HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 May 2008

COSOPT 20 mg/5 mg/mL, eye drops, solution in single dose container
Box of 60 0.2 ml single dose containers (CIP code: 377 057-2)

Applicant: MERCK SHARP & DOHME-CHIBRET

dorzolamide (hydrochloride)
timolol (maleate)

List I

Marketing Authorisation (MA) date: 14 November 2006 (mutual recognition procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

dorzolamide (hydrochloride)
timolol (maleate)

1.2. Background

COSOPT single-dose container is the first example of eye drops sold in single-dose containers combining a beta-blocker with another anti-glaucoma treatment. This presentation contains no preservative.

1.3. Indication

COSOPT is indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

1.4. Dosage

The dose is one drop of COSOPT in the conjunctival sac of the affected eye(s) two times daily.
If another topical ophthalmic agent is being used, COSOPT and the other agent should be administered at least ten minutes apart.

Paediatric use:
Efficacy and safety in paediatric patients have not been established.

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

S : Sensory organs
S01 : Ophthalmologicals
S01E : Antiglaucoma preparations and miotics
S01EC : Carbonic anhydrase inhibitors
S01EC03 : Dorzolamide

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicinal products

COSOPT, eyedrops, solution in multidose bottle. This presentation differs from the single-dose presentation in that it contains a preservative.

2.2.2. Medicinal products that are not strictly comparable

These are other fixed or flexible combinations of beta blockers with another antiglaucoma agent in eyedrop form, indicated as second-line treatment if beta blockers are insufficiently effective.

Table 1: Flexible combinations with beta blockers:

Pharmacological class	**Active ingredient**	**Proprietary product**
Carbonic anhydrase inhibitor	brinzolamide dorzolamide	AZOPT, bottle TRUSOPT 2%, bottle
Alpha-blocker	apraclonidine brimonidin	IOPIDINE, bottle ALPHAGAN, bottle
Sympathomimetic	dipivefrin pilocarpin	PROPINE, bottle ISOPTO-PILOCARPINE, bottle PILOCARPINE, bottle
Prostaglandin	bimatoprost latanoprost travoprost	LUMIGAN, bottle XALATAN, bottle TRAVATAN, bottle
Beta blocker	betaxolol	BETOPTIC 0.25%, single dose container BETOPTIC 0.25% and 0.5%, bottle
	befunolol	BENTOS 0.25% 0.5%, bottle
	carteolol	CARTEABAK 1% and 2% (bottle with antimicrobial filter) CARTEOL 0.5% bottle CARTEOL 1% and 2%, bottle CARTEOL 1% and 2%, single dose container CARTEOL SR 1%, bottle CARTEOL SR 2%, bottle CARTEOL SR 1% and 2%, single dose container
	levobunolol	BETAGAN 0.5%, single dose container BETAGAN 0.1% and 0.5%, bottle LEVOBUNOLOL ALCON 0.5%, bottle
	metipranolol	BETANOL 0.1% 0.3% 0.6%
	timolol	DIGAOL 0.25% and 0.50%, single dose container GAOPTOL 0.25% and 0.5%, single dose container NYOGEL 0.1%, eye gel OPHTIM 0.25%, 0.5%, single dose container TIMABAK 0.10%, 0.25%, 0.5% (bottle with antimicrobial filter) TIMOCOMOD 0.25 % and 0.50%, bottle TIMOLOL CHAUVIN 0.25% and 0.5%, bottle TIMOPTOL 0.10%, bottle, and generics TIMOPTOL 0.25%, bottle, and generics TIMOPTOL 0.50%, bottle, and generics TIMOPTOL SR 0.25% and 0.5%, bottle TIMOPTOL 0.10%, 0.25% and 0.50% Ocumeter Plus

Table 2: Fixed combinations with beta blockers:

Pharmacological class	Active ingredient	Proprietary product
Alpha-blocker/beta-blocker	brimonidin, timolol	COMBIGAN, bottle
Sympathomimetic/beta-blocker	pilocarpin, carteolol pilocarpin, timolol	CARPILO, bottle PILOBLOQ, bottle
Prostaglandin/beta-blocker	bimatoprost, timolol latanoprost, timolol travoprost, timolol	GANFORT, bottle XALACOM, bottle DUOTRAV, bottle

2.3. Medicines with a similar therapeutic aim

Laser treatment: trabeculoplasty, iridotomy, iridoplasty, cyclophotocoagulation, goniopuncture.
Surgical treatments: penetrating filtering surgery, non-perforating filtering surgery.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

A randomised, double-blind, 12-week equivalence study was carried out to compare single dose COSOPT with multidose COSOPT in terms of reduction in intraocular pressure in 261 patients with raised intraocular pressure ≥22 mmHg in one or both eyes. At all measurement points, the limits of the 95% confidence interval of the difference between the treatments was within the interval [-1.5+1.5] mmHg, which was specified beforehand as the interval within which the difference between the treatments may be considered to be negligible. Therefore, these results mean that it is possible to conclude that these two formulations of COSOPT are equivalent.

3.2. Safety

No adverse effects specific to COSOPT in single dose containers were observed in any of the clinical studies; adverse effects were limited to those previously reported for multidose COSOPT, dorzolamide hydrochloride and/or timolol maleate.

3.3. Conclusion

A randomised, double-blind, 12-week efficacy study showed that the two formulations of COSOPT, single dose and multidose preparations, were equivalent in terms of reduction in intraocular pressure in patients with raised intraocular pressure ≥22 mmHg in one or both eyes.
The safety profile for single dose COSOPT was similar to that of multidose COSOPT.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Glaucoma is a serious condition that can lead to blindness.

This proprietary drug is intended to provide curative treatment.

Public health benefit:

Chronic open-angle glaucoma is a clinical condition that represents a moderate public health burden, including for the sub-population of patients involved here (who require second-line treatment).

Improved management of glaucoma is a public health need falling within the scope of identified priorities (GTNDO priorities[1]).
However, given the available data, COSOPT in a single dose container is not expected to have an additional benefit in terms of morbidity, in comparison to COSOPT in a multidose bottle.
This product therefore does not provide an additional response to the identified public health need.
For this reason, the proprietary drug COSOPT in single dose container is not expected to benefit public health.

The efficacy/safety ratio is high.

There are numerous alternative treatments. This medicinal product is a second-line treatment, to be given after failure of beta blocker eyedrops.

The actual benefit of COSOPT 20 mg/5 mg/mL eye drops, solution in single dose containers, is substantial.

4.2. Improvement in actual benefit

COSOPT 20 mg/5 mg/mL, eyedrops, solution in single dose container, does not provide any improvement in actual medical benefit (IAB level V) in comparison with COSOPT, eyedrops, solution in a multidose bottle.

4.3. Therapeutic use

4.3.1. Treatment strategy for chronic open-angle glaucoma

Glaucoma treatment is primarily based on treatment of increased ocular tone 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 trabeculoplasty can be used after medical treatment has failed and before considering 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 and 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 tone-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.

1 French National Technical Objective Definition Group (DGS-2003)

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 cannot be managed using topical treatment, the latter type of treatment may be given in combination with acetazolamide, a carbonic anhydrase inhibitor, given systemically. The common and disabling adverse effects of acetazolamide (metabolic acidosis, hypokalaemia, kidney stones) limit its use.

4.3.2. Therapeutic use of this product

COSOPT is a second-line treatment, to be used if beta blocker eyedrops monotherapy is not sufficient.

4.4. Target Population

The prevalence of glaucoma is of the order of 2% in those aged over 40, i.e. around 540,000 people are affected.
The available epidemiological data do not enable us to identify how many patients are affected by the indications for COSOPT as defined in the MA. 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, which represents a total of between 300,000 and 330,000 patients.

4.5. 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 indications and at the dosage given in the Marketing Authorisation.

4.5.1. Packaging

Appropriate for the prescription conditions.

4.5.2. Reimbursement rate

65%.