Common Drug Review

Fixed-Dose Combination Review Report

October 2015

Drug	brinzolamide / brimonidine tartrate ophthalmic suspension (Simbrinza)
Indication	For reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.
Listing request	As per indication
Manufacturer	Alcon Canada Inc.

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ABBREVIATIONS

ADR	adverse drug reactions
AUC	area under the curve
BAK	benzalkonium chloride
BB	beta blocker
BID	twice daily
CAI	carbonic anhydrase inhibitors
CDR	CADTH Common Drug Review
CI	confidence interval
C_{max}	maximum concentration
FDC	fixed-dose combination
IOP	intraocular pressure
OAG	open-angle glaucoma
OHT	ocular hypertension
PK	pharmacokinetics
QD	once daily
RCT	randomized controlled trial
SAE	serious adverse event
TID	three times daily

EXECUTIVE SUMMARY

Simbrinza (brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, referred to herein as brinzolamide/brimonidine fixed-dose combination [FDC]) is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. The approved dose of brinzolamide/brimonidine FDC is one drop twice daily. The objective of this review is to evaluate the manufacturer-submitted evidence on the place in therapy, bioequivalence, safety, and costs of brinzolamide/brimonidine FDC in the indicated population.

Indication under review
For reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.
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Brinzolamide (Azopt) and brimonidine (Alphagan and generics) are both available for use as single-drug ophthalmic products. The primary rationale for combining brinzolamide and brimonidine into one product is to reduce the number of drops used by patients. Brinzolamide/brimonidine FDC is the only combination topical treatment for IOP available in Canada that does not contain a beta blocker (BB). Therefore, it may have a place in therapy for patients who cannot use BBs because of existing reactive airway disease, diabetes, or cardiovascular disease. The Canadian Ophthalmological Society does not specify the sequence in which the various topical drugs available for treatment of open-angle glaucoma or ocular hypertension should be used, although the authors emphasize the importance of using the fewest drugs at the lowest doses to achieve the target IOP. Based on input from the clinical expert consulted for this CADTH Common Drug Review (CDR), brinzolamide/ brimonidine FDC is not likely to be used as initial therapy, but is more likely to be used in patients who are insufficiently controlled on other topical drugs, intolerant to these drugs, or who have contraindications to their use.

The manufacturer cited two phase 3, randomized controlled trials (RCTs) to illustrate the efficacy profile of brinzolamide/brimonidine FDC: Study 040[1,2] and Study 041.[3,4] These studies were the basis of the manufacturer's submission to Health Canada. Study 040 compared patients using twice-daily brinzolamide/brimonidine FDC with a group using only brinzolamide and a third group using only brimonidine. At month three, the mean diurnal IOP change from baseline 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 the FDC and individual components were –1.4 mm Hg and –1.5 mm Hg, respectively ($P < 0.0001$). Two other phase 3 trials have studied brinzolamide/brimonidine FDC administered three times daily, the dose approved in the US.

Study 041 was a non-inferiority study that compared a group of patients using twice-daily brinzolamide/ brimonidine FDC with a group using twice-daily brinzolamide plus brimonidine. The non-inferiority of brinzolamide/brimonidine FDC compared with brinzolamide plus brimonidine given as separate drops, at month three, was the primary outcome of the study, and the study met the predetermined criterion for non-inferiority. The between-group difference was –0.1 mm Hg with an upper bound of the 95%

confidence interval (CI) equal to 0.2 mm Hg, which was below the pre-specified non-inferiority margin of 1.5 mm Hg.

The harms profile of taking brinzolamide/ brimonidine FDC appears similar to that of the individual components (brinzolamide 10 mg/mL and brimonidine 2 mg/mL) based on the limited harms data provided in this submission, but there are other harms data from phase 3 studies including serious adverse event data that were not presented by the manufacturer.

The brinzolamide/brimonidine FDC product monograph indicates that there were no clinically significant changes in steady-state pharmacokinetics of either drug when dosed in combination versus the corresponding monotherapies. The manufacturer provided a summary of the results of a pharmacokinetic study, C-10-010. The overall area under the curve (AUC) for brimonidine twice daily (given as brinzolamide/brimonidine FDC) was statistically lower than brimonidine given separately twice daily. Mean brinzolamide plasma concentrations observed were described as comparable after topical ocular administration with brinzolamide/brimonidine FDC or brinzolamide 1% in the twice-daily regimen; however, numerical results were not reported. Overall, the results of C-10-010 indicate that systemic exposure of brimonidine and brinzolamide administered as the FDC is either similar or lower than the individual components administered separately, hence the risk of systemic adverse effects is also expected to be similar.

At the submitted price, brinzolamide/brimonidine FDC ($[redacted] per eye daily) is less expensive than the individual components of brinzolamide ($0.23) and brimonidine ($0.08), resulting in a cost saving of $[redacted] per eye daily. Compared with 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).

When brinzolamide/brimonidine FDC is compared with other combination treatments taken as individual drugs, the potential savings are between $[redacted] and $[redacted] per eye daily. However, when compared with brimonidine, pilocarpine, carbachol, or latanoprost used concomitantly with timolol 0.5%, brinzolamide/brimonidine FDC is expected to incur an additional cost ranging from $[redacted] to $[redacted] per eye daily.

1. INTRODUCTION

Simbrinza (brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, referred herein as brinzolamide/brimonidine fixed-dose combination [FDC]) is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. The approved dose of brinzolamide/brimonidine FDC is one drop twice daily. The objective of this review is to evaluate the manufacturer-submitted evidence on the place in therapy, bioequivalence, safety, and costs of brinzolamide/brimonidine FDC in the indicated population.

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2. RATIONALE AND PLACE IN THERAPY

2.1 Manufacturer-Submitted Information on Rationale (Verbatim)

Simbrinza (brinzolamide/brimonidine FDC) has been shown to be safe and efficacious in the treatment of patients with open-angle glaucoma (OAG) and ocular hypertension (OHT):

- Brinzolamide/brimonidine FDC is the only fixed combination that is beta-blocker (BB)-free, providing a therapeutic option for patients in whom BBs are contraindicated.
- In clinical studies, brinzolamide/brimonidine FDC twice daily was statistically superior in IOP-lowering efficacy, compared with either of the individual components alone, and non-inferior to the individual components used concomitantly.
- The safety profile of brinzolamide/brimonidine FDC is similar to that of the individual components, resulting in no additional risk to patients.
- As a fixed-dose combination product, brinzolamide/brimonidine FDC is convenient and has potential for increased patient compliance.

Brinzolamide/brimonidine FDC twice-daily ophthalmic suspension is the only beta-blocker (BB) free fixed-combination indicated for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). BB use is not appropriate for all patients with glaucoma.(5) Brinzolamide/brimonidine FDC therefore creates the opportunity to provide a new therapeutic option for use in patients in whom BBs are contraindicated (e.g., patients with obstructive lung disease and congestive heart failure).

In clinical studies, brinzolamide/brimonidine FDC twice daily was statistically superior in IOP-lowering efficacy, compared with either of the individual components alone, and non-inferior to the individual components used concomitantly:

- *SIMBRINZA Phase 3 Superiority Study (1, 2):* efficacy results demonstrated that brinzolamide/brimonidine FDC was superior to both brinzolamide and brimonidine with respect to mean diurnal IOP reduction from baseline at Month 3.
  - At Month 3, the mean diurnal IOP change from baseline was -7.9 mmHg in the brinzolamide/brimonidine FDC group, -6.5 mmHg in the brinzolamide group, and -6.4 mmHg in the brimonidine group.
  - The mean difference between the combination and each of its active components was significant [mean difference of brinzolamide/brimonidine vs. brinzolamide alone and brimonidine alone was -1.4 mmHg and -1.5 mmHg, respectively (both $p< 0.0001$)].
  - The mean IOP reduction from baseline at all time points with brinzolamide/brimonidine FDC was 6–9 mmHg (representing a reduction of up to 34%).
- *SIMBRINZA Phase 3 Non-Inferiority Study (3)*: efficacy results demonstrated that brinzolamide/brimonidine FDC was non-inferior to brinzolamide 10 mg/mL plus brimonidine 2 mg/mL (administered as separate drops) with regard to the mean diurnal IOP reduction from baseline at Month 3.
  - At Month 3, the mean diurnal IOP reduction from baseline was similar for patients in the brinzolamide/brimonidine FDC group and in the brinzolamide plus brimonidine group (diurnal IOP reductions relative to baseline of 8.5 and 8.3 mmHg, respectively).
  - The between-group difference was -0.1 mmHg with an upper bound of the 95% CI equal to 0.2 mmHg, which was below the pre-specified non-inferiority margin of 1.5 mmHg.
  - The mean IOP reduction from baseline at all time points with brinzolamide/brimonidine FDC was 7–10 mmHg (representing a reduction of up to 37%).

- The safety profile of brinzolamide/brimonidine FDC was similar to that of the individual components, resulting in no additional risk to patients.(4)

Because glaucoma is a chronic disease requiring frequent topical administrations and long-term treatment, it is important to minimize the safety risk. Both preservative load and systemic side effects are minimized by a substantial reduction in preservative concentration, and by the absence of a beta-blocker, respectively. As topical glaucoma medications are applied frequently and usually over the long term, preservative toxicity becomes an important factor. Brinzolamide/brimonidine FDC is designed with a lower benzalkonium chloride (BAK) concentration (0.03 mg/mL) than other IOP-lowering medications (e.g., 80% and 40% less than the monocomponent agents, Azopt [brinzolamide; 0.15 mg/mL BAK] and Alphagan [brimonidine; 0.05 mg/mL BAK] respectively, and 40% less than the FDC product, Combigan [brimonidine + timolol; 0.05 mg/mL BAK]). FDC products reduce cumulative exposure to BAK even when they are BAK-preserved, compared with administering two IOP-lowering monotherapy agents concomitantly (6, 7).

In addition, by providing the convenience of two well-established IOP-lowering medications in a single formulation, brinzolamide/brimonidine FDC has the potential to improve patient compliance to treatment by reducing the number of drops administered per day and total number of bottles. A FDC product reduces medication burden by 50% compared to the burden when both individual components are used concomitantly. Furthermore, reduced compliance is observed with certain combination products due to formulation differences and ocular discomfort.(8, 9)

There are also known difficulties in administration of eye drops, particularly with increasing complexity of dose regimen.(10, 11) Less than optimal patient compliance with the dosing schedule can reduce therapeutic benefit and lead to disease progression and visual field loss. As such, there is significant value to a new FDC that provides effective IOP lowering, reduces medication burden, enhances compliance, and provides a safe and efficacious new therapeutic option.

2.1.1 Pharmacological rationale for the combination

The two components of brinzolamide/brimonidine FDC lower IOP – a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss in patients with OAG and OHT – by suppressing the formation of aqueous humour from the ciliary process in the eye.

The mechanism of action by which brimonidine reduces aqueous humour production differs from that of brinzolamide, and so it could be expected that the mechanisms of action of the two drugs in a FDC would complement each other. Brinzolamide is a carbonic anhydrase inhibitor (CAI) that reduces sodium and fluid transport across the ciliary epithelium and thereby decreases aqueous humour production (12). Brimonidine is an α2-agonist that stimulates uveoscleral outflow by unknown mechanisms (13) and also inhibits aqueous humour production by activating the α2 adrenergic receptors in the ciliary epithelium and down-regulating the levels of intracellular cyclic adenosine monophosphate (13). While α-agonists reduce IOP by decreasing aqueous humour production, with chronic use, they also increase uveoscleral outflow (13, 14). Brimonidine may also provide a neuroprotective effect on IOP-independent mechanisms, which would lower the risk of disease progression (15).

Brinzolamide and brimonidine have each been shown to be individually safe and effective in the treatment of elevated IOP in patients with OAG or OHT (16-19).

2.2 Manufacturer-Submitted Information on Place in Therapy (Verbatim)

The overarching management goals in patients with glaucoma are to preserve visual function by slowing or halting progression of the disease and to maintain or improve the health-related quality of file (HRQoL) of glaucoma patients.(5) IOP lowering is the only clinically established method of treating glaucoma. According to the Canadian Ophthalmological Society (COS) glaucoma clinical practice guidelines, the most common method for lowering IOP and treating patients with glaucoma involves medical therapy and the use of topical agents in the form of eye drops.(5)

The classes of IOP-lowering agents that are currently available are miotics, prostaglandin analogues, alpha-2 adrenergic agonists, beta blockers, and topical CAIs. CAIs (such as brinzolamide 1% and dorzolamide 2%) are commonly used to lower IOP. In the past, BBs (such as timolol 0.25% or 0.5% and betaxolol 0.25%) were the common first-line treatment for lowering IOP in glaucoma patients, however patients and physicians were given a variety of choices with the development of newer agents over the past 15 years. Prostaglandin analogues (such as travoprost 0.004%, latanoprost 0.005%, and bimatoprost 0.01%) are a very popular treatment choice due to the combination of effectiveness and tolerability over BBs. Finally, α2 agonists (such as brimonidine 0.2%) work by increasing uveoscleral outflow or decreasing aqueous production.(5)

As many as 40% of patients treated for glaucoma are unable to achieve adequate control of IOP with a single medication. (20) COS glaucoma clinical practice guidelines recommend that in treating patients with glaucoma, clinicians should utilize the minimum number of medications with the minimum dosing frequency in order to maximize patient QoL and adherence to medical therapy.(5) In addition, there is concern that patients with asthma, chronic obstructive pulmonary disease, sinus bradycardia, or greater than first-degree heart block should not be prescribed non-cardioselective BBs due to the possibility of exacerbating these conditions. Hence, there is an unmet need for a convenient medical therapy that is effective in controlling OAG and OHT with an improved dosing regimen, which is well tolerated by patients and enhances compliance/adherence.

Brinzolamide/brimonidine FDC twice-daily ophthalmic suspension is the only BB-free fixed-combination indicated for reduction of IOP in patients with OAG or OHT for whom monotherapy provides insufficient IOP reduction AND when the use of brinzolamide/brimonidine FDC is considered appropriate. Brinzolamide/brimonidine FDC contains the most commonly prescribed doses of brinzolamide 1% and brimonidine 0.2%. The recommended dose is one drop of brinzolamide/brimonidine FDC in the affected eye(s) two times daily. If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed 1 drop in the affected eye(s) 2 times daily. There were no cases of overdose reported in the clinical development program for brinzolamide/brimonidine FDC. If overdose with brinzolamide/brimonidine FDC occurs, treatment should be symptomatic and supportive; the patient's airway should be maintained.

The mechanism of action by which brimonidine reduces aqueous humour production differs from that of brinzolamide, and so it could be expected that the mechanisms of action of the two drugs in a fixed combination would complement each other. Brinzolamide/brimonidine FDC has been demonstrated to produce greater IOP-lowering efficacy than either active agent alone.

In clinical studies, brinzolamide/brimonidine FDC twice daily was statistically superior in IOP-lowering efficacy, compared with either of the individual components alone, and non-inferior to the individual components used concomitantly.(1-3) A mean IOP reduction of up to 37% from baseline was achieved at

all time points across the two Phase 3 studies. The safety profile is similar to that of the individual components, resulting in no additional risk to patients.(4)

Unlike timolol-containing combinations, brinzolamide/brimonidine FDC is not contraindicated in patients with respiratory disorders (e.g., asthma, COPD), sinus bradycardia, 2nd or 3rd degree AV block, cardiac failure, and cardiogenic shock due to the possibility of exacerbating these conditions. Therefore, brinzolamide/brimonidine FDC is the only fixed combination that is BB-free, providing a therapeutic option for patients in whom BBs are contraindicated.

Furthermore, brinzolamide/brimonidine FDC is dosed from a single bottle. This fixed-combination reduces the complexity of the patient regimen by combining two agents with synergistic mechanisms of action in one bottle. Reducing the number of drops per day and total number of bottles facilitates long-term adherence and reduces the overall medication burden to the patient.

Given the unmet need that still exists for a convenient medical treatment option and the clinical benefits demonstrated with brinzolamide/brimonidine FDC in controlling OAG and OHT, brinzolamide/brimonidine FDC should be considered for funding as a treatment for reducing elevated IOP in adult patients with OAG and OHT, in line with the Health Canada indication.

2.3 CDR Reviewer Comments

Canadian clinical guidelines recommend the use of topical drugs for IOP reduction.[5] These include alpha-2 adrenergic agonists (e.g., brimonidine), BBs (e.g., timolol), carbonic anhydrase inhibitors (e.g., brinzolamide), cholinergic drugs (e.g., pilocarpine), and prostaglandin analogues (e.g., latanoprost). The authors did not specify the sequence or the number of drugs to use. The authors emphasize the importance of using the fewest drugs at the lowest doses to achieve the target IOP.

The clinical expert consulted for this CADTH Common Drug Review (CDR) stated that the common approach in Canadian practice is to begin medical treatment using a prostaglandin analogue, as drugs in this class are slightly more effective at lowering IOP than BBs.[5] If IOP is not sufficiently reduced, the prostaglandin analogue could be replaced by or supplemented with a BB, either as a combination product or as an individual product. If the use of BBs is contraindicated or if there is insufficient IOP reduction, carbonic anhydrase inhibitors may be used, with or without an alpha-2 adrenergic agonist.

The clinical expert stated that neither the brinzolamide/brimonidine FDC nor its individual components would be used for initial therapy of open-angle glaucoma or OHT. Studies 040 and 041 described by the manufacturer in Section 1.3 appeared to align with this view in that the included patients had open-angle glaucoma or ocular hypertension that was insufficiently controlled on monotherapy, or were on multiple IOP-lowering medications, at the time of study entry. The clinical expert stated that brinzolamide/brimonidine FDC is appropriate for use in this population. The primary rationale for combining brinzolamide and brimonidine into one product is to reduce the number of drops used by patients, which may improve patient compliance. Improved compliance may slow deterioration of visual field loss, but this has not been proven empirically.[5]

Brinzolamide/brimonidine FDC is the only combination topical treatment for IOP available in Canada that does not contain a BB. Therefore, it may have a place in therapy for patients who cannot use BBs because of existing reactive airway disease, diabetes, or cardiovascular disease.

The clinical expert for this CDR agreed with the manufacturer's assertion that reducing exposure to BAK could result in lower rates of irritation and may also improve compliance.

2.3.1 Clinical evidence

The manufacturer cites two phase 3, randomized controlled trials (RCTs) to illustrate the efficacy profile of brinzolamide/brimonidine FDC: Study 040[1,2] and Study 041.[3,4] These studies were the basis of the manufacturer's submission to Health Canada. There were at least two other phase 3 RCTs performed using a brinzolamide/brimonidine FDC product, but these studies were not cited by the manufacturer for reasons unstated (Study 033, Study 039),[6-9] possibly because these studies used a three-times-daily dosage regimen rather than the twice-daily regimen that was used in Study 040 and Study 041 and is the approved regimen in Canada. The approved dosing frequency in Canada is twice daily for the components sold individually: Azopt (brinzolamide 1%) and Alphagan (brimonidine 0.2%). Study 033 and Study 039 were the basis of the manufacturer's submission to the FDA, and brinzolamide/brimonidine FDC is recommended for use three times daily in the US.

The superiority study mentioned by the manufacturer (Study 040) randomized 560 patients with an average baseline IOP of ~27 mm Hg (brinzolamide/brimonidine FDC: N = 193; brinzolamide: N = 192; brimonidine: N = 175). The study met its primary end point of mean change in diurnal IOP from baseline to month three.[2]

The non-inferiority study mentioned by the manufacturer (Study 041) randomized 890 patients with an average baseline IOP of ~26 mm Hg (brinzolamide/brimonidine FDC: N = 451; brinzolamide plus brimonidine: N = 439). The manufacturer's clinical study report states that the manufacturer selected 1.5 mm Hg as a non-inferiority margin because of historical convention in similar studies and because it was the minimal clinically relevant change; however, no citations were provided to support this approach.[4] The non-inferiority of brinzolamide/brimonidine FDC compared with brinzolamide plus brimonidine given as separate drops at month three was the primary outcome of the study (mean change: –0.1 mm Hg [95% CI,–0.5 to 0.2]). The criterion for non-inferiority was met.

3. BIOEQUIVALENCE

3.1 Manufacturer-Submitted Information on Bioequivalence (Verbatim)

Since brinzolamide/brimonidine FDC is intended for topical ocular use only, bioavailability and/or bioequivalence assessment in ocular tissues comprising the site of action is unfeasible due to ethical considerations related to ocular tissue sampling. Therefore, no *in vivo* systemic bioavailability or bioequivalence studies were conducted with brinzolamide/brimonidine FDC. The formulation intended for marketing was used in the conduct of all clinical studies. A study to evaluate the steady state pharmacokinetics (PK) of brimonidine in plasma, and red blood cell saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of brinzolamide/brimonidine dosed TID or BID, and to compare it to the steady state PK following dosing with the individual components (i.e., brinzolamide or brimonidine) in healthy subjects has been completed (not submitted to the CDR due to tailored combination filing requirements). Please note that Health Canada's approval of brinzolamide/brimonidine FDC is based on the BID dosing regimen. Pharmacokinetic parameters of the individual components (i.e., brinzolamide and brimonidine) are provided below.

3.1.1 Pharmacokinetics

Study C-10-010 was conducted to compare the steady-state PK of brimonidine in plasma and red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of brinzolamide/brimonidine FDC dosed TID or BID to the individual components in healthy subjects. Mean brinzolamide plasma concentrations observed at Day 107 in this study were comparable after topical ocular administration with brinzolamide/brimonidine FDC or brinzolamide 1% in the twice daily (BID) regimen.

With respect to brimonidine systemic exposures, mean plasma C_{max} was slightly greater with brinzolamide/brimonidine FDC BID (0.0724 ng/mL) compared with brimonidine 0.2% BID (0.0639 ng/mL) at Day 21 (Table 1). However, the overall AUC for brinzolamide/brimonidine FDC BID was lower than brimonidine BID, suggesting the increased exposure observed with the combination product BID regimen may be related to inter-subject variability. Overall, the systemic plasma half-life was similar for both the combination product and brimonidine in both the BID and TID regimens. As such, the individual components have uncomplicated and similar pharmacokinetic characteristics.

TABLE 1: COMPARISON OF BRIMONIDINE MEAN (MINIMUM TO MAXIMUM) PK PARAMETERS ON DAY 21 AFTER ADMINISTRATION OF BRINZOLAMIDE/BRIMONIDINE FDC OR BRIMONIDINE 2 MG/ML (TID OR BID) IN HEALTHY SUBJECTS IN STUDY C-10-010.

Day	PK Parameters	Brinz/Brim BID	Brimonidine 2 mg/mL BID	Brinz/Brim TID	Brimonidine 2 mg/mL TID
21	N	24	24	23	24
	C_{max} (ng/mL)	0.0724 (0.0234-0.179)	0.0639 (0.0279-0.114)	0.0545 (0.0186-0.122)	0.0574 (0.0085-0.137)
	T_{max} (hr)*	0.50 (0.25-1.00)	0.75 (0.25-2.00)	0.67 (0.25-1.50)	1.00 (0.25-1.52)
	$AUC_{0\text{-}last}$ (ng*hr/mL)	0.196 (0.0580-0.408)	0.243 (0.0985-0.457)	0.215 (0.0530-0.538)	0.233 (0.0249-0.496)
	$t_{1/2}$ (hr)	2.57 (1.37-4.69)	2.38 (1.75-3.99)	2.43 (1.69-3.35)	2.48 (1.48- 6.86)

*T_{max} is expressed as median with range (minimum to maximum)

No *in vitro* studies have been conducted with brinzolamide/brimonidine FDC. The *in vitro* studies of brinzolamide and brimonidine have been reported previously in the new drug applications for AZOPT (brinzolamide 10 mg/mL suspension) and ALPHAGAN (brimonidine tartrate 2 mg/mL solution).

3.1.3 Absorption

Brinzolamide is absorbed through the cornea following topical ocular administration. The drug is also absorbed into the systemic circulation where it binds strongly to carbonic anhydrase in red blood cells. Plasma drug concentrations are very low. Whole blood elimination half-life is prolonged (>100 days) in humans due to red blood cell carbonic anhydrase binding.

Plasma brimonidine levels peak within 1 – 4 hours and decline with a systemic half-life of approximately 3 hours.

3.2 CDR Reviewer Comments

The manufacturer provided a summary of the results of the C-10-010 pharmacokinetic study. Few details were provided in the original submission from the manufacturer regarding the methods used in this study, for example, the sample size, or the rationale for reporting results at day 107 for brinzolamide and day 21 for brimonidine. However, the following additional information was provided as part of the manufacturer's comments on the draft CDR report:

- Study C-10-010 was a six-group pharmacokinetic study comparing brinzolamide/brimonidine FDC to brinzolamide and brimonidine administered alone.
- Separate twice-daily and three-times-daily groups were included for each formulation tested. The sample size was 23 to 24 subjects per group.
- The rationale for collecting pharmacokinetic data on days 21 and 107 for brimonidine and brinzolamide, respectively, was based on the times required to achieve steady-state for the two drugs.
- Summary statistics for the various pharmacokinetic parameters were calculated. The only statistical comparisons of the pharmacokinetic data were calculations of the least squares means ratios and the corresponding 90% confidence intervals (CIs) of maximum concentration (C_{max}) and area under the curve (AUC_{0-t}) for each drug in the FDC versus the same drug administered alone. These calculations were performed separately for the twice-daily and three-times-daily posologies. The only case where the least squares means ratio confidence interval did not bracket unity (i.e., there was a statistically significant difference) was for brimonidine in the FDC and brimonidine alone both dosed twice daily. In this case the total exposure to brimonidine was lower for the FDC compared with brimonidine administered alone.

The C_{max} was slightly greater for brimonidine (given as brinzolamide/brimonidine FDC twice daily) compared with brimonidine given separately twice daily; however, this was not flagged as a statistically significant difference in the additional information provided by the manufacturer. The brinzolamide/brimonidine FDC product monograph contains the following statement based on the results of the C-10-010 study: "A clinical study was conducted comparing systemic pharmacokinetics of brinzolamide and brimonidine in the fixed combination (BID or TID) versus the two agents administered separately. No clinically significant changes in steady-state pharmacokinetics of either drug were observed when dosed in combination compared with those of the corresponding monotherapies."[10]

Overall, the results of C-10-010 indicate that systemic exposure of brimonidine and brinzolamide administered as the FDC is either similar or lower than the individual components administered separately, hence the risk of systemic adverse effects is also expected to be similar.

4. HARMS

4.1 Manufacturer-Submitted Information on Harms (Verbatim)

The safety profile of brinzolamide/brimonidine FDC was similar to that of the individual components (brinzolamide 10 mg/mL and brimonidine 2 mg/mL) and did not result in additional risk to patients relative to the known risks of the individual components.

Table 2 summarizes adverse drug reactions (ADRs) assessed by the examining physician as related to the use of study medications reported at an incidence of ≥ 1% in clinical trials C-10-041 and C-10-040 (data pooled).

The most frequent ocular ADRs observed with the use of brinzolamide/brimonidine FDC were non-serious local ocular side effects (e.g., hyperemia of the eye, ocular allergic type reactions, blurred vision, and ocular discomfort). Common systemic ADRs reported with its use were non-serious and included dysgeusia, oral dryness, and fatigue/drowsiness. The majority of ADRs leading to patient discontinuation from study were non-serious local ocular side effects (e.g., ocular discomfort, ocular hyperemia, and ocular allergic type reactions). The incidence of patients discontinuing due to these events was similar between brinzolamide/brimonidine FDC and concomitant dosing with the individual components (brinzolamide 10 > mg/mL + brimonidine tartrate 2 mg/mL).

The Canadian Ophthalmological Society has acknowledged that beta-blocker (i.e., timolol-containing combinations) use may not be appropriate for all patients with glaucoma. Unlike timolol-containing combinations, brinzolamide/brimonidine FDC is not contraindicated in patients with respiratory disorders (e.g., asthma, COPD), sinus bradycardia, 2nd or 3rd degree AV block, cardiac failure, and cardiogenic shock.

TABLE 2: ADVERSE DRUG REACTIONS OCCURRING IN ≥ 1% OF PATIENTS - C-10-040/C-10-041

Coded Adverse Event	Brinz/Brim BID N=645 N (%)	Brinz + Brim BID N=436 N (%)	Brinz BID N=192 N (%)	Brim BID N=175 N (%)
Eye Disorders				
Ocular hyperaemia	27 (4.2)	17 (3.9)	1 (0.5)	8 (4.6)
Vision blurred	18 (2.8)	13 (3.0)	1 (0.5)	2 (1.1)
Conjunctival hyperaemia	10 (1.6)	13 (3.0)	3 (1.6)	4 (2.3)
Conjunctivitis allergic	17 (2.6)	9 (2.1)	0 (0)	3 (1.7
Eye pain	18 (2.8)	8 (1.8)	3 (1.6)	0 (0)
Eye pruritus	14 (2.2)	8 (1.8)	3 (1.6)	4 (2.3)
Eye irritation	14 (2.2)	7 (1.6)	4 (2.1)	3 (1.7)
Conjunctivitis	12 (1.9)	5 (1.1)	0 (0)	1 (0.6)
Eye allergy	8 (1.2)	6 (1.4)	0 (0)	2 (1.1)
Foreign body sensation in eyes	5 (0.8)	5 (1.1)	2 (1.0)	2 (1.1)
Punctate keratitis	4 (0.6)	6 (1.4)	1 (0.5)	2 (1.1)
Lacrimation increased	6 (0.9)	4 (0.9)	0 (0)	2 (1.1)
Dry eye	4 (0.6)	3 (0.7)	1 (0.5)	3 (1.7)
Asthenopia	2 (0.3)	0 (0)	0 (0)	2 (1.1)
Gastrointestinal disorders				
Dry mouth	18 (2.8)	14 (3.2)	2 (1.0)	9 (5.1)
Nervous system disorders				
Dysgeusia	22 (3.4)	16 (3.7)	4 (2.1)	2 (1.1)
Somnolence	14 (2.2)	15 (5.4)	0 (0)	4 (2.3)
Headache	6 (0.9)	3 (0.7)	1 (0.5)	2 (1.1)
Dizziness	0 (0)	3 (0.7)	1 (0.5)	3 (1.7)
Vascular disorders				
Hypotension	2 (0.3)	1 (0.2)	0 (0)	2 (1.1)

Source: SIMBRINZA Product Monograph(4)

4.2 CDR Reviewer Comments

The brinzolamide/brimonidine FDC product monograph concludes that the safety profile of brinzolamide/brimonidine FDC was similar to that of the individual components and did not result in additional risk to patients relative to the known risks of the individual components.[10]

The manufacturer presented the pooled data from Studies 040 and 041 for adverse drug reactions occurring in ≥ 1% of patients in Studies 040 and 041. While there are no apparent differences between brinzolamide/brimonidine FDC and co-administration of brinzolamide and brimonidine in the listed adverse events (AEs), the manufacturer did not present any serious adverse event (SAE) data for Studies 040 and 041. Indeed, the rates of SAE were slightly higher in the brinzolamide/brimonidine FDC groups (2.4% to 2.6%) compared with the other treatment groups (1.0% to 1.6%) in these studies.[1,3] There was no particular pattern to the observed SAEs.

It should also be noted that Studies 040 and 041 represent only half of the patient exposure to brinzolamide/brimonidine FDC in phase 3 trials. It would have been informative for the manufacturer to

include the AE data from the studies of the three-times-daily regimen (Studies 033 and 039) in the pooled data analysis, or to present the data from these studies alongside the analysis of Studies 040 and 041. For example, there were 29 SAEs mentioned in the publications for Studies 033 and 039, but there were no details provided regarding these SAEs.[6,7,9]

5. PHARMACOECONOMIC EVALUATION

5.1 Manufacturer-Submitted Cost Information (Verbatim)

TABLE 3: COST COMPARISON OF NEW COMBINATION PRODUCT AND INDIVIDUAL COMPONENTS

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)**
brinzolamide/ brimonidine (SIMBRINZA)	**brinzolamide 1%/brimonidine 0.2%**	**Suspension**	**$[redacted]* per 10mL bottle or $[redacted] per ml**	**One drop BID**	**$[redacted]**
brinzolamide (Azopt†)	brinzolamide 1%	Suspension	$3.4120 per mL§	One drop BID	$0.2252
brimonidine (Alphagan‡, Apo-, PMS-, Ratio-, Sandoz-brimonidine)	brimonidine 0.2%	Solution	$1.1550 per mL§	One drop BID	$0.0762
Total (brinzolamide + brimonidine)	brinzolamide 1% + brimonidine 0.2%	**Suspension + Solution**	**$4.5670 per ml**	**One drop BID + One Drop BID**	**$0.3014**

*The submitted price is a Confidential Price that will become effective following the release of a recommendation for SIMBRINZA from the Canadian Drug Expert Committee (CDEC) to participating provincial/federal drug plans.
§Price for brinzolamide 1% and brimonidine 0.2% was extracted from the Ontario Drug Benefit Formulary/Comparative Drug Index: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
** Daily cost was calculated as: Cost per bottle / (Drops per mL * bottle size (mL) / [total drops per day]). A drop size for SIMBRINZA of 0.033mL/drop was assumed for all products.
†Two patents for Azopt (brinzolamide) 1% have expired; one process patent for Azopt was issued on 2003-11-18
‡Expiry date of Alphagan 0.2% formulation patent is on June 17, 2016, however generic products are available

SIMBRINZA fixed combination (brinzolamide 1%/brimonidine 0.2%) has a daily drug cost of $[redacted]. The individual component brinzolamide 1% has a daily drug cost of $0.2252 and the individual component brimonidine 0.2% has a daily drug cost of $0.0762. When the individual components are used concomitantly (ie. brinzolamide 1% + brimonidine 0.2%), the daily drug cost is $0.3014. Therefore, with the confidential submitted pricing, there is cost savings of $[redacted] per day by using brinzolamide/brimonidine FDC compared to when both individual components are used concomitantly.

TABLE 4: COST COMPARISON TABLE

Drug/Comparator	Strength†	Dosage Form†	Price ($)**	Recommended Daily Use†	Average Daily Drug Cost ($)***
brinzolamide/brimonidine (SIMBRINZA)	**brinzolamide 1%/brimonidine 0.2%**	**Suspension**	**$[redacted]* per 10mL bottle**	**One drop BID**	**$[redacted]**
brimonidine (Alphagan‡, Apo-, PMS-, Ratio-, Sandoz- brimonidine)	brimonidine 0.2%	Solution	$1.1550 per mL	One drop BID	$0.0762
brimonidine tartrate & timolol maleate (Combigan)	Combigan 0.2% & 0.5%	Solution	$41.8900 per 10mL bottle	One drop BID	$0.2765
brinzolamide (Azopt†)	brinzolamide 1%	Suspension	$3.4120 per mL	One drop BID	$0.2252
brinzolamide & timolol maleate (Azarga)	Azarga 1% & 0.5%	Suspension	$22.4100 per 5mL bottle	One drop BID	$0.2958
dorzolamide HCL & timolol maleate (Cosopt)	Cosopt 2% and 0.5%	Solution	$2.0951 per mL	One drop BID	$0.1383
latanoprost & timolol maleate (Xalacom)	Xalacom 50mcg/mL & 5mg/mL	Solution	$31.6200 per 2.5mL bottle	One drop once daily	$0.4174
travoprost & timolol maleate (DuoTrav)	DuoTrav 0.5% & 0.004%	Solution	$65.3200 per 5mL bottle	One drop once daily	$0.4311

*The submitted price is a Confidential Price that will become effective following the release of a recommendation for SIMBRINZA from the Canadian Drug Expert Committee (CDEC) to participating provincial/federal drug plans.
**Cost for comparators was extracted from the Ontario Drug Benefit Formulary/Comparative Drug Index: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
*** Daily cost was calculated as: Cost per bottle / [Drops per mL * bottle size (mL) / (total drops per day)]. A drop size for SIMBRINZA of 0.033mL/drop was assumed for all products.
†Dosage information was obtained from each drug/comparator Product Monograph and the Ontario Drug Benefit Formulary/Comparative Drug Index: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp

5.2 CDR Reviewer Comments

The CDR reviewer noted a few issues for consideration.

As noted in the manufacturer's submission, two patents for Azopt (brinzolamide 1%) have expired, although a process patent has been issued in 2003.[11] The implications of the process patent on the potential availability of a generic brinzolamide is not clear; however, in the event that a generic brinzolamide is introduced, the cost savings associated with brinzolamide/brimonidine FDC will be impacted. Further, in the case where the cost of either (or both) individual component(s) is lower in any of the jurisdictions than what is presented in the manufacturer's analysis, the brinzolamide/brimonidine FDC may be more costly than the concomitant use of the individual components.

The manufacturer's cost comparison did not include cost savings from dispensing fees. Brinzolamide/brimonidine FDC would incur a single dispensing fee rather than two dispensing fees each time a claim is made, leading to possibly increased cost savings associated with

brinzolamide/brimonidine FDC. The savings in dispensing fees will vary depending on the frequency of claims (e.g., every 30 days or 100 days).

The manufacturer's estimation of the daily drug cost was based on the assumption of a drop size of 0.033 mL/drop (~30.3 drops/mL) for brinzolamide/brimonidine FDC and all comparator drugs. A literature search was conducted by CDR reviewers to identify the most widely used standard for the number of drops of solution per mL, with no definitive result. However, the results of a study comparing the number of drops of ophthalmic drugs with the commonly used standard of 20 drops per mL found that more than 80% (n = 19) of studied drugs had greater than 20 drops per mL, of which 21% (n = 4) had greater than 30 drops/mL.[12] Therefore, the manufacturer's assumption of 0.033 mL/drop (30.3 drops/mL) for all products appears reasonable.

The comparators cost table submitted by the manufacturer (Table 4) did not include other treatments that are approved for this indication and are recommended in the Canadian Ophthalmological Society's glaucoma clinical practice guidelines.[5] An updated cost comparison table was prepared by CDR reviewers using the manufacturer's assumption of drop size (~30.3 drops/mL) including comparator treatments that were not included in the manufacturer's submission. The CDR cost comparison table also included the expected daily drug costs when bilateral applications are required (Table 5).

As presented in the manufacturer's primary cost comparison analysis and when rounding to the second decimal, the brinzolamide/brimonidine FDC ($[redacted] per eye) is cost-saving by $[redacted] per eye daily compared with the sum of the costs of the individual components brinzolamide and brimonidine ($0.31 per eye).

Based on the CDR cost comparison table, compared with other FDC products, the potential savings for brinzolamide/brimonidine FDC range between $[redacted] and $[redacted] per eye daily, except when compared with dorzolamide/timolol FDC, where brinzolamide/brimonidine FDC is expected to incur an additional cost of $[redacted] per eye daily.

When brinzolamide/brimonidine FDC is compared with other combination treatments taken as individual drugs, the potential savings are between $[redacted] and $[redacted] per eye daily. However, when compared with brimonidine, pilocarpine, carbachol, or latanoprost used concomitantly with timolol 0.5%, brinzolamide/brimonidine FDC is expected to incur an additional cost between $[redacted] and $[redacted] per eye daily.

TABLE 5: COMMON DRUG REVIEW COST COMPARISON TABLE FOR DRUGS USED IN GLAUCOMA

Drug/Comparator	Strength	Dosage Form	Price ($/mL)	Recommended Daily Use	Daily Drug Cost ($)[a] (One Eye)	Daily Drug Cost ($)[a] (Both Eyes)
Brinzolamide/brimonidine (Simbrinza)[b]	1% to 0.2%	Ophthalmic suspension	[redacted]	One drop BID	[redacted]	[redacted]
Individual components						
Brinzolamide (Azopt)	1.00 %	Ophthalmic suspension	3.4120	One drop BID	0.23	0.45
Brimonidine (Alphagan and generics)	0.20 %	Ophthalmic solution	1.1550	One drop BID	0.08	0.15
Alpha-2 adrenergic agonists						
Apraclonidine[c,d]	0.5%	Ophthalmic solution	4.5640	One drop BID	0.30	0.60
Brimonidine (Alphagan and generics)	0.15 % 0.20 %	Ophthalmic solution	1.7325 1.1550	One drop BID	0.11 0.08	0.23 0.15
Beta adrenergic antagonists						
Betaxolol (Betoptic S)	0.25 %	Ophthalmic suspension	2.3940	One drop BID	0.16	0.32
Timolol (Timoptic and generics)	0.25 % 0.50 %	Ophthalmic solution	0.9678 1.2145	One drop BID	0.06 0.08	0.13 0.16
Timolol gel-forming solution (Timoptic XE, Timolol maleate EX)	0.25 % 0.50 %	Ophthalmic solution	2.9540 2.7300	One drop BID	0.20 0.18	0.39 0.36
Levobunolol (Betagan and generics)	0.25 % 0.50 %	Ophthalmic solution	0.9334 1.1515	One drop BID	0.06 0.08	0.12 0.15
Carbonic anhydrase inhibitors						
Brinzolamide (Azopt)	1.00 %	Ophthalmic suspension	3.4120	One drop BID	0.23	0.45
Dorzolamide (Trusopt and generics)	2.00%	Ophthalmic solution	3.0700	One drop BID	0.20	0.41
Parasympathomimetics (cholinergic drugs)						
Pilocarpine (generics)	1.00% 2.00% 4.00%	Ophthalmic solution	0.2227 0.2567 0.2913	One drop QID	0.03 0.03 0.04	0.06 0.07 0.08
Carbachol (Isopto Carbachol)	1.50% 3.00%	Ophthalmic solution	0.7047 0.8477	One drop TID	0.07 0.08	0.14 0.17
Prostaglandin derivatives						
Bimatoprost (Lumigan)	0.01%	Ophthalmic solution	11.286	1 drop QD	0.37	0.74

Drug/Comparator	Strength	Dosage Form	Price ($/mL)	Recommended Daily Use	Daily Drug Cost ($)[a] (One Eye)	Daily Drug Cost ($)[a] (Both Eyes)
Latanoprost (Xalatan and generics)	0.005%	Ophthalmic solution	3.8332	1 drop QD	0.13	0.25
Travoprost (Travatan and generics)	0.004%	Ophthalmic solution	5.7520	1 drop QD	0.19	0.38
Combination products						
Brimonidine + timolol maleate (Combigan)	0.2% to 0.5%	Ophthalmic solution	4.1890	One drop BID	0.28	0.55
Brinzolamide + timolol maleate (Azarga)	1% to 0.5%	Ophthalmic suspension	4.4820	One drop BID	0.30	0.59
Dorzolamide + timolol maleate (Cosopt and generics)	2% to 0.5%	Ophthalmic solution	2.0951	One drop BID	0.14	0.28
Latanoprost + timolol maleate (Xalacom and generics)	50 mcg to 5 mg/mL	Ophthalmic solution	11.0700	1 drop QD	0.42	0.84
Travoprost + timolol maleate	0.004% to 0.5%	Ophthalmic solution	13.0640	1 drop QD	0.43	0.86

BID = twice daily; QD = daily; QID = four times daily; TID = three times daily.
[a] To determine daily cost, a drop size of 0.033 mL/drop (approximately 30.3 drops/mL) was assumed for all products.[12]
[b] Source: Manufacturer's submission.
[c] Alberta Drug Benefit List, February 2015.[13]
[d] Apraclonidine 1% drops are indicated to control postsurgical intraocular pressure.[14]
Source: Ontario Drug Benefit Formulary (online) February 2015, unless indicated otherwise.[15]

6. CURRENT PATENT STATUS

6.1 Manufacturer-Submitted Information Regarding Patent Status (Verbatim)

Brand Name: Simbrinza® ophthalmic suspension
Generic Name: brinzolamide 1%/brimonidine 0.2%

Generic Name	Patent Number	DIN	Strength and Dosage	Date Granted	Date Expired
brimonidine tartrate	2225626	02236876	0.2% ophthalmic solution	2002-09-03	2016-06-17
brimonidine tartrate	2225626	02236877	0.5% ophthalmic solution	2002-09-03	2016-06-17
brinzolamide	2274680	NA	NA	2003-11-18	NA

Note:
†Two patents for Azopt (brinzolamide) 1% have expired, one process patent for Azopt was issued on 2003-11-18
‡Expiry date of Alphagan 0.2% and 0.5% formulation patents are on June 17, 2016
Patent Information available at Health Canada Patent Register: http://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp and http://brevets-patents.ic.gc.ca/opic-cipo/cpd/eng/search/number.html

7. PATIENT INPUT INFORMATION

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

Three patient groups submitted patient input.

The Canadian Council of the Blind (CCB) has more than 1,500 members with all officers and directors being blind or visually impaired, which gives a unique sensitivity to the needs of the blind community. The CCB reported that it receives support from Bayer, Merck Frosst, Novartis, and Pfizer as well as from the following non-pharmaceutical entities: VIA Rail, Cannondale, Community Foundation of Ottawa, Lions Club, Keith Communications Inc., and Human Resources and Skills Development Canada (HRSDC). However, the nature of the support was not described.

The Canadian National Institute for the Blind (CNIB) provides programs and services including advocating for medication safety, equal access, and an inclusive society to help blind and partially sighted Canadians overcome the challenges of sight loss, increase their independence, and achieve their goals. The CNIB also promotes research and training into effective prevention, diagnosis, treatment, and rehabilitation of eye disease patients. The group occasionally receives unrestricted educational grants from Alcon Canada, Bayer Canada, Novartis Canada, and Pfizer Canada, which CNIB described as relatively small amounts.

The Foundation Fighting Blindness (FFB) is committed to advancing retinal disease research, education, and public awareness, and is involved with patient advocacy activities. The organization receives $4.2 million per year in donations from various stakeholders. Novartis has contributed approximately $365,000 to the FFB through both sponsorship and donations since 2004, while Alcon has contributed about $60,000 since 2005, which, according to the group, is about 1.5% of annual fundraising each year.

None of the groups had any potential conflicts of interest that may influence or have the appearance of influencing the input they provided.

2. Condition and Current Therapy-Related Information

Information for the input was gathered from conversations with patients, online and printed literature sources, and the product monograph.

Glaucoma is a group of eye diseases that lead to progressive damage of the optic nerve and can result in gradual, irreversible loss of vision and eventually blindness, if left untreated. Open-angle glaucoma (OAG) accounts for 90% of all glaucoma cases in Western nations. The initial stages of OAG presents with little or no symptoms. Therefore, patients may experience as much as 40% irreversible peripheral vision loss before noticing the disease.

The condition impacts the socioeconomic life and mental health of patients. Their friends may withdraw not knowing how to deal with the situation, and the patients themselves may go into isolation because they are unable to move independently in environments they previously considered familiar. Patients are no longer able to perform what used to be routine tasks such as driving, reading, watching TV, threading a needle, identifying medications, and preparing meals. In addition, they become more prone

to falls and injuries. Loss of employment and the cost of treatment impact patients economically. The limited ability of OAG patients to perform daily activities may lead to frustration, and thoughts of progressive vision loss, potential loss of employment and other privileges, as well as concerns about diminished quality of life could result in depression.

The goal of therapy in glaucoma is to lower intraocular pressure (IOP) to slow or halt progression of the disease, preserve visual function, and maintain or improve the health-related quality of life of patients. Current treatment options include medical treatment, laser therapy, or surgery. Drugs for glaucoma are usually in the form of eye drops that are used to either reduce production of aqueous humor or increase its outflow from the eye.

None of the patient groups provided information about the adequacy of current medication to manage the condition. Pain associated with some of the medications was mentioned as an important hardship. Patients described limitations associated with current therapy largely in relation to contraindications of beta blocker (BB) drugs in patients with certain respiratory and cardiovascular comorbidities due to BBs' ability to exacerbate these conditions, and, in rare cases, cause sudden death. Beta blocker therapy for glaucoma was also said to significantly lower ability to exercise, and concern was expressed regarding the significant risk of beta blocker use in the elderly due to the higher likelihood of comorbidities in this population.

3. Related Information About the Drug Being Reviewed

Patients' expectations were that Simbrinza will lower IOP, lessen the chance of damage to the optic nerve, and reduce vision loss. One patient group, "…expected that there will be improvement with this new drug by arresting the progress of glaucoma. With decreased IOP the possibility of returning to work, regaining independence and living a 'normal' life provides hope for the patient." Furthermore, patient groups expect Simbrinza to be safer than beta blockers, lead to greater treatment adherence compared with multiple co-administered drugs, and improve patients' quality of life. In addition, Simbrinza is expected to provide cost savings and be appealing to patients who need to avoid beta blockers.

Some patients expressed willingness to experience some temporary adverse effects if the drug was going to prevent further loss of sight. Patients indicated that serious side effects were not acceptable, since most of them are not experiencing side effects with their current treatment. Based on knowledge that the condition is likely to change as they age, and that current drugs and treatments might cease to work effectively, some patients expressed the desire for new drugs to meet their changing needs. The availability of new drugs was also felt to impart patients with greater choice that may allow for better quality of care.

None of the patients groups had members with personal experience with Simbrinza.

REFERENCES

Manufacturer references

1. Alcon, Data on File/C-10-040 CSR, 2013. *This data will be made available upon request.*
2. Aung T, Laganovska G, Hernandez Paredes TJ, Branch JD, Tsorbatzoglou A, Goldberg I. Twice-Daily Brinzolamide/Brimonidine Fixed Combination versus Brinzolamide or Brimonidine in Open-Angle Glaucoma or Ocular Hypertension. Ophthalmology2014 Jul 23.
3. Alcon, Data on File/C-10-041 CSR, 2013. *This data will be made available upon request.*
4. Alcon Canada Inc. SIMBRINZA Product Monograph. Date of Preparation: November 2013.
5. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. Can J Ophthalmol2009;44 Suppl 1:S7-93.
6. Khouri AS, Realini T, Fechtner RD. Use of fixed-dose combination drugs for the treatment of glaucoma. Drugs Aging2007;24(12):1007-16.
7. Rossi GC, Pasinetti GM, Scudeller L, Raimondi M, Lanteri S, Bianchi PE. Risk factors to develop ocular surface disease in treated glaucoma or ocular hypertension patients. Eur J Ophthalmol2013 May-Jun;23(3):296-302.
8. Lanzl I, Raber T. Efficacy and tolerability of the fixed combination of brinzolamide 1% and timolol 0.5% in daily practice. Clin Ophthalmol2011;5:291-8.
9. Mundorf TK, Rauchman SH, Williams RD, Notivol R. A patient preference comparison of Azarga (brinzolamide/timolol fixed combination) vs Cosopt (dorzolamide/timolol fixed combination) in patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol2008 Sep;2(3):623-8.
10. Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology2005 May;112(5):863-8.
11. Sleath B, Robin AL, Covert D, Byrd JE, Tudor G, Svarstad B. Patient-reported behavior and problems in using glaucoma medications. Ophthalmology2006 Mar;113(3):431-6.
12. DeSantis L. Preclinical overview of brinzolamide. Surv Ophthalmol2000 Jan;44 Suppl 2:S119-29.
13. Toris CB, Camras CB, Yablonski ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. Am J Ophthalmol1999 Jul;128(1):8-14.
14. Walters TR. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: a review of safety, efficacy, dose response, and dosing studies. Surv Ophthalmol1996 Nov;41 Suppl 1:S19-26.
15. De Moraes CG, Liebmann JM, Greenfield DS, Gardiner SK, Ritch R, Krupin T. Risk factors for visual field progression in the low-pressure glaucoma treatment study. Am J Ophthalmol2012 Oct;154(4):702-11.
16. Derick RJ, Robin AL, Walters TR, Barnebey HS, Choplin N, Schuman J, Kelley EP, Chen K, Stoecker JF. Brimonidine tartrate: a one-month dose response study. Ophthalmology1997 Jan;104(1):131-6.
17. Konstas AG, Stewart WC, Topouzis F, Tersis I, Holmes KT, Stangos NT. Brimonidine 0.2% given two or three times daily versus timolol maleate 0.5% in primary open-angle glaucoma. Am J Ophthalmol2001 Jun;131(6):729-33.
18. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol1997 Jul;115(7):847-52.

19. Silver LH. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Brinzolamide Primary Therapy Study Group. Am J Ophthalmol1998 Sep;126(3):400-8.

20. Barnebey HS, Orengo-Nania S, Flowers BE, Samples J, Mallick S, Landry TA, Bergamini MV. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. Am J Ophthalmol2005 Jul;140(1):1-7.

21. Ontario MoHLTC. Ontario Drug Benefit Formulary/Comparative Drug Index. Accessed on November 2014, from: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp

CDR references

1. Aung T, Laganovska G, Hernandez Paredes TJ, Branch JD, Tsorbatzoglou A, Goldberg I. Twice-daily brinzolamide/brimonidine fixed combination versus brinzolamide or brimonidine in open-angle glaucoma or ocular hypertension. Ophthalmology. 2014 Dec;121(12):2348-55.

2. Clinical study report: C-10-040. Safety and IOP-lowering efficacy of brinzolamide 10 mg/mL/brimonidine 2 mg/mL fixed combination eye drops, suspension compared to brinzolamide 10 mg/mL eye drops, suspension and brimonidine 2 mg/mL eye drops, solution in patients with open-angle glaucoma or ocular hypertension [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Alcon Canada Inc.; 2013 May 8.

3. Gandolfi SA, Lim J, Sanseau AC, Parra Restrepo JC, Hamacher T. Randomized trial of brinzolamide/brimonidine versus brinzolamide plus brimonidine for open-angle glaucoma or ocular hypertension. Adv Ther [Internet]. 2014 Nov 28 [cited 2015 Jan 9];31:1213-27. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4271137/pdf/12325_2014_Article_168.pdf

4. Clinical study report: C-10-041. Efficacy and safety of brinzolamide 10 mg/mL/brimonidine 2 mg/mL eye drops, suspension compared to brinzolamide 10 mg/mL eye drops, suspension plus brimonidine 2 mg/mL eye drops, solution in patients with open-angle glaucoma or ocular hypertension [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Alcon Canada Inc.; 2013 May 3.

5. Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee, Canadian Ophthalmological Society. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. Can J Ophthalmol [Internet]. 2009 Jun [cited 2015 Jan 15];44(Suppl 1):S7-93. Available from: http://www.supereyecare.com/residents/GlaucomaCOSGuidelines.pdf

6. Realini T, Nguyen QH, Katz G, DuBiner H. Fixed-combination brinzolamide 1%/brimonidine 0.2% vs monotherapy with brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension: results of a pooled analysis of two phase 3 studies. Eye [Internet]. 2013 Jul [cited 2015 Jan 9];27(7):841-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3709402/pdf/eye201383a.pdf

7. Katz G, DuBiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. JAMA Ophthalmol. 2013 Jun;131(6):724-30.

8. Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. Six-month results from a phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. Clin Ophthalmol [Internet]. 2013 [cited 2015 Jan 9];7:1053-60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678899/pdf/opth-7-1053.pdf

9. Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. J Ocul Pharmacol Ther [Internet]. 2013 Apr [cited 2015 Jan 9];29(3):290-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3696917
10. PrSIMBRINZA® (brinzolamide / brimonidine tartrate ophthalmic suspension) 1% / 0.2% w/v [product monograph]. Mississauga (ON): Alcon Canada Inc.; 2014 Dec.
11. CDR submission: PrSIMBRINZA® (brinzolamide / brimonidine tartrate ophthalmic suspension) 1% / 0.2% w/v. Company: Alcon Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Alcon Canada Inc.; 2014 Oct 30.
12. Watanabe SL, Morreale AP, Zelman LA. Quantity and cost of commonly used ophthalmic solutions at a Veterans Affairs Health System. Am J Health Syst Pharm. 2004 Mar 15;61(6):612-6.
13. Interactive drug benefit list [Internet]. Edmonton: Alberta Health [cited 2015 Jan 6]. Available from: https://www.ab.bluecross.ca/dbl/idbl_main1.html
14. Iopidine® 1% (Apraclonidine Hydrochloride Ophthalmic Solution, USP); Iopidine® 0.5% (Apraclonidine Hydrochloride Ophthalmic Solution, USP) [product monograph] [Internet]. Mississauga (ON): Alcon Canada Inc.; 1994 Feb 15. [cited 2015 Jan 6]. Available from: http://www.alcon.ca/pdf/Product_pharma/Product_pharma_iopidine_eng.pdf
15. Ontario Drug Benefit Formulary/Comparative Drug Index [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2014 Dec 18 [cited 2015 Jan 6]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp