AZARGA 10 mg/mL + 5 mg/mL, eye drops, suspension
Box containing 1 x 5 mL bottle (CIP: 391 266-4)

Applicant: ALCON
Brinzolamide (10 mg/ml), timolol (5 mg/ml)
ATC Code (2008): S01ED51
List I
Date of marketing authorisation (centralised procedure): 25 November 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Brinzolamide 10 mg/ml, timolol 5 mg/ml

1.2. Indication
"Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction."

1.3. Dosage
"Use in adults, including the elderly
The dose is one drop of AZARGA in the conjunctival sac of the affected eye(s) twice daily.

Nasolacrimal occlusion or gently closing the eyelid after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) twice daily.

When substituting another ophthalmic antiglaucoma agent with AZARGA, the other agent should be discontinued and AZARGA should be started the following day.

Paediatric patients
AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Use in hepatic and renal impairment
No studies have been conducted with AZARGA or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. No dosage adjustment is necessary in patients with hepatic impairment or in patients with mild to moderate renal impairment.

AZARGA has not been studied in patients with severe renal impairment (creatinine clearance <30 ml/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZARGA is therefore contraindicated in patients with severe renal impairment (see section 4.3).

Method of administration
For ocular use.

Instruct patients to shake the bottle well before use.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use."
2 SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2008)
S: Sensory organs
S01: Ophthalmologicals
S01E: Antiglaucoma preparations and miotics
S01ED: Beta blocking agents
S01ED51: Timolol, combinations

2.2 Medicines in the same therapeutic category

Dual therapies combining a carbonic anhydrase inhibitor and a beta-blocker.

- Products administered as associations:
  - carbonic anhydrase inhibitors:
    - brinzolamide: AZOPT 10 mg/ml
    - dorzolamide: TRUSOPT 2 %
  - beta blockers: timolol, betaxolol, befunolol, carteolol, levobunolol, metipranolol.

- Product combining two active substances (fixed-dose combination):
  - dorzolamide, timolol: COSOPT 20 mg + 5 mg/mL, eye drops, solution (multi-dose bottle and single-dose containers)

It should be noted that the indication for COSOPT is restricted to cases in which beta-blocker monotherapy is not sufficient.

2.3 Medicines with a similar therapeutic aim

Other antiglaucoma eyedrops used as monotherapy or dual therapy: beta-blockers, prostaglandins, parasympathomimetics (pilocarpine), sympathomimetics, anhydrase inhibitors, alpha-2 adrenergic receptor agonists.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
The dossier includes two phase III comparative studies:
- one non-inferiority study versus COSOPT (dorzolamide/timolol) (C-05-10),
- one superiority study versus dorzolamide and versus timolol (C-05-24).

AZARGA has not been compared with separate administration of the two components of the combination.
**Study C-05-10: non-inferiority study versus COSOPT (dorzolamide/timolol)**

Randomised double-blind non-inferiority study, lasting 12 months, the main objective of which was to compare the efficacy of AZARGA (brinzolamide/timolol) with that of COSOPT (dorzolamide/timolol) in 437 patients aged over 18 with open-angle glaucoma or ocular hypertension with a mean baseline intraocular pressure (IOP) of between 25 and 27 mmHg and for whom the investigator considered that combined treatment would be helpful.

**Treatment:**
- fixed-dose combination of brinzolamide 10 mg/mL + timolol 5 mg/mL (AZARGA) (n=220)
- fixed-dose combination of dorzolamide 20 mg/mL + timolol 5 mg/mL (COSOPT) (n=217)
The treatments were administered twice daily (at 8am and 8pm) for 12 months.

**Primary endpoint:** mean intraocular pressure (IOP) measured at 8am, 10am and 4pm after 6 months of treatment.

Non-inferiority was established if the upper limit of the 95% confidence interval (95% CI) of the difference in mean IOP on three occasions (8am, 10am and 4pm) and at 6 months between AZARGA and COSOPT was less than 1.5 mmHg.

A difference in mean IOP of ≥ 1.5 mmHg between the two treatments was considered to be clinically relevant.

**Results** (per-protocol):
Reduction in mean IOP from baseline was between 7.2 and 9.2 mmHg in the AZARGA group and between 7.4 and 8.9 mmHg in the COSOPT group.

The upper limit of the 95% confidence interval of the difference in mean IOP between AZARGA and COSOPT on three occasions (8am, 10am and 4pm) and at 6 months was less than 1.5 mmHg. As a result, AZARGA was demonstrated to be non-inferior to COSOPT in terms of reduction in mean IOP on all occasions and for all visits (see table 1).

**Table 1: Comparison of mean IOP on each measurement, for AZARGA and COSOPT**

<table>
<thead>
<tr>
<th>Study C-05-10</th>
<th>AZARGA</th>
<th>COSOPT</th>
<th>AZARGA vs COSOPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 419</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial IOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td>8h</td>
<td>27.3</td>
<td>27.3</td>
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<tr>
<td></td>
<td>10h</td>
<td>25.9</td>
<td>26.1</td>
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<tr>
<td></td>
<td>16h</td>
<td>24.8</td>
<td>24.8</td>
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<tr>
<td>IOP at 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>months</td>
<td>8h</td>
<td>18.5</td>
<td>18.9</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>10h</td>
<td>17.1</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>16h</td>
<td>17.3</td>
<td>17.2</td>
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<tr>
<td>IOP at 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>months</td>
<td>8h</td>
<td>18.5</td>
<td>19.0</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>10h</td>
<td>17.0</td>
<td>17.3</td>
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<tr>
<td></td>
<td>16h</td>
<td>17.5</td>
<td>16.9</td>
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<tr>
<td>IOP at 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>months</td>
<td>8h</td>
<td>18.6</td>
<td>18.7</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>10h</td>
<td>17.2</td>
<td>17.0</td>
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<tr>
<td></td>
<td>16h</td>
<td>17.5</td>
<td>16.9</td>
</tr>
</tbody>
</table>
**Study C-05-24**: superiority study versus monotherapy (brinzolamide or timolol)

Randomised double-blind study, lasting 6 months, comparing the efficacy and safety of AZARGA (brinzolamide/timolol) with those of brinzolamide and timolol as monotherapies, in 523 patients aged over 18 with open-angle glaucoma or ocular hypertension with a mean baseline intraocular pressure (IOP) of between 25 and 27 mmHg.

**Treatment:**
- fixed-dose combination of brinzolamide + timolol (AZARGA) (n=174)
- brinzolamide (n=174)
- timolol (n=175)

The treatments were administered twice daily (at 8am and 8pm) for 6 months.

**Primary endpoint:** Mean IOP measured at 8am and 10am after 2 weeks, 3 months and 6 months of treatment.

**Results** (intention-to-treat):
Reduction in mean IOP from baseline was between 8.0 and 8.7 mmHg in the AZARGA group, between 5.1 and 5.6 mmHg in the brinzolamide group and between 5.7 and 6.9 mmHg in the timolol group, administered twice daily.

The reduction in mean IOP obtained with AZARGA was greater than that obtained with brinzolamide and timolol, on all occasions and at all study visits (see table 2).

The difference in mean IOP between AZARGA and brinzolamide was between -3.3 and -2.9 mmHg, and the difference between AZARGA and timolol was between -1.8 and -1.3 mmHg. These differences in mean IOP (greater than the 1.5 mmHg threshold) are clinically relevant.

| Table 2: Comparison of mean IOP at each measurement occasion between AZARGA and brinzolamide and between AZARGA and timolol (ITT results) |
|---|---|---|---|---|---|---|
| **Study C-05-24** | **n = 517** | **AZARGA** | **brinzolamide** | **timolol** | **AZARGA vs brinzolamide** | **AZARGA vs timolol** |
| Initial IOP (mmHg) |  |  |  |  |  |
| 8h | 27.1 | 27.1 | 27.0 |  |  |  |
| 10h | 25.8 | 25.6 | 25.4 |  |  |  |
| IOP at 2 weeks (mmHg) |  |  |  |  |  |
| 8h | 18.6 | 22.0 | 20.1 | -3.3 | <0.001 | -1.4 | 0.0008 |
| 10h | 17.1 | 20.4 | 18.8 | -3.3 | <0.001 | -1.7 | <0.0001 |
| IOP at 3 months (mmHg) |  |  |  |  |  |
| 8h | 18.8 | 21.5 | 20.1 | -2.7 | <0.001 | -1.3 | 0.0031 |
| 10h | 17.2 | 20.4 | 19.0 | -3.2 | <0.001 | -1.8 | <0.0001 |
| IOP at 6 months (mmHg) |  |  |  |  |  |
| 8h | 19.0 | 21.9 | 20.4 | -2.9 | <0.001 | -1.4 | 0.0011 |
| 10h | 17.8 | 20.5 | 19.6 | -2.7 | <0.001 | -1.8 | <0.001 |

Note: the Committee considers that these results must be interpreted with great caution, given the large number of tests applied.

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1 Kaback M, Scoper SV et al. Intraocular Pressure-Lowering Efficacy of Brinzolamide 1%/Timolol 0.5% Fixed Combination Compared with Brinzolamide 1% and Timolol 0.5%. Ophthalmology 2008; 115:1728-1734.
3.2. Adverse effects

Studies C-05-10 and C-05-24

In the non-inferiority study (C-05-10) comparing AZARGA and COSOPT, 21 patients stopped treatment because of an adverse effect (8 in the AZARGA group and 13 in the COSOPT group). The adverse effect profile of AZARGA was similar to that of COSOPT. The percentage of patients experiencing eye pain was 2.7% for AZARGA and 6.5% for COSOPT.

Eye irritation was observed in 2.7% of patients receiving AZARGA and 10.6% of those treated with COSOPT.

The percentage of patients experiencing visual disturbance was 3.6% for AZARGA (eye drops, suspension) and 0.5% for COSOPT (eye drops, solution).

In the study C-05-24, which compared AZARGA to monotherapy (brinzolamide or timolol), 17 patients stopped treatment because of an adverse effect (8 in the AZARGA group, 3 in the brinzolamide group and 6 in the timolol group).

The incidence of eye irritation in the AZARGA and timolol groups was similar. Visual disturbance was observed more frequently in patients receiving AZARGA or brinzolamide.

In the SPC, it is stated that the most commonly reported adverse effect reported in these two clinical studies that included 394 patients treated with AZARGA was transient blurred vision during instillation (3.6%), which persisted for a few seconds or a few minutes. Dysguesia (bitter or unusual taste in the mouth after instillation) was a frequently-occurring treatment-linked adverse effect (≥1/100 to < 1/10).

In addition to the safety data obtained during the clinical studies cited above, the dossier includes two randomised trials (C-05-49 and C-07-47) comparing AZARGA (brinzolamide/timolol) with COSOPT (dorzolamide/timolol).

Study C-05-49

Randomised double-blind study, lasting 1 week, comparing ocular discomfort observed in treatment with AZARGA (brinzolamide/timolol) with ocular discomfort observed for COSOPT (dorzolamide/timolol), in 95 patients aged over 18 with open-angle glaucoma or ocular hypertension, who had been treated with a monotherapy for at least a month at the time of inclusion.

Treatment:
- fixed-dose combination of brinzolamide + timolol (AZARGA) (n=48)
- fixed-dose combination of brinzolamide + timolol (COSOPT) (n=47)

The treatments were administered twice daily (at 8am and 8pm) for 1 week.

Primary endpoint: mean ocular discomfort score at 1 week, measured using a 5-unit scale (0 = no discomfort, 1 = mild discomfort, 2 = moderate discomfort, 3 = severe discomfort, 4 = very severe discomfort). Ocular discomfort was defined as one of (in particular) the following symptoms: ocular burning sensation or stinging.

Secondary endpoints: ocular pain and irritation, visual disturbance.

2 Vold SD, Evans RM et al. One-Week Comfort Study of BID-Dosed Brinzolamide 1%/Timolol 0.5% Ophthalmic Suspension Fixed Combination Compared to BID-Dosed Dorzolamide 2%/Timolol 0.5% Ophthalmic Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension. Journal of ocular pharmacology and therapeutics 2008, 24 (6): 601-5
Results:
After one week of treatment, mean ocular discomfort score was lower for AZARGA than for COSOPT (0.77 vs 1.53, p ≤ 0.05).

The percentage of patients experiencing ocular pain was 10.4% for AZARGA and 23.4% for COSOPT.
Ocular irritation was observed in 8.3% of patients treated with AZARGA and 17.0% of those treated with COSOPT.
The percentage of patients experiencing visual disturbance was 18.8% for AZARGA (eye drops, suspension) and 2.1% for COSOPT (eye drops, solution).

In no cases was treatment stopped because of an adverse effect.

NB: The primary objective of this study was limited to assessment of just one ocular adverse effect (ocular discomfort), over a limited period (1 week). However, there are other frequently-occurring ocular adverse effects such as visual disturbance (which can be attributed to the suspension formulation) that should be taken into account when assessing overall incidence of adverse effects.
It is difficult to assess the clinical relevance of this difference after 1 week of treatment, and it is difficult to estimate the real effect in terms of long-term compliance.

Study C-07-47
Randomised double-blind crossover 2-day study comparing patient preference in terms of tolerability of instillation following administration of one drop of AZARGA (brinzolamide/timolol) on day 1 and one drop of COSOPT (dorzolamide/timolol) on day 2 in both eyes or vice versa, in 129 patients with open-angle glaucoma or ocular hypertension.

Primary endpoint: percentage of patients with a preference for one or other treatment (either a preference for the first eye drops to be instilled, no preference, or a preference for the second eye drops).

Secondary endpoints: Ocular discomfort score, measured using a 10-point scale from 0 (no discomfort) to 9 (very severe discomfort).

Results (Intention-to-treat):
Of the 106 patients who expressed a preference for one of the two eyedrops, the percentage of patients who preferred AZARGA was 79.2% (84/106) and the percentage of patients who preferred COSOPT was 20.8% (22/106) (p<0.05).
After a single instillation into each eye, the ocular discomfort score was 1.4 points for AZARGA and 2.9 points for COSOPT (p<0.05).

NB: It is difficult to assess the clinical relevance of these patient preference data over such a short period (2 days).
3.3. Conclusion

The efficacy of AZARGA has been assessed using two phase III, randomised double-blind studies involving patients with open-angle glaucoma or ocular hypertension with baseline mean intraocular pressure of between 25 and 27 mmHg.

Reduction in mean intraocular pressure at 12 months in patients treated with AZARGA (brinzolamide/timolol) was not inferior to reduction on COSOPT (dorzolamide/timolol). Reduction in mean intraocular pressure obtained with AZARGA was statistically superior to that achieved with brinzolamide monotherapy and with timolol monotherapy.

No studies have compared AZARGA with concurrent administration of brinzolamide and timolol as separate preparations.

The safety profile of AZARGA was generally similar to that of COSOPT. Studies comparing AZARGA with COSOPT in terms of ocular discomfort and patient preference over a short period (1 week and 2 days) do not enable any strict conclusions to be drawn as to the relative tolerability of AZARGA and COSOPT.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

2.1. Actual benefit

Glaucoma is a serious condition that can lead to blindness.

This product is intended to provide preventative treatment for the complications of this disease.

Public Health Benefit:

Chronic open-angle glaucoma and intraocular hypertension are clinical conditions that represent a moderate public health burden, including the sub-population of patients receiving dual therapy.

Improved management of glaucoma and intraocular hypertension is a public health need that falls within the scope of identified priorities (GTNDO³).

However, this product, which is a fixed-dose combination of two existing antiglaucoma treatments, is not expected to have any impact on morbidity in comparison with concurrent administration of its separate components, particularly in view of the lack of data showing improved compliance with AZARGA.

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

For this reason, AZARGA is not expected to benefit public health.

The efficacy/adverse effect ratio is high.

There are numerous alternative treatments. This medicinal product is a second-line therapy.

The actual benefit provided by AZARGA, eye drops, suspension, is substantial.

³ French National Technical Objective Definition Group (DGS-2003)
4.1. Improvement in actual benefit

AZARGA, a fixed-dose combination of brinzolamide and timolol, provides no improvement in actual benefit (IAB V) in comparison with concurrent use of its separate components.

4.2. Therapeutic use

Glaucoma treatment is primarily based on treatment of ocular hypertension which is generally associated with the disease. Except for the most serious cases, for which surgery is required soon after diagnosis, treatment is medical at first. In the majority of cases, surgical treatment is only indicated when medical treatment fails. However, surgery is the preferred treatment for advanced glaucoma or for young patients. Laser trabeculectomy can be used after medical treatment has failed and before surgery. Medical treatment is generally prescribed “for life” and must not be discontinued unexpectedly. The choice of treatment is primarily based on the contraindications and adverse effects of each therapeutic class.

Many medicinal products are available, acting locally or systemically, and involving various mechanisms:

- **reduction in aqueous humour secretion:**
  - Beta blocking agents
  - alpha 2 adrenergic receptor agonists
  - carbonic anhydrase inhibitors

- **increased elimination of aqueous humour:**
  - adrenaline and combinations with adrenaline
  - miotics and parasympathomimetics
  - prostaglandins.

Beta blocker eyedrops and prostaglandin analogues are prescribed as first-line treatments.

It is possible to prescribe several pressure-reducing eyedrops in combination, as long as no more than three are prescribed. A prostaglandin analogue and a beta blocker may be prescribed as components of a dual therapy regimen, if one or the other has proved ineffective as first-line monotherapy. Other tone-reducing eyedrops are prescribed:

- either as first-line treatment as a monotherapy, if beta blockers and prostaglandin analogues are contraindicated;
- or as a second-line treatment, as a monotherapy or in combination with beta blockers or prostaglandin analogues if these are not sufficiently effective.

In some cases that do not respond to topical treatment, the latter type of treatment may be given in combination with acetazolamide, a carbonic anhydrase inhibitor, given systemically. However, the common and disabling adverse effects of acetazolamide (metabolic acidosis, hypokalaemia, kidney stones) limit its use.

4.3. Target Population

The percentage of patients treated for glaucoma is estimated to be 2% of French people aged over 40, i.e. 650,000 people, and it is estimated that around 400,000 people have glaucoma that is not diagnosed because the functional signs that are suggestive of the disease do not appear until a very late stage. (source: GTNDO - April 2003).
The available epidemiological data do not enable us to identify how many patients are affected by the indications for AZARGA as laid down in the marketing authorisation. According to the prescribing data (IMS), around 22% of patients with glaucoma are treated with second-line monotherapy and 30-40% with a combination including a beta blocker.

4.4. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage given in the marketing authorisation.

4.4.1 Packaging: the packaging is appropriate to prescription requirements.

4.4.2 Reimbursement rate: 65%