5 days before the inclusion visit (D0).
At the inclusion visit, IOP must be between 22 and 34 mmHg in both eyes.

Inclusion criteria:
- age ≥ 18 years
- open angle glaucoma or ocular hypertension in one or both eyes already treated with XALATAN as monotherapy for at least 9 months (with three available IOP measurements spaced 3 months apart)
- IOP stable on treatment (≤ 18 mmHg)
- stable field of vision, defined from 2 available visual field tests, with the second most recent performed within the previous 18 months and the most recent performed within the previous 6 months, and with an interval of at least 6 months between the two tests
- corneal thickness ≥ 500 µm and ≤ 580 µm
- IOP between 22 and 34 mmHg in both eyes at the inclusion visit, after withdrawal of treatment (brinzolamide) 5 days previously.

Treatment groups:
- MONOPROST
- XALATAN

Dosage: 1 drop in the affected eye(s) once daily at 21:00 (± 1 hour) for 3 months.

Primary efficacy endpoint:
Change in IOP (measured in the morning at 09:00 ± 1 hour) observed between D0 and D84 in the eye most affected (or the right eye if there was no difference in IOP between the two eyes).

Statistical analysis:
The analysis of the primary efficacy endpoint was conducted in a modified ITT population, defined as patients included who had received at least one dose of treatment and for whom data from at least one IOP follow-up visit was available for the most affected eye, taking into account all evaluable points.
A mixed model for repeated measurements was used with the following adjustment variables: baseline IOP, treatment, visit, country, treatment with visit interaction and baseline IOP with visit interaction.

The differences between the treatments were evaluated using a 95% confidence interval (CI) and MONOPROST was considered to be non-inferior to XALATAN if the upper limit of the 95% CI did not exceed 1.5 mmHg (non-inferiority threshold).

Results:

Out of 404 patients included and randomised:
- 402 were treated: 213 in the MONOPROST group and 189 in the XALATAN group
- 392 patients completed the study: 206 in the MONOPROST group and 186 in the XALATAN group.

Ten patients left the study prematurely: 7 (3.3%) in the MONOPROST group and 3 (1.6%) in the XALATAN group. Four patients withdrew because of an adverse effect: 3 patients in the MONOPROST group (intolerance to the medicinal product, ocular pruritus and major depression) and 1 patient in the XALATAN group (allergic conjunctivitis and migraine in the same patient). The other patients were excluded for non-medical reasons and an IOP below the inclusion criterion.

The modified ITT population consisted of 353 patients: 189 (88.3%) in the MONOPROST group and 164 (86.3%) in the XALATAN group.

Patient demographics were comparable between the groups.
The patients included had a mean age of 64.7 ± 11.5 years (24 to 93 years).
On D-42, the IOP value was 15.5 ± 1.8 mmHg in the MONOPROST group and 15.4 ± 1.8 mmHg in the XALATAN group.
On D0, the mean IOP value was 24.1 ± 1.8 mmHg in the MONOPROST group and 24.0 ± 1.7 mmHg in the XALATAN group.

Change in IOP at 3 months:
After 3 months (D0-D84), the reduction in IOP was -8.6 ± 2.6 mmHg in the MONOPROST group and -9.0 ± 2.4 mmHg in the XALATAN group, i.e. a difference of 0.417 ± 0.215 mmHg with a 95% CI of [-0.006; 0.840].
As the upper limit of the 95% CI for the difference between treatments is lower than the predefined non-inferiority threshold (1.5 mmHg), it can be concluded that MONOPROST is non-inferior to XALATAN in terms of change in IOP at 3 months.

08.2 Safety/Adverse effects

Data from the phase III study versus XALATAN

In addition to monitoring the occurrence of all types of ocular and systemic adverse events, the study protocol provided for an evaluation at each visit of subjective ocular symptoms during instillation and some time after instillation, as well as of ocular signs observed during slit lamp examination.

The subjective ocular symptoms on instillation (pruritus, burning/stinging, blurred vision, sticky eye sensation, dry eye sensation, foreign body sensation) and some time after instillation (dry eye sensation, irritation/stinging/burning, pruritus, watering, foreign body sensation, glare/sensitivity to light) were evaluated by the patient using the following scale:
- 0 = not present
- 1 = present but not troubling
- 2 = troubling
- 3 = very troubling

The total score calculated was the sum of the scores obtained divided by the number of symptoms experienced.

The clinical signs observed with a slit lamp were as follows:
- eyelid abnormality

- corneal puncture
- inflammation of anterior chamber
- change in iris pigmentation
- abnormal eyelash appearance/hypertrichosis
- abnormal coloration of eyelids

Their severity was evaluated using the following scale:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

The severity of conjunctival hyperaemia was evaluated using the McMonnies scale (with a score of 1 to 6).

Occurrence of ocular adverse events:

The overall incidence of ocular adverse events was 8.5% (18/213) in the MONOPROST group and 11.6% (22/189) in the XALATAN group.

The incidence of treatment-related ocular adverse events was 3.8% (8/213) in the MONOPROST group and 5.3% (10/189) in the XALATAN group. In both groups, the incidence of each individual ocular adverse event was low: 0.5% with the exception of coloration of the cornea (1.6%) and intolerance to the medicinal product (2.1%) in the XALATAN group (see Table 1).

The occurrence of an ocular adverse event required treatment to be stopped in 2 patients in the MONOPROST group (1 case of intolerance to treatment on D7 and 1 case of moderate pruritus on D28) and in 1 patient in the XALATAN group (moderate allergic conjunctivitis on D9). In all cases, these adverse events were treatment-related and the symptoms resolved when treatment was stopped.

No ocular serious adverse events were reported.

Table 1: Treatment-related adverse events (and adverse events with an inconclusive link to treatment)

	MONOPROST (N=213)	**XALATAN (N=189)**
Ocular adverse events:	**n (%)**	**n (%)**
Intolerance to the medicinal product	1 (0.5)	4 (2.1)
Ocular pruritus	1 (0.5)	1 (0.5)
Photophobia	1 (0.5)*	1 (0.5)
Eye irritation	1 (0.5)	-
Eyelid pruritus	1 (0.5)	-
Abnormal ocular sensation	1 (0.5)	-
Optic disc haemorrhage	1 (0.5)*	-
Blurred vision	1 (0.5)	1 (0.5)
Foreign body sensation	1 (0.5)	1 (0.5)
Ocular discomfort	1 (0.5)	1 (0.5)
Corneal staining	-	2 (1.6)
Allergic conjunctivitis	-	1 (0.5)
Dry eye	-	1 (0.5)
Increased lacrimal secretion	-	1 (0.5)
Conjunctival hyperaemia	-	1 (0.5)
Distichiasis	-	1 (0.5)

* no conclusion possible as to a causal link

Ocular symptoms on instillation:
The total score for ocular symptoms on instillation was lower in the MONOPROST group than in the XALATAN group on D42 (score: 0.15 ± 0.51 versus 0.41 ± 1.03; p = 0.001) and on D84 (score: 0.18 ± 0.66 versus 0.46 ± 1.05; p = 0.001). However, in both groups, these symptoms were mild (scores below 1, with a score of 1 corresponding to symptoms that are present but not troubling) and the clinical relevance of the difference between the groups is difficult to assess.

Ocular symptoms some time after instillation:
The total score for ocular symptoms some time after instillation was not significantly different between the MONOPROST and XALATAN groups on D42 (0.47 ± 1.19 versus 0.65 ± 1.54, p=0.057) and on D84 (0.47 ± 1.37 versus 0.69 ± 1.73, p=0.053).
Treatment-related ocular adverse events occurring some time after instillation were observed in 3.8% of patients on MONOPROST and in 5.3% of patients on XALATAN.

Ocular signs (slit lamp examination):
Conjunctival hyperaemia[3] was present in both groups, but was less frequent in the MONOPROST group than in the XALATAN group on D42 (20.2% versus 30.6%) and on D84 (21.4% versus 29.1%) (see Table 2).

For the other signs, in particular those characteristic of prostaglandin analogues (change in iris coloration, abnormal appearance/hypertrichosis of the eyelids), no difference was observed between the groups.

Table 2: Conjunctival hyperaemia score (in the most affected eye) at each visit

Visit	MONOPROST (N = 213)				XALATAN (N = 189)				*p*
	Hyperaemia score				Hyperaemia score				
	2	3-4	5-6	total	2	3-4	5-6	total	
D0	36 (17.0)	15 (7.0)	1 (0.5)	52 (24.5)	38 (20.1)	5 (2.6)	-	43 (22.7)	NA
D15	42 (20.1)	15 (7.1)	-	57 (27.2)	50 (26.9)	11 (5.9)	-	61 (32.8)	0.181
D42	31 (14.9)	11 (5.3)	-	**42 (20.2)**	41 (22.0)	16 (8.6)	-	**57 (30.6)**	**0.003**
D84	34 (16.5)	10 (4.9)	-	**44 (21.4)**	40 (21.5)	14 (7.6)	-	**54 (29.1)**	**0.019**

The data are expressed as number of patients (%).

Systemic adverse events:
No treatment-related systemic effects were reported in the MONOPROST group, versus 4 (2.1%) in the XALATAN group (2 episodes of headache in the same patient, 1 case of dizziness, 1 case of migraine, 1 case of palpitations and 1 case of muscle weakness). All of these were mild.

SPC data
The most common adverse effects have been ocular effects, primarily (≥ 1/10): increased iris pigmentation, mild to moderate conjunctival hyperaemia, eye irritation (burning, grittiness, itching, stinging and foreign body sensation), eyelash and vellus hair changes (increased length, thickness, pigmentation and number: vast majority of reports in the Japanese population). Systemic adverse effects have been rare.

[3] The severity of conjunctival hyperaemia was measured using a photographic scale derived from the McMonnies questionnaire (2 = mild, 3-4 = moderate, 5-6 = severe).

08.3 Summary & discussion

A randomised single-blind study (investigator blinded) compared latanoprost in a single-dose container without preservatives (MONOPROST) with latanoprost in a multi-dose bottle with a preservative (XALATAN) administered for 3 months to 404 adult patients with open angle glaucoma or ocular hypertension. The non-inferiority of MONOPROST to XALATAN was demonstrated in terms of mean reduction in intraocular pressure (IOP) measured in the morning: -8.6 ± 2.6 mmHg vs. -9.0 ± 2.4 mmHg, i.e. a difference of 0.417 ± 0.215 mmHg, with the upper limit of the 95% CI [-0.006; 0.840] being below the predefined non-inferiority threshold (1.5 mmHg).

The adverse events observed with MONOPROST and XALATAN were primarily ocular. The incidence of these ocular events was 4.7% with MONOPROST and 8.5% with XALATAN.
The score for ocular symptoms on instillation was lower with MONOPROST than with XALATAN but the difference (a maximum of 0.26 points on a scale of 0 to 3) is not clinically relevant and the scores were low (<1 meaning non-troubling symptoms).
The score for symptoms occurring some time after instillation was no different between MONOPROST and XALATAN.
The incidence of conjunctival hyperaemia observed with a slit lamp was lower with MONOPROST than with XALATAN on D42 (20.2% versus 30.6%) and on D84 (21.4% versus 29.1%) but all cases of hyperaemia were mild to moderate with the exception of 1 severe case on MONOPROST.
The signs observed with prostaglandin analogues (change in iris coloration, eyelash hypertrichosis) did not differ between the groups.

In conclusion, MONOPROST was non-inferior to XALATAN in terms of change in IOP at 3 months. The safety profile for both medicinal products is similar with, however, a lesser incidence of conjunctival hyperaemia on MONOPROST than on XALATAN. No long-term safety data is available for these medicinal products, which are intended for long-term administration. Consequently, no conclusions can be drawn from the currently available data as to the benefits of the MONOPROST formulation over the XALATAN formation.

09 THERAPEUTIC USE

MONOPROST, a latanoprost-based eye drops solution, is a first-line therapy for the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension. As it is preservative free, its use is preferable to use of the same drug with a preservative, especially for patients with dry eye syndrome or another ocular surface disease.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Ocular hypertension can progress to open angle glaucoma, which is a serious disease that can lead to blindness.

◗ This proprietary medicinal product is intended as curative therapy for increased IOP and as preventative therapy for complications of the disease.

◗ The efficacy/adverse effects ratio is high.

◗ There are numerous treatment alternatives.

◗ This proprietary medicinal product is a first-line therapy.

◗ Public health benefit:

Chronic open angle glaucoma is a clinical situation constituting a moderate public health burden.

Improved treatment of glaucoma is a public health need which is an established priority (GTNDO[4]).

However, in view of the available data, no additional impact on morbidity is expected from MONOPROST, latanoprost in a single-dose container, in comparison with XALATAN, latanoprost in a multi-dose bottle.

This proprietary medicinal product therefore does not provide an additional response to the identified public health need.

Consequently, the proprietary medicinal product MONOPROST is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of MONOPROST 50 µg/mL eye drops solution in a single-use container is substantial in the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension and at the dosages in the Marketing Authorisation.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension" and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

MONOPROST 50 µg/mL eye drops solution in a single-dose container does not provide an improvement in actual benefit (IAB V) when compared with XALATAN 0.005% eye drops solution.

[4] Groupe Technique National de Définition des Objectifs [National Technical Group for the Definition of Public Health Objectives] (DGS [Directorate-General for Health] 2003)

010.3 Target population

The target population of MONOPROST is defined as patients with open angle glaucoma or ocular hypertension.

There are few epidemiological data on glaucoma and ocular hypertension, and the available data are old.
In France, it was estimated that 650,000 patients were treated for glaucoma in 2003, i.e. 2% of the French population aged over 40 years, and that about 400,000 patients had unrecognised glaucoma due to the lack of clinically suggestive functional signs before a very late stage (source: GTNDO – April 2003). The most recent French data were published in 2006.

In an initial study conducted in a population of 2,074 adults (≥ 18 years)[5] covered by National Health Insurance in Ile de France who had just had a standard health check at the Centre d'investigations préventives et cliniques [Centre for Preventative and Clinical Investigations], the prevalence of patients with an IOP > 21 mmHg (ocular hypertension or glaucoma with elevated pressure) was 10% of men and 6.4% of women. If these data are extrapolated to the French population (2012 INED data), this is a total population of 4.1 million people. The prevalence of confirmed glaucoma was 2.2% in men and 3.0% in women.
However, the author considers these prevalences to be overestimations because of methodological bias, in particular the non-representative nature of the sample in relation to the general population. In addition, these results, based on systematic diagnosis, cannot reflect the reality of the population which will actually be treated.

A second study[6] estimated, from a national telephone survey conducted in a representative sample of 5,726 people, that the prevalence of patients treated with pressure-lowering eye drops is 4.1% of the population aged over 40 years, i.e. 1.3 million people.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions.

[5] Bron A., Baudouin C., Nordmann J-P et al. Prévalence de l'hypertonie oculaire et du glaucome dans une population française non sélectionnée. J Fr Ophtalmol 2006;29(6):635-641.

[6] Vilain M, Nordman JP, Renard JP et al. Enquête Française Glaucome et Hypertonie 1 Jour (EFGH1J). J Fr Ophtalmol 2006;29:520-5.