



Canadian Agency for
Drugs and Technologies
in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

BRINZOLAMIDE 1% / TIMOLOL 0.5% OPHTHALMIC SUSPENSION

(Azarga – Alcon Canada Inc.)

Indication: Elevated Intraocular Pressure

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that brinzolamide 1% / timolol 0.5% (Azarga) be listed in a similar manner to other carbonic anhydrase inhibitor/beta blocker combination products.

Reasons for the Recommendation:

1. In the Common Drug Review (CDR) systematic review that included two double-blind randomized controlled trials, the reduction in intraocular pressure at six months was greater for Azarga compared with either individual component given alone, and was similar for Azarga compared with the combination product of dorzolamide 2% / timolol 0.5% (Cosopt).
2. Azarga costs less than either individual component given alone and costs less than Cosopt.

Of Note:

The Committee noted that while Azarga costs less than other carbonic anhydrase inhibitor/beta blocker ophthalmic combination products, it costs more than prostaglandin analogue/beta blocker combination products.

Background:

Azarga is a combination of timolol, a beta-blocker, and brinzolamide, a carbonic anhydrase inhibitor. It has a Health Canada indication for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction, and when the use of combination therapy is appropriate.

Azarga is available as an ophthalmic suspension in 8 mL bottles containing 5 mL of brinzolamide 1.0% (10 mg/mL) and timolol 0.5% (5 mg/mL, as timolol maleate). The recommended dose is one drop to the affected eye, twice daily.

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Summary of CEDAC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) of Azarga and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials

Two double-blind, multi-centre, active-controlled, parallel group RCTs met the inclusion criteria for the CDR systematic review. No RCT was identified that compared Azarga with combination therapy using the individual components, brinzolamide (1.0%) twice daily and timolol (0.5%) twice daily.

- The Manni study (N = 437) was a one-year multinational, multi-centre, non-inferiority trial comparing two combination products: brinzolamide 1% / timolol 0.5% (Azarga) ophthalmic suspension and dorzolamide 2% / timolol 0.5% (Cosopt) ophthalmic solution.
- The Kaback study (N = 517) was a six-month multi-centre, superiority trial in the United States that evaluated three treatment groups: the combination product brinzolamide 1% / timolol 0.5% (Azarga), brinzolamide 1% alone, and timolol 0.5% alone.

Both trials included adults of at least 18 years of age diagnosed with either ocular hypertension or open-angle glaucoma whose IOP met the eligibility criteria (24 mm Hg to 36 mm Hg at 8 a.m.). Patients underwent a washout period if they were not treatment-naïve; the duration of the washout period was based on the duration of action and half-life of the medications.

Total withdrawals ranged from 7.3% to 12.9% across both studies.

Outcomes

The primary outcome measure in both trials was the mean reduction in IOP at six months. Other key outcomes were defined a priori in the CDR systematic review protocol. Of these outcomes, the Committee discussed adverse events.

None of the trials was designed to measure, or reported, clinical outcomes such as slowing or stopping the progression of visual field defects; but elevated IOP is considered an established surrogate marker of damage related to glaucoma.

Results

Efficacy or Effectiveness

- In the Manni study, the change in IOP in the Azarga group was non-inferior to the Cosopt group at six months. The upper 95% confidence limits of treatment group differences were below +1.5 mm Hg, which was the limit of clinical relevance used to establish non-inferiority.
- In the Kaback study, there was a statistically significant reduction in IOP for Azarga compared with either brinzolamide or timolol. Differences in IOP between Azarga and brinzolamide were -2.7 mm Hg and -2.9 mm Hg when measured at 8 a.m. and 10 a.m. respectively. Differences in IOP between Azarga and timolol were -1.4 mm Hg and -1.8 mm Hg when measured at 8 a.m. and 10 a.m. respectively. These differences may be considered clinically significant.

Harms (Safety and Tolerability)

- In the Manni study, there was a statistically significant increase in adverse events in the Cosopt group compared with the Azarga group (23.0% versus 14.1%, $P = 0.016$), the majority of which were eye irritation (10.6% versus 2.7%, $P = 0.002$, number needed to harm [NNH] = 13), and there was a higher incidence of blurred vision in the Azarga group compared with the Cosopt group (3.6% versus 0.5%, $P = 0.05$, NNH = 32).
- In the Kaback study, adverse events were similar between Azarga and either of its components used alone.
- In both studies, withdrawals due to adverse events were similar between treatment groups and ranged from 1.7% to 6.0% across both studies.

Cost and Cost-Effectiveness

Azarga costs \$21.00 for an 8 mL bottle containing 5 mL of the suspension. At the recommended dose (one drop twice daily in each affected eye), and assuming that both eyes are affected, the monthly cost of Azarga is \$25.20. Compared with the individual agents, brinzolamide (\$19.32 monthly) and timolol (\$9.08 monthly), the fixed-dose combination of Azarga results in a savings of \$3.20.

When compared with other ophthalmic combination products, including a carbonic anhydrase inhibitor and timolol, Azarga is associated with a monthly cost savings of \$8.89 compared with Cosopt (\$34.09 monthly). The cost of Cosopt is \$56.82 for a 10 mL bottle.

Compared with other combination products containing a prostaglandin analogue and timolol, which may also be used for the treatment of glaucoma, Azarga costs more than DuoTrav (\$19.53 monthly), Xalacom (\$22.95 monthly), and Combigan (\$24.07 monthly).

Other Discussion Points:

- The Committee discussed that there may be some patients who do not tolerate prostaglandin analogues and for whom treatment with carbonic anhydrase inhibitors would be considered.
- Patient compliance was not assessed in the included studies. Evidence from a recent systematic review of ocular hypotensive therapies suggests that the frequency of dosing can impact patient compliance where more than two doses per day were associated with worse compliance than two or fewer doses per day.
- The Committee noted that patents for brinzolamide and Cosopt will expire in the near future (April 2011 and April 2012 respectively), which may result in lower prices of generic products compared with Azarga.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:

None

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Conflicts of Interest:

One CEDAC member reported a conflict of interest and did not participate in the vote.

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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