EXHIBIT SJ 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-764

Alcon, Inc.
c/o Alcon Research, Ltd.
Attention: Michael E. Pfleger
Senior Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Mr. Pfleger:

Please refer to your new drug application (NDA) dated April 27, 2004, received April 28, 2004, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate Ophthalmic Solution, 0.15%.

We acknowledge receipt of your submissions dated April 27, May 11, June 28, July 6 and 19, August 24 and 25, September 2, and October 15, 2004, and January 3 and 20 (two), and February 1, 2, 3, 8, 22 and 25, 2005.

This NDA provides for the use of Brimonidine Tartrate Ophthalmic Solution, 0.15% when indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

We completed our review of this application. It is **tentatively approved** under 21 CFR 314.105 for use as recommended in the agreed upon labeling text submitted February 25, 2005. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention. Any significant change in the conditions outlined in this new drug application will require Agency review before final approval may be granted.

The listed reference drug product upon which you based your application is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until the period has expired for the following patents:

Allergan **U.S. Patent 5424078** expiration June 13, 2012, Pediatric extension December 13, 2012
Allergan **U.S. Patent 6562873** expiration July 10, 2021, Pediatric extension January 10, 2022
Allergan **U.S. Patent 6627210** expiration July 18, 2021, Pediatric extension January 18, 2022
Allergan **U.S. Patent 6641834** expiration July 28, 2021, Pediatric extension January 28, 2022
Allergan **U.S. Patent 6673337** expiration July 26, 2021, Pediatric extension January 26, 2022

Because the Agency is granting tentative approval for this application, when you believe that your application may be considered for final approval or if you believe that there are grounds for issuing a final approval letter prior to January 28, 2022, you may amend your application to notify the Agency of the circumstances that may affect the effective date of final approval. Your amendment must provide:

1. A copy of a final order or judgment from which no appeal may be taken (which might not be the one from the district court), or a statement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. A safety update as described in 21 CFR 314.50(d)(5)(vi(*b*), and

3. a. Updated final printed labeling or chemistry, manufacturing and controls data, as appropriate, and any other change in the conditions outlined in this application, or

   b. A statement that no such changes have been made to the application since the date of tentative approval.

At least 180 days prior to January 28, 2022, or when requested, submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. This information should include updated labeling, chemistry, manufacturing and controls data, and a safety update.

Failure to submit this amendment will prompt a review of the application that may result in rescission of the tentative approval letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Any change in the conditions outlined in this NDA requires our review before final approval may be granted.

Before we issue a final approval letter, this NDA is <u>not</u> deemed approved. If you believe that there are grounds for issuing the final approval letters before January 28, 2022, you should amend your application accordingly.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We request that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that the pediatric study requirement for this application has been fulfilled.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

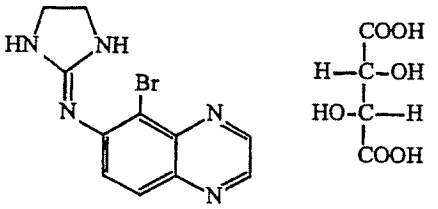
Attachment: Draft Labeling

Brimonidine Tartrate Ophthalmic Solution, 0.15%

Sterile

DESCRIPTION

Brimonidine Tartrate Ophthalmic Solution, 0.15% (1.5 mg brimonidine tartrate per mL equivalent to 1.0 mg brimonidine free base per mL) is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (1.5 mg/mL) and in the product vehicle (3.0 mg/mL) at pH 7.2. The structural formula is:



Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, Brimonidine Tartrate Ophthalmic Solution, 0.15% has a clear, greenish-yellow color. It has an osmolality of 250 – 350 mOsmol/kg and a pH of 6.6-7.4.

Each mL of Brimonidine Tartrate Ophthalmic Solution, 0.15% contains:
Active ingredient: brimonidine tartrate 0.15% (1.5 mg/mL)
Inactives: povidone; boric acid; sodium borate; calcium chloride; magnesium chloride; potassium chloride; mannitol; sodium chloride; POLYQUAD* 0.001% (0.01 mg/mL); purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of Action:
Brimonidine Tartrate Ophthalmic Solution, 0.15% is an alpha-2 adrenergic receptor agonist. It 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.

Pharmacokinetics:
In a pharmacokinetic study, 14 healthy subjects (4 males and 10 females) received a single topical ocular administration of Brimonidine Tartrate Ophthalmic Solution, 0.15%, one drop per eye. The peak plasma concentrations (C_{max}) and AUC $_{0\text{-inf}}$ were 73 ± 19 pg/mL and 375 ± 89 pg•hr/mL, respectively. T_{max} was 1.7 ± 0.7 hours after dosing. The systemic half-life was approximately

2.1 hours.

Brimonidine is metabolized primarily by the liver. *In vitro* metabolism data from human microsomal fractions and liver slices indicate that brimonidine undergoes extensive hepatic metabolism.

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% of the radioactivity recovered in the urine.

Special Populations

Brimonidine Tartrate Ophthalmic Solution, 0.15% has not been studied in patients with hepatic or renal impairment. Because of the low systemic drug exposure following topical ocular administration of Brimonidine Tartrate Ophthalmic Solution, 0.15%, no dose adjustment is necessary when treating patients with hepatic or renal impairment.

Clinical Evaluations:

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

A clinical study was conducted to evaluate the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% compared to Alphagan® P** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. The results indicated that Brimonidine Tartrate Ophthalmic Solution, 0.15% is equivalent in IOP-lowering effect to Alphagan® P (brimonidine tartrate ophthalmic solution), 0.15%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by 2 - 6 mm Hg.

INDICATIONS AND USAGE

Brimonidine Tartrate Ophthalmic Solution, 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Brimonidine Tartrate Ophthalmic Solution, 0.15% is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS

General:

Although Brimonidine Tartrate Ophthalmic Solution, 0.15% had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Brimonidine Tartrate Ophthalmic Solution, 0.15% has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Brimonidine Tartrate Ophthalmic Solution, 0.15% should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or

thromboangiitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients:
As with other drugs in this class, Brimonidine Tartrate Ophthalmic Solution, 0.15% may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions:
Although specific drug interaction studies have not been conducted with Brimonidine Tartrate Ophthalmic Solution, 0.15%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-2 agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with Brimonidine Tartrate Ophthalmic Solution, 0.15% in humans can interfere with its IOP-lowering effect. No data on the level of circulating catecholamines after Brimonidine Tartrate Ophthalmic Solution, 0.15% administration are available. Caution, however, is advised in patients taking tricyclic antidepressants, which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and a 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 60 and 50 times, respectively, the plasma drug concentration estimated in humans treated with one drop of Brimonidine Tartrate Ophthalmic Solution, 0.15% into both eyes.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese hamster ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Pregnancy: Teratogenic Effects: Pregnancy Category: B
Reproductive studies performed in rats and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to Brimonidine Tartrate Ophthalmic Solution, 0.15%. Dosing at this level produced an exposure in rats and rabbits that is 80 and 40 times higher than the exposure seen in humans, respectively.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Brimonidine Tartrate Ophthalmic Solution, 0.15% should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. In animal studies, brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events 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 or older (>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.

The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to **ADVERSE REACTIONS** section.)

Geriatric Use:
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS
Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritis.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, arthralgia, arthritis, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, chest pain, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, diabetes mellitus, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection, insomnia, joint disorder, keratitis, lid disorder, osteoporosis, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

The following events were reported in less than 1% of subjects: corneal erosion, nasal dryness, and taste perversion.

The following events have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia; iritis; miosis; skin reactions (including erythema, eyelid pruritis, rash, and vasodilation); and

tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

OVERDOSAGE
No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION
The recommended dose is one drop of Brimonidine Tartrate Ophthalmic Solution, 0.15% in the affected eye(s) three-times-daily, approximately 8 hours apart.

Brimonidine Tartrate Ophthalmic Solution, 0.15% may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED
Brimonidine Tartrate Ophthalmic Solution, 0.15% is supplied sterile in opaque white LDPE plastic bottles and natural tips with purple polypropylene caps as follows:

5 mL in 8 mL bottle	NDC 61314-144-05
10 mL in 10 mL bottle	NDC 61314-144-10
15 mL in 15 mL bottle	NDC 61314-144-15

Storage: Store at 15°-25° C (59° - 77°F).
Rx Only

Distributed by:
Falcon Pharmaceuticals
Fort Worth, Texas 76134
Manufactured by:
Alcon Manufacturing, Ltd.
Fort Worth, Texas 76134
Printed in USA
*POLYQUAD is a registered trademark of Alcon Manufacturing, Ltd.
**ALPHAGAN P is a registered trademark of Allergan, Inc.

Carton Label

EXHIBIT SJ 2

REDACTED IN ITS ENTIRETY

EXHIBIT SJ 3

REDACTED IN ITS ENTIRETY

EXHIBIT SJ 4

REDACTED IN ITS ENTIRETY

EXHIBIT SJ 5

REDACTED IN ITS ENTIRETY

EXHIBIT SJ 6

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., ALLERGAN SALES, LLC, Plaintiffs, v. ALCON, INC., ALCON LABORATORIES, INC., and ALCON RESEARCH, LTD., Defendants.	Civil Action No. 04-968-GMS

PLAINTIFFS ALLERGAN, INC. AND ALLERGAN SALES, LLC'S SUPPLEMENTAL RESPONSES TO DEFENDANTS' INTERROGATORIES NOS. 1 AND 5

Pursuant to Rule 33 of the Federal Rules of Civil Procedure,. Allergan, Inc. and Allergan Sales, LLC ("Plaintiffs") for their supplemental response to Defendants' Interrogatories No. 1 and 5, state as follows. The objections and answers are made according to the Federal Rules of Civil Procedure and the Local Rules of the United States District Court for the District of Delaware and are based upon information presently available to Plaintiffs. These objections and answers are without prejudice to Plaintiffs' right to use or rely on subsequently discovered information.

GENERAL OBJECTIONS

Plaintiffs incorporate their general and specific objections from their Responses to Defendants' First Set of Interrogatories (Nos. 1-11), dated January 4, 2005.

The General Objections are incorporated into each of Plaintiffs' responses to Defendants' interrogatories irrespective of whether such Objection is expressly referred to by Plaintiffs' answer to a specific Interrogatory. The repetition or omission of a particular General Objection or Objection to a Definition in a specific answer is not a waiver of any of Plaintiffs' General Objections.

Since discovery has just begun and Plaintiffs' investigation of Defendants' Interrogatories is ongoing, Plaintiffs reserve their right to supplement these objections and answers. The following answers reflect Plaintiffs' present knowledge, information, and belief, and as permitted by the Federal Rules of Civil Procedure, may be changed, modified, or supplemented based on discovery or as additional facts and circumstances come to Plaintiffs' attention. Plaintiffs reserve the right to produce evidence of any subsequently discovered fact, to alter or amend the objections and answers set forth herein, and otherwise to assert factual and legal contentions as additional facts are ascertained, analyses are made, and legal research is completed.

RESPONSES TO INTERROGATORIES

INTERROGATORY NO. 1:

For each of the '834 and '337 patents, identify each claim that Allergan contends will be infringed by Alcon's proposed product as alleged at paragraphs 18 and 22 of the Complaint, an explanation of Allergan's interpretation of each limitation of that claim, and an explanation of how each limitation of that claim is present, either literally or under the doctrine of equivalents, in Alcon's proposed product.

FIRST SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 1:

In addition to the foregoing general objections, Plaintiffs object to this Interrogatory to the extent it calls for the disclosure of information protected by the attorney-client privilege and/or work product doctrine. Plaintiffs further object to this interrogatory as premature, because discovery in this action has just begun, and Alcon has not provided any discovery beyond its paragraph IV certification and 505(b) application. Plaintiffs further object to this Interrogatory as premature in that it asks for contentions prior to the time required under the scheduling order. The parties' agreed-upon scheduling order does not require Plaintiffs to submit its claim contentions until March 14, 2005. Plaintiffs also object to this Interrogatory as overly broad and unduly

burdensome to the extent that it requests Plaintiffs to identify a construction of each element of each claim, when it is not evident at this stage of the proceedings which claim elements are disputed by the parties. *See, e.g., Pall Corp. v. Hemasure, Inc.*, 181 F.3d 1305, 1308 (Fed. Cir. 1999) (noting that "it is convenient for the court to concentrate on those aspects of the claim whose relation to the accused device is in dispute"); *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1580 (Fed. Cir. 1991) (noting that "it is efficient to focus on the construction of only the disputed elements or limitations of the claims").

Without waiver of any of the foregoing objections, Plaintiffs respond that, with respect to the '834 patent, Plaintiffs assert infringement of independent claims 1 and 10, and dependent claims 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14, 17, 18 and 20. With respect to the asserted '834 patent claims, Alcon has filed a section 505(b) application for a therapeutically effective 0.15% brimonidine tartrate ophthalmic solution for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed product has a pH greater than 7.0, includes Polyquad, a quaternary ammonium compound, as a preservative, and does not include any anionic cellulosic derivatives or carboxymethylcellulose. In the proposed product, brimonidine is soluble at about 21 degrees centigrade. Such a product meets all the limitations of the listed claims.

With respect to the '337 patent, Plaintiffs respond that Plaintiffs assert infringement of independent claim 1, and dependent claims 2, 3, 4, 6, 9, and 10. With respect to the asserted '337 patent claims, Alcon has filed a section 505(b) application for a therapeutically effective 0.15% brimonidine tartrate ophthalmic solution for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed product contains povidone, as well as Polyquad. Brimonidine tartrate is an alpha-2-adrenergic agonist. Povidone is a solubility enhancing component, as described in the specification. Polyquad is a preservative. Accordingly, Alcon's proposed product meets all the limitations of the listed claims.

INTERROGATORY NO. 5:

For each claim identified in response to Interrogatory No. 1, explain the contribution that each of the inventors named in the patents made to each claim therein.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 5:

In addition to the foregoing general objections, Plaintiffs object to this Interrogatory to the extent it calls for the disclosure of information protected by the attorney-client privilege and/or work product doctrine. Plaintiffs further object to this Interrogatory as having multiple subparts. Plaintiffs further object to this Interrogatory as seeking premature contention discovery.

Without waiver of any of the foregoing objections, Plaintiffs respond that Orest Olejnik and Edward Kerslake jointly contributed to each claim identified in response to Interrogatory No. 1.

Dated: February 4, 2005

FISH & RICHARDSON P.C.

By: _____

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