CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204251Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 204251
Related IND **Related NDAs**	IND 106293 See Section 2 of the document
Applicant Name	Alcon Research, Ltd.
Date of Submission **Date of Receipt**	June 19, 2012 June 19, 2012
PDUFA Goal Date	April 19, 2013
Proprietary Name / **Established (USAN) Name**	SIMBRINZA brinzolamide/brimonidine tartrate ophthalmic suspension 1%/0.2%
Formulation **Dose**	Topical ophthalmic suspension One drop in the affected eye(s) three times daily
Proposed Indication(s)	reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension
Action for NME	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lucious Lim, Bill Boyd 4/9/2013
CDTL Review	Bill Boyd 4/19/2013
Deputy Director	Wiley Chambers 4/19/2013
Statistical Review	Cheryl Dixon, Yan Wang 3/15/2013
Pharmacology/Toxicology Review	Andrew McDougal, Lori Kotch 3/15/2013, 4/9/2013
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo 3/22/2013
Product Quality Manufacturing Reviews	Maotang Zhou, Rapti Madurawe 3/13/2013, 4/17/2013
Product Quality Microbiology Review	Vinayak Pawar, John Metcalfe 12/21/2012
Methods Validation	Michael Trehy, John Kauffman 1/22/2013, 3/18/2013
OC/Facilities Inspection	Acceptable, CMC review 4/17/2013
OSI/DGCPC	Kassa Ayalew, Susan Leibenhaut, 2/19/2013, 2/20/2013 Kassa Ayalew, Susan Leibenhaut, Susan Thompson 2/22/2013
OSE/DMEPA Proprietary Name Conditionally Acceptable Letter	Jung Lee, Jamie Wilkins Parker 8/9/2012, 3/14/2013 Carol Holquist 8/17/2012
OSE/DMEPA Labeling Review	Jung Lee, Jamie Wilkins Parker, Carol Holquist 3/14/2013
OPDP/DPDP (formerly DDMAC)	Christine Corser 4/9/2013
Project Manager	Judit Milstein (DTOP), Althea Cuff (CMC)

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
ONDQA = Office of New Drug Quality Assessment
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

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1. Summary and Recommendations

SIMBRINZA is a combination product, ophthalmic suspension, containing two active ingredients, brinzolamide (1%) and brimonidine tartrate (0.2%), each of which is currently approved individually as a topical ophthalmic product for the same indication of reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Simbrinza was evaluated in two randomized masked Phase 3 trials (Study C-10-033 and Study C-10-039) and compared to each of the individual components at all visits; the data showed the combination to be superior to the individual components at each time point based on the primary analysis. Adverse reactions ranging from 1% to 5% included blurred vision, eye irritation, conjunctivitis, allergy, ocular hyperemia, eye pain, eye pruritus, dry eye, dry mouth and dysgeusia. No new adverse reactions were identified and rates of adverse reactions were comparable among the arms.

Warnings include sulfonamide (brinzolamide) hypersensitivity, risk of corneal edema in patients with low endothelial cell counts, cautions about use of the product in patients with acute angle-closure glaucoma, severe renal or hepatic impairment, severe cardiovascular disease, the potential for vascular insufficiency is noted, caution about contact lens wear due to the preservative, and risk of bacterial infection with contamination of the product.

Pediatric development and studies were discussed at the Pediatric Review Committee and are considered complete; the product is contraindicated in patients less than two years due to the brimonidine component. High rates of somnolence and decreased alertness were reported with this component in pediatric patients below 6 years of age.

All primary review disciplines including clinical, statistics, clinical pharmacology, pharmacology/ toxicology and manufacturing recommend approval. The Office of Compliance recommended that manufacturing facilities are "Acceptable," and Office of Scientific Investigations considered the clinical trial data acceptable. The proprietary name SIMBRINZA was found acceptable by DMEPA. Labeling with input from all disciplines as well as OSE and DPDP is finalized.

1.1 Deficiencies

None

1.2 Post-Marketing Studies:

None

1.3 Other Issues

None

2. Background

Brinzolamide ophthalmic *suspension* 1%, NDA 20816, was first approved April 1, 1998 under the trade name AZOPT (Alcon Laboratories, Inc); the current labeling of AZOPT is in PLR

format. The drug is a carbonic anhydrase inhibitor indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Brimonidine tartrate ophthalmic *solution*, an alpha-2-adrenergic receptor agonist, was approved for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma in several concentrations as summarized below:

Brimonidine tartrate concentration	NDA number	Date approved	Trade name	Applicant	Labeling format	Marketing status per Drugs@FDA
0.5%	20490	3/13/1997	Alphagan	Allergan	Old format, not PLR	Discontinued
0.2%	20613	9/6/1996	Alphagan	Allergan	Old format, not PLR	Discontinued
0.15%	21262	3/16/2001	Alphagan P	Allergan	PLR	
0.1%	21770	8/19/2005	Alphagan P	Allergan	PLR	

A detailed listing of FDA approved brinzolamide and brimonidine products, including generics, is included in the pharmacology/toxicology review.

The MO notes that in the time period between the product launch of brinzolamide (April 2008) to 31 March 2012, (b) (4) units of the drug product have been sold worldwide. For brimonidine, (b) (4) units have been sold worldwide since the product launch (June 2002) to 31 March 2012.

Alcon studied this combination product under IND 106293, submitted August 28, 2009. The rationale for the combination was that many patients often require 2 medications to allow for a clinically meaningful reduction in IOP, so the development of the fixed dose combination product would allow both drugs to be given in a single formulation. Currently there is no approved fixed combination product of these two components, so physicians would need to prescribe both of the individual drugs to the same patient. In a Phase 2 trial, C-09-038, 170 patients were randomized (1:1:1:1) to the fixed combination, the two drugs administered sequentially at least 10 minutes apart, and to the individual drugs.[1]

An End of Phase 2 meeting was held with November 15, 2010 and the Division agreed to a 3-month, factorial design trial comparing the fixed combination to the individual components. Comments were provided on the types of analyses needed in the application. Safety information from at least 100 patients treated for at least 6 months was requested; therefore

[1] Study C-09-038 evaluated four arms, SIMBRINZA, brinzolamide, brimonidine tartrate and both single drugs given to the same patient in a vehicle-controlled masked manner. The text from Section 5.3.5.1 provides the following summary about drug administration in this trial.

9.4.5. SELECTION AND TIMING OF DOSE FOR EACH PATIENT

Patients in all 4 study drug groups (Brinz/Brim, Brinz, Brim, and Brinz + Brim) began study drug instillation the morning after the second eligibility visit and, with the exception of the scheduled study visit days, continued dosing TID (at 8 AM, 3 PM, and 10 PM) for 6 weeks. During the on-therapy visits at Week 2 and Week 6, designated study personnel at each investigational center administered the study drugs to the patients at 8 AM and 3 PM; the patients self-administered the third dose at home. All patients instilled 2 study drugs in both eyes (the fixed combination product and the vehicle, one of the active components of the fixed combination product and the vehicle, or both active components of the fixed combination product). A time lapse of at least 10 minutes was required between instillations of each study drug.

C-10-039 was designed to collect an additional 3 months of safety information. The Division also agreed with the scope of information to be included in the CMC and nonclinical portions of the application.

The chemistry review notes that the SIMBRINZA product is developed based on Alcon's marketed products AZOPT (NDA 20816) and brimonidine tartrate ophthalmic solution 0.2% (ANDA 76-254). The application has been cleared for action from a 505(b)(2) perspective as noted in the email from Beth Duvall, April 8, 2013.

2.1 Available Products

There are currently multiple products available for the treatment of IOP including alpha-2 agonists, beta-adrenergic antagonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandin analogues, sympathomimetics, osmotics, and a number of combination products. A detailed list is found in the Clinical Reviews.

3. CMC/Product Quality Microbiology

The details of the product quality CMC is found in Dr. Zhou's reviews, sterility in Dr. Pawar's review and methods validation in Dr Trehy's reviews.

3.1 Product Quality

The chemist notes that Alcon currently holds NDA/ANDAs for both active ingredients which contain information on the drug substance:

- NDA 20-816 for brinzolamide ophthalmic suspension
- ANDA 76-254 for brimonidine tartrate ophthalmic solution 0.2%

The drug product is a sterile, preserved, multi-dose ophthalmic suspension formulation containing 1% brinzolamide and 0.2% brimonidine tartrate. The manufacturing process is described in the CMC review. The composition of the drug product is shown in the table below, from the CMC review (p 33).

Component	% w/v	Function	Compendial Status
Brinzolamide	1.0 [b,c]	Active ingredient	USP [d]
Brimonidine Tartrate	0.2 [b]	Active ingredient	NOC [e]
Carbomer 974P [f]	(b) (4)		NF
Sodium Chloride			USP
Mannitol			USP
Propylene Glycol			USP
Tyloxapol			USP
Boric Acid			NF
Benzalkonium Chloride	0.003 [g]	Preservative	NF
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH to approximately 6.5	pH Adjustment	NF
Purified Water	(b) (4)		USP

[a] FID = Formulation Identification Number
[b] Amount added based on purity of the raw material.
(b) (4)
[d] Although brinzolamide is a compendial (USP) material, the drug substance will be tested according to the currently approved AZOPT (NDA 20-816) specifications.
[e] NOC = Non-official Compendia.
(b) (4)
(b) (4)

The product will supplied in white low density polyethylene (LDPE) DROP-TAINER® bottles with a natural LDPE dispensing-tip and white polypropylene cap. The trade presentation will be 8 mL Simbrinza in a 10 mL bottle. (b) (4) A shelf life of 18 months is supported by stability data.

The final mutually agreed upon regulatory acceptance specifications for the critical quality attributes of the Brinzolamide/Brimonidine Suspension are presented in Table 3.2.P.5.1–1. (See CMC review, pp 61-62.)

Table 3.2.P.5.1-1 Regulatory Specification for Brinzolamide/Brimonidine Suspension

Test	Acceptance Criteria
Brinzolamide Identity (TLC)[a]	(b) (4)
Brinzolamide Identity (HPLC)[a]	
Brinzolamide Assay	
Brimonidine Tartrate Identity (TLC)[a]	
Brimonidine Tartrate Identity (HPLC)[a]	
Brimonidine Tartrate Assay	
Brinzolamide Impurities[b]	
(b) (4)	

(b) (4)	(b) (4)
Brimonidine Impurities[c]	
(b) (4)	
Any Single Unspecified Impurity	
Total Impurities	
Benzalkonium Chloride Identity[a]	
Benzalkonium Chloride Assay	
Boric Acid Identity[a]	
Boric Acid	
pH	
Osmolality	
Viscosity (b) (4)	
Appearance, Suspension	White to off-white
Color	
Uniformity	Uniform suspension
Redispersibility	(b) (4)
Particle Size, (b) (4)	
Bacterial Endotoxins Test[a]	
Sterility Test[d]	

a. Release test only

(b) (4)

d. If tested, will pass.
e. Tests revised based on the Agency's recommendation.
f. Tests added based on the Agency's recommendation.

The reviewer concludes that the CMC information as revised in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product. Labels and labeling contain adequate CMC information. An "Acceptable" site recommendation from the Office of Compliance was made on April 17, 2013.

3.2 Product Quality Microbiology

As summarized in the CMC review (p 49):

The drug product is a multi-dose product with 0.003% benzalkoniumchloride (b) (4) added for antimicrobial preservation. The antimicrobial effectiveness of the drug product has been determined using an organism challenge approach based on the USP <51>Antimicrobial Effectiveness Test.

The integrity of the container/closure system for Brinzolamide/Brimonidine Suspension is demonstrated by successful sterility tests on stability samples. These data show that USP <71>

Sterility Test requirements are met by Brinzolamide/Brimonidine Suspension initially and following storage for up to 39 weeks at room temperature.

Bacterial endotoxin testing was performed using the LAL kinetic chromogenic assay (KCA). All lots were tested according to the procedure outlined in USP <85> Bacterial Endotoxin Test. All samples tested meet the proposed Regulatory Acceptance Specification of LT 0.5 EU/mL.

Comment:
The application is recommended for approval from the product quality and microbiology sterility reviewers, labeling is adequate and an acceptable recommendation regarding the manufacturing facilities has been provided by the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

For details, see the Pharmacology/Toxicology review by Dr. McDougal and Kotch. Excerpts of new information are presented below:

The two topical ocular rabbit studies for the combination product did not identify new concerns for the local/eye toxicity

- Decreased intraocular pressure (IOP) is the intended pharmacological effect, and IOP was observed up to the D90 time point and earlier, but not at the D181 or D272 time points. The reason for the apparent lack of chronic activity in the rabbits is unclear, and the relevance to chronic patient dosing is unclear.
- Increased corneal thickness was also observed; the Applicant reports that this effect has been observed previously with brimonidine in rabbits and is a species-specific effect not observed in humans.
- The 9-month study detected a treatment-related increase in minimal conjunctival discharge. This effect has previously been noted clinically

Hepatocellular cytoplasmic vacuolization was observed in male rabbits at high doses, the vacuoles were PAS positive consistent with glycogen accumulation. The effect is consistent with brimonidine effect and may be species-specific. Pancreatic islet cell hyperplasia was seen. Considering the dose-response apparent for the liver and pancreas effects, the P/T reviewer concluded that brinzolamide is contributing to the liver toxicity of brimonidine, and noted that previous safety data (clinical and nonclinical) for brimonidine-alone may not be adequate to fully characterize the safety of the combination of brinzolamide plus brimonidine. (p 62)

Transient penile erection in male rabbits and urogenital swelling and discoloration in female rabbits was seen in the 6-week and 9-month rabbit studies. The same urogenital changes were observed for the positive control in the 6-week study, 0.2% brimonidine, as for the brinzolamide/brimonidine dose groups. The Applicant reports that similar effects were not observed clinically for brimonidine or the combination.

The P/T reviewer notes that rabbit PK exposure is substantially higher in rabbits than in

patients, and results of in rabbit may over predict systemic effects of brimonidine compared to clinical use (p 67). IOP reduction was also seen (intended effect) and sedation (labeled).

Comment:
The NDA is recommended for approval from a Pharmacology/Toxicology perspective and labeling recommendations included in the package insert.

5. Clinical Pharmacology/Biopharmaceutics

As summarized in Dr. Zhang's review, Clinical Study C-10-010 was conducted to describe the steady-state PK of brimonidine and brinzolamide in plasma, and the red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of the combination product, and the individual components (brinzolamide and brimonidine Tartrate) in 142 adult subjects. Steady state plasma concentrations of the drugs were comparable whether administered from the combination or single ingredient products.

Brinzolamide is a topically active sulfonamide carbonic anhydrase inhibitor (CAI). Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Brimonidine tartrate is an alpha adrenergic receptor agonist. Brimonidine tartrate has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow. The result is a reduction in IOP.

Comment:
The NDA is acceptable from the Clinical Pharmacology perspective.

6. Clinical Microbiology/Immunology

N/A

7. Clinical/Statistical-Efficacy

For details, see clinical reviews by Drs Lim, Boyd, Chambers and statistical review by Drs. Dixon and Wang. Excerpts from these reviews are included below.

Two randomized (1:1:1), factorial-design double-masked, Phase 3 safety and efficacy clinical trials compared SIMBRINZA to each of the two components. IOP was measured at 4 time points during each of 4 visits (baseline, Week 2, Week 6, Month 3). Study C-10-033 enrolled 660 patients at 68 sites and Study C-10-039 enrolled 690 at 64 sites in the US. The statistical review presents results for the ITT population based on the primary analysis while the clinical reviews present results on the ITT population using LOCF. Both disciplines conclude SIMBRINZA is effective and the IOP lowering treatment effect is statistically significantly greater at each time point at each visit. The results are presented below (Tables from statistical review).

Table 1. Mean (SD) IOP values at baseline

		SIMBRINZA™	Brinzolamide	Brimonidine
Study 1		(n=209)	(n=224)	(n=216)
	8 AM	26.9 (2.63)	27.1 (2.64)	27.0 (2.56)
	10 AM	25.3 (2.76)	25.4 (2.74)	25.4 (2.78)
	3 PM	23.7 (2.98)	23.8 (3.24)	24.0 (3.27)
	5 PM	23.2 (3.08)	23.6 (3.39)	23.7 (3.30)
Study 2		(n=218)	(n=229)	(n=232)
	8 AM	27.2 (2.75)	27.2 (2.72)	27.3 (2.73)
	10 AM	25.8 (3.09)	26.0 (3.20)	25.8 (3.02)
	3 PM	24.4 (3.67)	24.4 (3.58)	24.0 (3.39)
	5 PM	24.1 (3.71)	24.2 (3.86)	23.7 (3.58)

Table 2 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP*

	SIMBRINZA	**Brinzolamide**		**Brimonidine**	
Study 1	(N=209)	(N=224)		(N=216)	
	Mean	Mean	Difference (95% CI)**	Mean	Difference (95% CI)**
Week 2					
8 AM	20.4	22.0	-1.6 (-2.3, -0.9)	22.4	-2.0 (-2.7, -1.3)
10 AM	17.1	20.5	-3.4 (-4.1, -2.7)	19.4	-2.3 (-3.0, -1.6)
3 PM	18.4	20.4	-1.9 (-2.6, -1.3)	20.6	-2.2 (-2.9, -1.5)
5 PM	16.6	19.7	-3.2 (-3.9, -2.5)	18.4	-1.9 (-2.6, -1.2)
Week 6					
8 AM	20.4	21.9	-1.5 (-2.2, -0.8)	22.6	-2.3 (-3.0, -1.6)
10 AM	17.5	20.2	-2.7 (-3.4, -2.0)	19.5	-2.0 (-2.7, -1.3)
3 PM	18.9	20.2	-1.2 (-1.9, -0.5)	21.1	-2.1 (-2.8, -1.4)
5 PM	17.0	19.7	-2.6 (-3.3, -1.9)	18.6	-1.5 (-2.2, -0.8)
Month 3					
8 AM	20.5	21.6	-1.1 (-1.8, -0.4)	23.3	-2.8 (-3.5, -2.1)
10 AM	17.2	20.4	-3.2 (-3.9, -2.5)	19.7	-2.5 (-3.2, -1.8)
3 PM	18.7	20.4	-1.8 (-2.5, -1.1)	21.3	-2.6 (-3.3, -1.9)
5 PM	17.0	20.0	-3.0 (-3.7, -2.3)	18.8	-1.8 (-2.5, -1.1)
	SIMBRINZA	**Brinzolamide**		**Brimonidine**	
Study 2	(N=218)	(N=229)		(N=232)	
Week 2	Mean	Mean	Difference (CI)	Mean	Difference (CI)
8 AM	20.5	22.2	-1.7 (-2.4, -1.0)	22.8	-2.4 (-3.1, -1.7)
10 AM	17.4	20.7	-3.3 (-4.0, -2.6)	19.2	-1.8 (-2.5, -1.2)
3 PM	18.7	20.5	-1.7 (-2.4, -1.1)	21.1	-2.3 (-3.0, -1.6)
5 PM	16.5	20.1	-3.6 (-4.3, -2.9)	18.3	-1.8 (-2.4, -1.1)
Week 6					
8 AM	20.7	21.9	-1.2 (-1.9, -0.5)	23.2	-2.5 (-3.2, -1.8)
10 AM	17.4	20.5	-3.1 (-3.8, -2.4)	19.7	-2.3 (-3.0, -1.6)
3 PM	19.3	20.2	-0.8 (-1.5, -0.2)	21.2	-1.9 (-2.6, -1.2)
5 PM	16.9	19.9	-3.0 (-3.7, -2.3)	18.5	-1.7 (-2.4, -1.0)
Month 3					
8 AM	21.1	22.0	-1.0 (-1.7, -0.3)	23.2	-2.2 (-2.9, -1.5)
10 AM	18.0	20.8	-2.8 (-3.5, -2.1)	19.9	-1.9 (-2.6, -1.2)
3 PM	19.5	20.7	-1.2 (-1.9, -0.5)	21.5	-2.0 (-2.7, -1.3)
5 PM	17.2	20.4	-3.2 (-3.9, -2.5)	18.9	-1.7 (-2.4, -1.0)

*Based on the Intent-to-Treat Population defined as all patients who received study drug and completed at least 1 on-therapy study visit. The estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
** Treatment difference is SIMBRINZA minus individual component. CI= Confidence Interval.

The applicant was asked to include a figure summarizing the IOP at each of the 4 time points at each of the 4 visits in per study in the labeling; an example was provided based on the clinical review of visits on the X axis and IOP measurements on the Y axis. The applicant commented that a change from baseline provides information that is useful to the clinician and provided the bar graph presentation of the results for Study 1 (C-10-033) and Study 2 (C-10-039), as shown below.

Figure 1. Mean IOP Change from Baseline (Study 1)

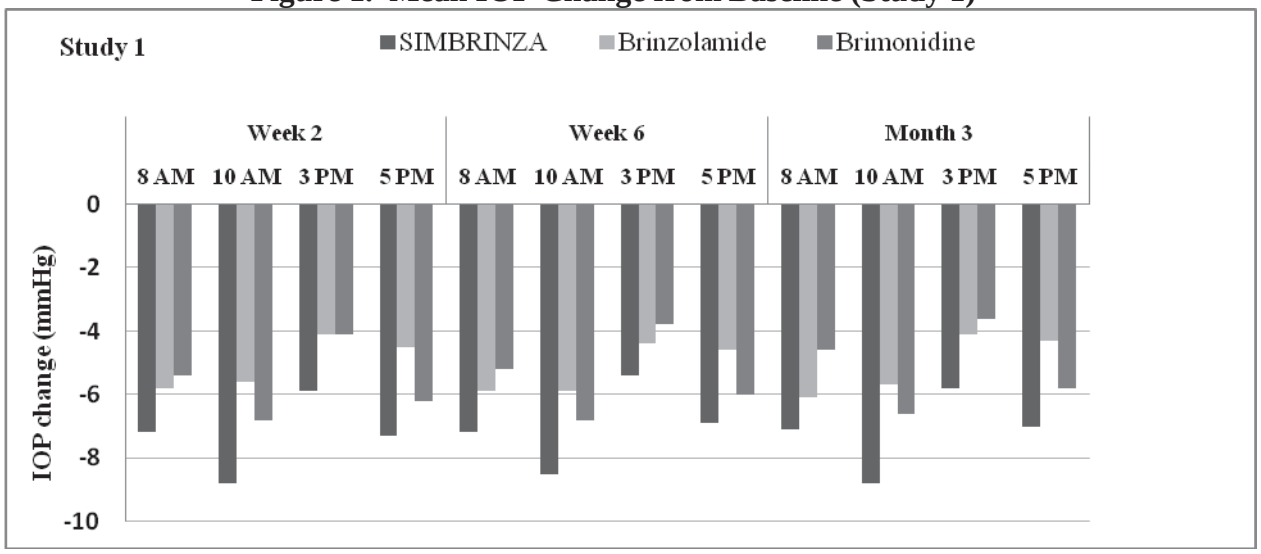
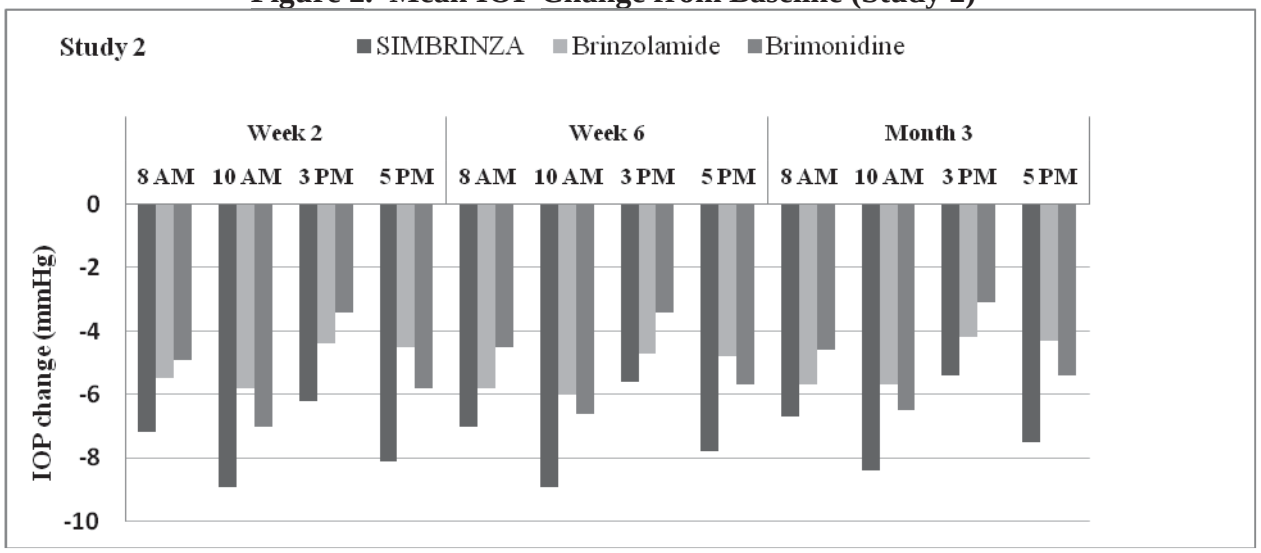


Figure 2. Mean IOP Change from Baseline (Study 2)



Comment:
The clinical reviewers and statistical reviewers concluded the studies have demonstrated efficacy and recommend the application be approved. The labeling contains tabular and graphic presentation of results consistent with the Guidance to Industry on Clinical Studies.

8. Safety

The safety evaluation is summarized in the reviews by Dr. Lim, Dr. Boyd, and Dr. Chambers and by Dr. Dixon and Dr. Wang.

A total of 550 patients received the combination in 5 trials, 585 received brinzolamide and 578 brimonidine. Of these 435, 460 and 455 were treated in the two Phase 3 studies, respectively. There were approximately 12% discontinuations in the Phase 3 trials, most due to adverse reactions. Approximately 10 patients in each of the three arms reported serious adverse events, mostly single reports of various systemic events.

8.1 Common Adverse Reactions

Common adverse reactions reported in these studies were essentially analogous to adverse reactions previously reported with one or the other ingredient when used in treatment of IOP. The pooled adverse reactions from the two Phase 3 trials are presented below (See MO review) and common ones are reflected in approved labeling. In addition, the labeling includes brief summaries of adverse reactions reported with each component; these are taken from approved labeling of the individual components.

Number (%) of Patients with Adverse Events Reported by ≥ 1 % of Patients
Studies C-10-033 and C-10-039 Pooled

Adverse Event	Brinz/Brim TID N=435 N (%)	Brinz TID N=460 N (%)	Brim TID N=455 N (%)
OCULAR			
Eye Disorders			
Vision blurred	23 (5.3)	30 (6.5)	1 (0.2)
Eye irritation	20 (4.6)	5 (1.1)	12 (2.6)
Eye allergy	15 (3.4)	1 (0.2)	8 (1.8)
Conjunctivitis allergic	12 (2.8)	2 (0.4)	11 (2.4)
Conjunctivitis	11 (2.5)		14 (3.1)
Ocular Hyperaemia	9 (2.1)	5 (1.1)	6 (1.3)
Eye pain	9 (2.1)	8 (1.7)	5 (1.1)
Eye pruritus	9 (2.1)	4 (0.9)	6 (1.3)
Conjunctival hyperaemia	8 (1.8)	5 (1.1)	6 (1.3)
Dry eye	6 (1.4)	4 (0.9)	8 (1.8)
NON-OCULAR			
Gastrointestinal Disorders			
Dry mouth	14 (3.2)		11 (2.4)
Nervous System Disorders			
Dysgeusia	17 (3.9)	38 (8.3)	1 (0.2)

Comment:
The clinical and statistical reviewers recommend approval. Labeling will include information from the current studies, and safety summaries of the individual products from the approved labeling.

9. Advisory Committee Meeting

The application was not discussed before a public advisory committee.

10. Pediatrics

A waiver of pediatric studies has been requested for the fixed combination. After discussion at a Pediatric Review Committee meeting in March 2013, the final determination was that pediatric studies were completed or extrapolated for the age group 2 to <17 years (DARRTS pediatric record dated March 11, 2013) and the product is contraindicated in patients under the age of 2 years due to adverse reactions reported with the brimonidine component.[2] The MO notes that the individual component, brimonidine has been studied in pediatric patients, ages 2 to 7 years. This information is reflected in labeling. Somnolence and decreased alertness was seen in 50-83% of patients, ages 2 to 6 years. The individual component, brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

The addendum to the original CMC review notes that Office of Compliance issues a recommendation of "Acceptable" on April 17, 2013.

11.2 Office of Scientific Investigation (OSI) Audits

The OSI review states that two clinical investigator sites were inspected and data derived from both inspected sites are considered reliable (NAI).

11.3 Debarment Certification

Alcon Research, Ltd. certified that it did not and will not use in any capacity the services of any person debarred under subsections 306 of the FD&C Act in connection with this application.

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[2] Alphagan P labeling http://www.allergan.com/assets/pdf/alphaganp_pi.pdf
(brimonidine tartrate ophthalmic solution) 0.15%

8.4 Pediatric Use
ALPHAGAN® P is contraindicated in children under the age of 2 years. [*See Contraindications (4.1*)].
During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

11.4 Financial Disclosure

Alcon adequately disclosed financial arrangements with clinical investigators (see MO review).

11.5 Other Regulatory Issues

None identified.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPDP and ONDQA.

- **Package insert (PI):** The PI is written in PLR format. Preliminary format and content comments were reviewed by Leanna Kelly. DMEPA and OPDP provided labeling recommendations that have been addressed. Content of Section 14 CLINICAL STUDIES was discussed internally and with the applicant to provide presentation of data consistent with the Guidance to Industry on Clinical Studies. Although the applicant's primary endpoint was IOP at Month 3, the clinical team considered IOP at all time points was important/significant. (b) (4) Therefore, tables and graphs, consistent with recommendations from OPDP, other review staff, and the Guidance to Industry on Clinical Studies, include data from all visits.

- **Carton and Container Labels**: The labels have been reviewed by the Division, ONDQA and DMEPA. The carton/container submitted April 16, 2013 incorporated the labeling recommendations.

- **Proprietary Name**: DMEPA concluded that the proposed proprietary name SIMBRINZA is acceptable. A letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA August 17, 2012. A final review dated February 15, 2013 (within 90 days of the PDUFA goal date) found the name acceptable.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA is recommended for approval, all disciplines agree the application can be approved; labeling has been discussed internally, with the applicant and finalized. The trade name SIMBRINZA is acceptable. Inspections of facilities and clinical sites are acceptable. Pediatric information and studies are complete.

13.2 Risk Benefit Assessment

The data contained in this submission establishes the efficacy of the fixed combination of brinzolamide/ brimonidine tartrate ophthalmic suspension 1%/0.2% dosed three times daily for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension. Efficacy was

demonstrated by showing that the combination was superior to each individual component at each of the measured time points in two randomized, masked, factorial-design Phase 3 clinical trials. The rates of adverse reactions reported in these trials were comparable to those seen with the individual components. The labeling provides an overview of the risks associated with the product, as well as the benefits in IOP reduction from the two Phase 3 trials. Geriatric patients comprised half of the study population and the benefit was seen in both adult and geriatric patients. This product offers another option for the treatment of IOP.

13.3 Recommendation for other Postmarketing Requirements and Commitments
None

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/s/

RENATA ALBRECHT
04/19/2013