CDEC FINAL RECOMMENDATION

BRINZOLAMIDE/BRIMONIDINE
(Simbrinza — Alcon Canada Inc.)
Indication: Glaucoma and Ocular Hypertension

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that brinzolamide/brimonidine fixed-dose combination (FDC) be listed for reducing intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) demonstrated that brinzolamide/brimonidine FDC twice daily was statistically superior to the individual components alone and non-inferior to the individual components used in combination for lowering IOP.
2. At the submitted price ($[redacted] per 10 mL bottle), the daily cost of brinzolamide/brimonidine FDC ($[redacted] per eye) is less than the daily cost of the individual components of brinzolamide and brimonidine administered separately ($0.31 per eye).

Background:
Brinzolamide/brimonidine (1%/0.2%) is an FDC ophthalmic suspension indicated for the reduction of IOP in adults with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. Brinzolamide/brimonidine FDC is available as a 10 mL bottle and the product monograph recommends a dose of one drop in the affected eye(s) two times daily.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the therapeutic rationale, place in therapy, bioequivalence, efficacy, and harms for the combined use of brinzolamide and brimonidine; a critique of the manufacturer's pharmacoeconomic evaluation; and information submitted by patient groups about outcomes and issues important to individuals living with glaucoma.

Patient Input Information
The following is a summary of information provided by three patient groups that responded to the CDR call for patient input:

- Vision loss associated with glaucoma negatively impacts the social, financial, and emotional well-being of those who are affected. Patients may lose or experience a reduction in their independence, ability to perform routine tasks, and ability to work. In addition, they become more prone to falls and injuries.
- The reduced ability to perform daily activities may lead to frustration, and the prospect of progressive vision loss, potential loss of employment and growing isolation, as well as concerns about diminished quality of life can result in depression.
- Patients whose other health conditions make them unable to take a treatment that includes a beta blocker would welcome an FDC treatment such as brinzolamide/brimonidine that does not include a beta blocker.

Clinical Trials

The CDR review included two phase 3, multi-centre, double-blind, parallel group, active-controlled RCTs (study 40 and study 41). Both studies were six months in duration and were conducted in patients with open-angle glaucoma or ocular hypertension who, in the opinion of the investigator, were insufficiently controlled on monotherapy or already using multiple IOP-lowering medications. Study 40 was a three-group superiority study that randomized 560 patients with an average baseline IOP of approximately 27 mm Hg to brinzolamide/brimonidine FDC (n = 193), brinzolamide (n = 192), or brimonidine (n = 175), each administered twice daily. Study 41 was a two-group non-inferiority trial that randomized 890 patients with an average baseline IOP of approximately 26 mm Hg to brinzolamide/brimonidine FDC (n = 451) or brinzolamide plus brimonidine (n = 439), each administered twice daily.

The manufacturer also provided a summary of the results of study C-10-010, a six-group pharmacokinetic study comparing brinzolamide/brimonidine FDC with brinzolamide and brimonidine administered separately (each treatment provided with either twice-daily or three-times-daily dosing).

Outcomes

CDEC discussed the following outcomes:

- Change from baseline in diurnal IOP and mean IOP
- Serious adverse events, total adverse events, ocular adverse events, and withdrawals due to adverse events.

The primary end point for both study 40 and study 41 was mean change from baseline in diurnal IOP at three months.

Efficacy

- Brinzolamide/brimonidine FDC was statistically superior to both brinzolamide and brimonidine with respect to mean diurnal IOP reduction from baseline at three months. The mean change from baseline in diurnal IOP was −7.9 mm Hg in the brinzolamide/brimonidine FDC group, −6.5 mm Hg in the brinzolamide group, and −6.4 mm Hg in the brimonidine group.
- The mean differences between brinzolamide/brimonidine FDC and the individual components were −1.4 mm Hg (95% confidence interval [CI], −1.9 to −0.8) and −1.5 mm Hg (95% CI, −2.0 to −0.9) versus brinzolamide and brimonidine, respectively.

- Brinzolamide/brimonidine FDC was non-inferior to brinzolamide plus brimonidine at three months, achieving the primary outcome of the study. The differences in change from baseline in mean diurnal IOP were:
  - 3 months: −0.1 mm Hg (95% CI, −0.5 to 0.2)
  - 6 months: 0.1 mm Hg (95% CI, −0.3 to 0.4).

Harms (Safety and Tolerability)

- Harms associated with brinzolamide/brimonidine FDC were similar to those associated with combination use of the two individual components.
- The proportions of patients who experienced at least one adverse event were:
  - Study 41: 38.9% with brinzolamide/brimonidine FDC and 41.5% with brinzolamide plus brimonidine
  - Study 40: 46.1% with brinzolamide/brimonidine FDC, 31.3% with brinzolamide, and 40.6% with brimonidine.
- The proportions of patients who experienced at least one serious adverse event were:
  - Study 41: 2.4% with brinzolamide/brimonidine FDC and 1.8% with brinzolamide plus brimonidine
  - Study 40: 2.6% with brinzolamide/brimonidine FDC, 1.0% with brinzolamide, and 1.7% with brimonidine.
- The proportions of patients who withdrew due to adverse events were:
  - Study 41: 10.6% with brinzolamide/brimonidine FDC and 13.3% with brinzolamide plus brimonidine
  - Study 40: 11.9% with brinzolamide/brimonidine FDC, 0.5% with brinzolamide, and 8.6% with brimonidine.
- Non-serious local ocular adverse events, including ocular discomfort, ocular hyperemia, and ocular allergic-type reactions, were the most commonly reported adverse events leading to discontinuation.

Pharmacokinetics

Study C-10-010 demonstrated that systemic exposure of brimonidine/brinzolamide FDC is either similar to or lower than the individual components administered separately. The product monograph states that no clinically significant changes in steady-state pharmacokinetics of either drug were observed when dosed in combination compared with those of the corresponding monotherapies.

Cost and Cost-Effectiveness

The manufacturer submitted a comparison of drug costs for brinzolamide/brimonidine FDC with the individual components of brinzolamide and brimonidine. At the submitted price, brinzolamide/brimonidine FDC ($[redacted] per eye daily) is less expensive than the individual components of brinzolamide ($0.23 per eye daily) and brimonidine ($0.08 per eye daily), resulting in a cost saving of $[redacted] per eye daily. Brinzolamide/brimonidine FDC would incur a single dispensing fee rather than two dispensing fees each time a claim is made.

Compared to other FDC products for open-angle glaucoma or ocular hypertension, brinzolamide/brimonidine FDC is less expensive (cost savings ranging from $[redacted] to $[redacted] per eye daily), except when compared with dorzolamide/timolol FDC (incremental cost of $[redacted] per eye daily).

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

May 20-21, 2015 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice 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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