

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-764

PHARMACOLOGY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-764
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 4/28/2004
PRODUCT: Brimonidine Tartrate Ophthalmic solution, 0.15%
INTENDED CLINICAL POPULATION: Open-angle glaucoma and ocular hypertension
SPONSOR: Alcon Research Ltd.
DOCUMENTS REVIEWED: Vol. C1.1-1.10
REVIEW DIVISION: Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products (HFD-550)
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Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: Based on the non-clinical data and previous human experience of brimonidine tartrate ophthalmic solution, the NDA is approvable.
- B. Recommendation for nonclinical studies: Nil
- C. Recommendations on labeling:

Based on plasma levels in animals and human pharmacokinetic data on 0.15% brimonidine tartrate solution with Polyquad, the animal to human dose ratios were modified as follows. The changes are shown in bold letters.

The proposed label:

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II. Summary of nonclinical findings

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- A. Brief overview of nonclinical findings: Brimonidine ophthalmic solutions up to 0.2% did not show any toxicity to eyes in the rabbit model. The preservative Polyquad at 0.001% concentration was also devoid of any ocular toxicity. Polyquad is already approved in several OTC products. Brimonidine ophthalmic solution is distributed in several tissues in the eye, aqueous humor and bioavailable in the systemic circulation. A transient hyperglycemia was noted in rabbits although clinical significance of the change is unknown. A 3-month ocular safety study showed that brimonidine 0.15% solution with Polyquad, a preservative, had a low systemic bioavailability than Alphagan P.
- B. Pharmacologic activity: Brimonidine is an α_2 -adrenergic receptor agonist and reduces intra ocular pressure in normal and experimentally induced ocular hypertension. Brimonidine also antagonize prostaglandin-induced hyperemia in the rabbit eye. Data signified that brimonidine may have both pre-synaptic and post synaptic activity in the adrenergic system. Brimonidine induces a mild sedative effect that is common for α_2 -adrenergic agonists. This group of drugs also has hypertensive effects.
- C. Nonclinical safety issues relevant to clinical use: Nil

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-764

Review number: One

Sequence number/date/type of submission: 000, April 27, 2004

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Alcon Research Ltd

Manufacturer for drug substance: _____

Reviewer name: Asoke Mukherjee

Division name: Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD #: 550

Review completion date: July 22, 2004

Drug:

Trade name: Nil

Generic name: Brimonidine Tartrate Ophthalmic solution, 0.15%

Code name: AL-8923A

Chemical name: 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine L-tartrate

CAS registry number: 79570-19-7

Molecular formula/molecular weight: C₁₁H₁₀BrN₅, C₄H₆O₆, 442.23 as salt

Structure:

Relevant INDs/NDAs/DMFs: NDA 20-613, NDA 21-262, NDA 21-770, IND 32,292 and DMF _____

Drug class: α₂-adrenergic agonist

Intended clinical population: Patients with open-angle glaucoma and ocular hypertension

Clinical formulation:

Component	% W/V
Brimonidine Tartrate	0.15%
Polyquad	0.001%
Povidone _____	_____
Boric acid _____	_____
Sodium Borate _____	_____

Component	% W/V
Calcium chloride, _____	_____
Magnesium chloride, _____	_____
Potassium Chloride	_____
Mannitol	_____
Sodium Chloride	_____
Sodium hydroxide	_____
Purified water	_____

Route of administration: Ophthalmic drops

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-764 are owned by Alcon or are data for which Alcon has obtained a written right of reference. Any information or data necessary for approval of NDA 21-764 that Alcon does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that Alcon does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-764.

Studies reviewed within this submission:

1. Distribution of brimonidine in ocular tissues and plasma following a single topical ocular administration of a 0.15% brimonidine ophthalmic solution in male New Zealand F₁ cross rabbits, vol 1.1 and module 4.
2. Brimonidine plasma concentrations from Alcon study N-02-095, three-month topical ocular safety study of brimonidine PQ ophthalmic solution in pigmented rabbits, vol 1.1 and module 4.
3. Three-month topical ocular irritation and systemic toxicity evaluation of brimonidine PQ ophthalmic solution in pigmented rabbits, vol 1.3 and module 4.

Studies not reviewed within this submission:

Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 **Primary pharmacodynamics:** A single dose of 50 µg brimonidine showed about 10-16% reduction in the IOP in normal rabbits that lasted for 2 to 4 hours. Contralateral eye also showed a reduction of IOP. Brimonidine ophthalmic solution showed about 13% reduction of IOP in laser-induced ocular hypertension in cynomolgus monkeys.

Mechanism of action: No new data for the mechanism of action was submitted in the NDA. The mechanism of action of brimonidine is considered to be due to inhibition of aqueous humor formation and increased aqueous humor outflow as indicated in page 1, vol 1.1 and module 2.

Drug activity related to proposed indication: Brimonidine is a selective agonist to α_2 -adrenergic receptor. It is approved for the treatment of lowering IOP up to 0.2% ophthalmic solution.

2.6.2.3 Secondary pharmacodynamics: Brimonidine reduced prostaglandin DP receptor-induced ocular hyperemia in guinea-pig model at 5-12.5 μg doses in the eye. Brimonidine increased blood sugar levels due to inhibition of insulin release. As a pharmacological class, brimonidine also showed sedative and hypotensive actions.

2.6.2.4 Safety pharmacology: No safety pharmacology data were reviewed.

2.6.2.5 Pharmacodynamic drug interactions: No pharmacodynamic drug interaction study was submitted in the NDA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

[Pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

Primary and secondary pharmacology tabulated summaries are shown below (page 2, module 2 and vol 2).

Primary pharmacology:

Organ/system evaluated	Species/strain	Route of admin.	Dose, mg/kg	Gender and number/gr	Finding	GLP	Report #
IOP	NZ albino rabbits	Topical, ocular	5, (0.01%), 15 (0.03%) and 50 (0.1%) μg in 2x25 μL	7 females (5 and 50 μg doses), 10 females (15 μg dose)	5, 15 and 50 μg decreased IOP up to 4 hrs, contralateral eye showed a decrease in IOP at 15 and 50 μg . Pupil diameter was not affected in drug treated eyes. IOP slightly increased in vehicle treated eyes.	No	TR#026:39500:0596 M4, V1
Intraocular pressure	Cynomolgus monkeys	Topical, ocular	50 μg	6-9/gr, M & F	Vehicle effect was equivalent to the effect of 50 μg in laser-induced hypertensive eyes	No	TR# 027:39500:0606 M4,V1
Intraocular pressure	Cynomolgus monkeys	Topical, ocular	150 μg	6-9/gr, M & F	IOP significantly reduced at 1 and 3 hrs after dose	No	TR# 075:39500:1096 M4,V1
Intraocular pressure	Cynomolgus monkeys	Topical, ocular	3.6 μg AL-6598 + 60 μg brimonidine (AL-8923A)	6-9/ gr, M & F	The combination lowered IOP in laser-induced hypertensive eyes	No	TR# 129:39500:1198, M4, V1
Intraocular	Cynomolgus	Topical,	50 μg	6-9/gr, M & F	50 μg	No	TR# 146:39500:196,

Organ/system evaluated	Species/strain	Route of admin.	Dose, mg/kg	Gender and number/gr	Finding	GLP	Report #
pressure	monkeys	ocular	brimonidine and 50 µg Quinpirole (AL-3133A)	F	brimonidine and 50 µg quinpirole did not show synergistic effect		M4, V1

AL-6598, a prostaglandin DP receptor agonist, AL-3133A, dopaminergic agonist

Safety Pharmacology:

Organ System	Species/Strain	Route of admin.	Dose, mg/kg	Gender and number/gr	Finding	GLP	Report #
Neuropharmacology profile	Mice, CD-1	subcutaneous	Vehicle, 10, 30 and 100 µg brimonidine ; 10 µg brimonidine + 3 µg AL-6598	Male, 10/gr	No changes in neurological signs and temperature	Yes	TR #003:39730:0599, M4 and V1
Potential of barbiturate sleeping time	Mice, CD-1	subcutaneous	Vehicle, 3, 10, 30, 100 µg brimonidine; 10 µg brimonidine + 3 µg AL-6598 combination	Male, 10/gr	Brimonidine increased mean sleep time by 15-158%. Combination increased sleep time by 25%	Yes	TR 004:39730:0599, M4, V1

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Acute and chronic administration of brimonidine up to 0.2% ophthalmic solution showed distribution of the drug in aqueous humor, cornea, conjunctiva, iris and ciliary body. Brimonidine is also bioavailable in the systemic circulation following ophthalmic delivery. Rabbits treated with 0.15% brimonidine and Polyquad had a lower systemic plasma levels than 0.15% brimonidine containing Purite preservative.

The sponsor conducted a clinical pharmacology study # C-03-01 to compare pharmacokinetic of brimonidine after a single ocular drop in each eye of 0.15% brimonidine tartrate Polyquad preserved formulation or Alphagan P (0.15% brimonidine with Purite) in healthy volunteers. Results showed that systemic exposure to brimonidine was comparable for both solutions. Fifteen 18-44 years old male and female subjects were enrolled. Mean pharmacokinetic parameters after a single dose of brimonidine tartrate ophthalmic solution, 0.15%, PQ or Alphagan P are shown in the table below.

C _{max} (ng/ml)	482	1880	1090	10300	1.07
T _{1/2β} (h)	0.9	2.6	1.7	ND	1.0
T _{1/2α} (h)	66	82	11	ND	ND
AUC _{0-8hr} (ng.h/ml)	530	4200	2330	61600	0.840
AUC ₀₋₄₈ (ng.h/ml)	597	9580	3340	508000	ND

ND, not determined

Above data suggest that a single drop of 0.15% brimonidine is distributed in the anterior chamber of the rabbit eye. Tissue concentrations were maximum up to two hours after dosing and started declining thereafter.

2.6.4.5 Metabolism: The sponsor did not submit any data on metabolism of brimonidine.

2.6.4.6 Excretion: The sponsor did not submit any data on metabolism of brimonidine.

2.6.4.7 Pharmacokinetic drug interactions: The sponsor did not submit any data on nonclinical drug interactions of brimonidine.

2.6.4.8 Other Pharmacokinetic Studies: The plasma exposure data after repeat doses in rabbits are reviewed under the 3-month ocular safety review.

2.6.4.9 Discussion and Conclusions: Brimonidine is bioavailable in the ocular tissues and systemic circulation following ocular administration in rabbits.

2.6.4.10 Tables and figures to include comparative TK summary

See the table under tabulated summary below. Detailed data tables are shown in pages 10 and 11.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

[Pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

The following table shows tabulated summary:

Study #	Study description	Drug/Dose	Result
C-03-01	Systemic exposure in healthy human volunteers	Alphagan P, brimonidine 0.15% PQ One drop in each eye	Both Alphagan P and brimonidine 0.15% PQ showed a similar systemic exposure
TDOC-0001260	Distribution of brimonidine tartrate 0.15% PQ in male NZ rabbit eyes	Brimonidine 0.15% PQ, one drop into right eye	<ol style="list-style-type: none"> 1. Distribution of brimonidine was maximum in the iris-ciliary body. 2. Brimonidine was distributed in the anterior chamber of eye 3. Maximum concentrations of brimonidine were observed up to 2

			hours in most of the ocular tissues.
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2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Ophthalmic administration of brimonidine 0.15% and 0.2% solutions did not show any ocular safety concern in the rabbit eyes. However, brimonidine was bioavailable in the systemic circulation and caused transient hyperglycemia in the rabbit model.

One year toxicity study for Polyquad was conducted in rabbit eyes. Scanning electron microscopy of corneas showed that topical ocular administration of two drops of 0.001 and 0.01% Polyquad, three times per day for one year to rabbits produced no corneal changes. Corneas of animals treated with 0.05% Polyquad exhibited isolated areas of cell sloughing. The corneal changes in 0.05% Polyquad was a reversible change. However, Polyquad is used as a preservative in other ophthalmic products e.g. diclofenac sodium ophthalmic solution 0.1% and Tears Natural Forte marketed by the same sponsor.

Genetic toxicology: No genotoxicity studies were submitted in the NDA.

Carcinogenicity: No carcinogenicity data were submitted for the NDA 21-764.

Reproductive toxicology: No reproductive safety data were submitted in the NDA.

Special toxicology: No special toxicology study was submitted in the NDA.

2.6.6.2 Single-dose toxicity: No single dose toxicity study report was reviewed in the NDA.

2.6.6.3 Repeat-dose toxicity

Study title: Three-month topical ocular irritation and systemic toxicity evaluation of brimonidine PQ ophthalmic solution in pigmented rabbits, vol. 1.10 and module 4.

Key study findings: No ophthalmic and systemic toxicity was observed at 0.2% brimonidine P at one drop three times a day for 90 days. Transient hyperglycemia was noted in brimonidine treated rabbits.

Study no.: N-02-095

Volume vol 1.3#, and **page #:** 1

Conducting laboratory and location: Alcon Research Ltd, Texas

Date of study initiation: July 10, 2002

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: The lot number and purity of brimonidine ophthalmic solutions and the vehicle is shown in the table below.

Assay	Interval	Vehicle Lot#02-31665	0.15% Brimonidine PQ, Lot #02-31663	0.2% Brimonidine PQ, Lot #02-31666
Brimonidine strength (% label)	Initial	-	—	—
Brimonidine strength (% label)	Post study	-	—	—
Brimonidine identity	Initial	Negative	Positive	Positive
Brimonidine identity	Post study	Negative	Positive	Positive
Polyquad strength (% label)	Initial	—	—	—
Polyquad strength (% label)	Post study	—	—	—
Polyquad identity	Initial	Positive	Positive	Positive
Polyquad identity	Post Study	Positive	Positive	Positive

Methods

Doses:

Study design:

Group/treatment	Animal		Volume	Treatment/day	Study days
	male	Female			
1. Untreated control	7 (3)	7 (3)	80 µL	3	98-99 (35-36)
2. vehicle	7 (3)	7 (3)	80 µL	3	98-99 (35-36)
3. 0.15% Brimonidine PQ	7 (3)	7 (3)	80 µL	3	98-99 (35-36)
4. 0.2% Brimonidine PQ	7 (3)	7 (3)	80 µL	3	98-99 (35-36)
5. Alphagan P ophthalmic solution	7 (3)	7 (3)	80 µL	3	98-99 (35-36)
6. Alphagan ophthalmic solution	7 (3)	7 (3)	80 µL	3	98-99 (35-36)

Alphagan P and Alphagan contain 0.15 and 0.2% brimonidine, respectively. Figure in the parenthesis for animal column represents number of animals treated for interim period. Figure in the column study days represents treatment duration for interim sacrifice. Each group had a total of 7 rabbits/sex, 3 rabbits were sacrificed after one month of treatment and remaining 4 rabbits were sacrificed after three months of treatment.

Species/strain: New Zealand F₁ cross pigmented rabbits

Number/sex/group or time point (main study): Seven male and seven female rabbits

Route, formulation, volume, and infusion rate: The test article or vehicle was instilled in both eyes of each animal at one drop three times a day. Each drop was approximately 40 µL.

Satellite groups used for toxicokinetics or recovery: Satellite group of 3 rabbits/sex/group was allotted for one month interim data collection.

Age: Approximately 4-4.5 months

Weight: Approximately 2.4-3.6 kg

Sampling times: Nil

Unique study design or methodology (if any): Nil

Observations and times:

Mortality: Each animal was observed twice daily for mortality or moribund conditions.

Clinical signs: Each animal was examined twice daily for clinical signs. Also physical changes in the body surface were examined twice per week.

Body weights: Body weights were recorded prior to dosing, and on days 7, 14, 21, 28, 35, 49, 63, 77, 91 and 99.

Food consumption: Food consumption was not recorded.

Ophthalmoscopy: Eye examinations were conducted by slit lamp before randomization. Rabbits that showed normal eye were enrolled for the treatment. Animals with slight conjunctival congestion were also randomized for the study. Conjunctiva and corneal changes were examined on prestudy and days 7, 21, 35, 63 and 98. Lens were examined at prescreen, days 35 and 98 after dilatation of pupil with 1% Mydriacyl. Fundus, optic nerve head, vessels of retina and choroid were examined by an indirect ophthalmoscope at predose and on days 28 and 98. Observation of the posterior chamber was indicated as within normal limits (WNL) or abnormal (AB).

Corneal thickness and IOP were determined by pachymetry and pneumatonometer, respectively, before treatment and on days 34 and 97 for those animals assigned to 3 months of treatment.

EKG: No EKG was recorded.

Hematology: Blood samples were collected on days 20-21 and days 86-87 for standard hematological examination and coagulation parameters.

Clinical chemistry: Blood samples collected for hematology were used for clinical chemistry parameters in the serum.

Toxicokinetics: Blood samples (3 ml) were collected from 4/sex/time point from group 3 and 4 rabbits on day 1, day 29 and day 92. Samples were also taken from 4/sex/time point from groups 5 and 6 rabbits on day 2, day 30 and day 93. Samples were taken immediately before last dose of the day, 0.5, 1 and 2 hours after the last dose of the day.

Urinalysis: No urine analysis was conducted.

Gross pathology: Animals were sacrificed by sodium pentobarbital. All animals were examined for external abnormalities. Eyes and adnexa were fixed in solution for 4 hours, rinsed and fixed in formalin. All other tissues were fixed in 10% buffered formalin.

Organ weights (specify organs weighed if not in histopathology table): Weights of following organs were recorded:

Liver, kidney, heart, adrenal, gonad, spleen and brain.

Histopathology: Adequate Battery: yes (x), no ()—explain

Tissues from eyes, adnexa and lacrimal tissues from all animals and protocol specified tissues from groups 1, 4 and 6 were examined histologically. In addition any tissue with

gross lesion was examined. Remaining tissues were fixed and retained for future evaluation.

Peer review: yes (), no (x)

Results

Mortality: No mortality was reported.

Clinical signs: No treatment related clinical sign was observed.

Body weights: The average body weight (g) of male rabbits is shown in the table below.

Group	Predose	Day 35	Day 91
1	3.25	3.33	3.50
2	2.98	3.15	3.48
3	3.35	3.50	3.70
4	2.80	3.03	3.20
5	3.20	3.35	3.55
6	2.90	3.13	3.33

The average body weight (g) of female rabbits is shown in the table below.

Group	Predose	Day 35	Day 91
1	3.08	3.18	3.48
2	2.78	2.90	3.30
3	2.90	3.05	3.43
4	2.98	3.18	3.53
5	2.95	3.15	3.43
6	2.85	3.00	3.35

Above data do not show treatment related change in the body weight at 35 and 91 days of the treatment in male and female rabbits.

Ophthalmoscopy: slight conjunctival congestion score of 1 out of 3 was noted in group 3, 4 and 6. However, incidences were not consistently present in all animals and all time points. Therefore, its relevance to the treatment is unknown. Swelling, conjunctival discharge, flare, iritis, neovascularization, corneal cloudiness and pupillary reflex were not changed due to the treatment. Indirect ophthalmoscopic examination showed no treatment related changes in the fundus and retina. No treatment related changes were noted in the pachymetric measurements for corneal thickness. Statistically significant changes were noted in 0.15% brimonidine treated male and female rabbits. However, these changes were not biologically significant. The treatment had no effect on the intraocular pressure when compared to the vehicle and untreated control groups except a reduction in the IOP to 14.87 mm of Hg in the left eye in Alphagan P treated male rabbits on day 97. The untreated rabbits showed an IOP of 19.12 mm of Hg. The difference was not statistically significant.

EKG: EKG was not recorded in the rabbit.

Hematology: Other than incidental changes, the treatment had no biologically significant effect on hematology parameters. WBC ($10^3/\mu\text{L}$) in Alphagan treated female rabbits on day 21 was 4.5 compared to 8.2 in the untreated control. A similar trend was also noted on day 87. There was no treatment related changes in the coagulation parameters.

Clinical chemistry: Serum cholesterol and glucose levels were changed in several drug treated groups as shown in the table below.

Parameter	Day	Sex	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Glucose, mg/dL	20	Male	125.5	124.3	264.0*	312.7*	179.2	264.0*
Glucose, mg/dL	86	Male	124.5	116.2	120.2	115.5	123.2	114.5
Glucose, mg/dL	21	Female	124.7	124.7	219.0	295.0*	290.0	281.7*
Glucose, mg/dL	87	Female	119.5	118.0	140.5	171.0*	140.7	118.0
Cholesterol, mg/dL	20	Male	47.0	46.0	30.2	28.0	25.2	32.2
Cholesterol, mg/dL	86	Male	29.5	30.5	18.6*	28.0	26.0	19.0*
Cholesterol, mg/dL	21	Female	57.2	66.5	37.5*	36.2*	34.5*	40.2
Cholesterol, mg/dL	87	Female	53.7	60.7	29.7*	27.7*	32.0*	33.2*

There was a transient increase in the average serum glucose levels on day 20-21 in male and female rabbits that was not evident on days 86-87. The average cholesterol levels were also decreased in the brimonidine treated rabbits. Cholesterol levels for untreated male rabbits were between 26 to 69 mg/dL and that of untreated female rabbits were between 42-60 mg/dL. Hyperglycemic effect of brimonidine is due to inhibition of insulin release. However, tachyphylaxis could have occurred on continuous treatment. Hyperglycemic effect is not apparent in the clinical study in brimonidine ophthalmic solution approved in the past.

Urinalysis: Urine analysis was not conducted in the study.

Gross pathology: Gross pathology showed depressed foci in the kidney in untreated and treated animals. The sponsor stated that the cause of the lesion was infestation with *Encephalitozoon cuniculi*. No other gross changes were observed.

Organ weights (specify organs weighed if not in histopath table):

There was no treatment related changes in the organ weight.

Histopathology: Adequate Battery: yes (x), no ()—explain

Peer review: yes (), no (x)

Histopathology data for all tissues were presented for untreated, vehicle treated 0.2% brimonidine PQ and brimonidine 0.2% treated rabbits only. However, histology data for eye tissues from all animals in groups 1-8 were presented.

No treatment related effect was noted in choroid, ciliary body, cornea, eyelid, Harderian gland, iris, lacrimal gland, lens and nosolacrimal duct. No treatment related systemic toxicity was also noted in the study.

Toxicokinetics:

Mean brimonidine plasma AUC_{0-2 hr} (pg.hr/ml) is shown in the table below. Data for male and female rabbits were combined.

Treatment (group)	Day 1, 2	Day 29, 30	Day 92, 93
0.15% Brimonidine PQ, gr 3	670	859	865
0.2% Brimonidine PQ, gr 4	1260	2580	2200
0.15% Alphagan P, gr 5	1060	1040	1910
0.2% Alphagan, gr 6	1060	1390	1770

Mean C_{max} for brimonidine in the plasma is shown in the table below.

Treatment (group)	Day 1, 2	Day 29, 30	Day 92, 93
0.15% Brimonidine PQ	746	956	1020
0.2% Brimonidine PQ	1360	2370	2300
Alphagan P, 0.15%	1160	816	2160
Alphagan 0.2%	1170	1480	2260

Above data show that 0.15% brimonidine PQ had low systemic bioavailability than 0.15% Alphagan P both at the beginning and end of dosing period.

Histopathology inventory (optional)

Study	3- Month			
Species	Rabbit			
Adrenals	X			
Aorta	X			
Bone Marrow smear	X			
Bone (femur)	X			
Brain	X			
Cecum	X			
Cervix				
Colon	X			
Duodenum	x			
Epididymis	x			
Esophagus	x			
Eye	x			
Fallopian tube	x			
Gall bladder	x			
Gross lesions	x			
Harderian gland	x			
Heart	x			
Ileum	x			
Injection site				
Jejunum	x			

Study	3- Month			
Kidneys	x			
Lachrymal gland	x			
Larynx	x			
Liver	x			
Lungs	x			
Lymph nodes, cervical	x			
Lymph nodes mandibular				
Lymph nodes, mesenteric	x			
Mammary Gland	x			
Nasal cavity	x			
Optic nerves	x			
Ovaries	x			
Pancreas	x			
Parathyroid	x			
Peripheral nerve	x			
Pharynx				
Pituitary	x			
Prostate	x			
Rectum	x			
Salivary gland	x			
Sciatic nerve	x			
Seminal vesicles	x			
Skeletal muscle	x			
Skin	x			
Spinal cord	x			
Spleen	x			
Sternum	x			
Stomach	x			
Testes	x			
Thymus	x			
Thyroid	x			
Tongue	x			
Trachea	x			
Urinary bladder	x			
Uterus	x			
Ureter	x			
Vagina	x			
Zymbal gland				

X, histopathology performed
 *, organ weight obtained

2.6.6.4 Genetic toxicology: No genetic toxicity data were submitted in the NDA.

2.6.6.5 Carcinogenicity: No carcinogenicity data submitted in the NDA.

Toxicokinetics: See 3-month ocular safety review. The sponsor submitted pharmacology review for NDA 20-613 dated May 28, 1996 in module 4 and vol 1.5. The pharmacokinetic data for mouse and rat carcinogenicity studies were provided. The average plasma brimonidine concentrations in mice were 0.18, 0.82 and 4.4 ng/ml at 0.1, 0.5 and 2.5 mg/kg, respectively. The average plasma brimonidine concentrations in rats were 0.297, 0.64 and 3.60 ng/ml at 0.05, 0.25 and 1.0 mg/kg, respectively.

Teratogenicity of brimonidine was investigated in Sprague Dawley rats at 0.066, 0.66 and 1.650 mg/kg as a base. The plasma levels of brimonidine on day 6 of gestation were 0.7, 5.54 and 15.1 ng/ml at 0.066, 0.66 and 1.65 mg/kg, respectively. Plasma levels of brimonidine on gestation day 15 were 0.62, 5.8 and 19.5 ng/ml at 0.066, 0.66 and 1.65 mg/kg base, respectively.

Teratogenicity study in rabbits was conducted at 0.165, 0.66 and 3.3 mg/kg base. Mean plasma brimonidine concentrations on gestation day 6 were 0.24, 2.90 and 6.33 ng/ml at 0.165, 0.66 and 3.33 mg/kg, respectively. The plasma brimonidine concentrations on day 18 were 0.24, 0.74 and 1.42 ng/ml at 0.165, 0.66 and 3.33 mg/kg base, respectively.

2.6.6.6 Reproductive and developmental toxicology: No reproductive and developmental study report was submitted in the NDA.

2.6.6.7 Local tolerance: See 3-month ocular toxicity review.

2.6.6.8 Special toxicology studies: No special toxicology study report was submitted in the NDA.

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures : See individual study review

2.6.7 TOXICOLOGY TABULATED SUMMARY

[Pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect, as available and as provided by the sponsor]

Study #	Study description	Drug/Dose	Result
N-02-095	3-month topical ocular irritation and systemic toxicity of brimonidine ophthalmic solutions in pigmented rabbit eyes	Brimonidine 0.15% PQ, 0.2% PQ, Alphagan P and Alphagan were used in the study. Test articles or vehicle was instilled into both eyes at one drop 3 times a day.	Slight conjunctival congestion and transient hyperglycemia were noted due to brimonidine 0.15 PQ, 2% PQ, and Alphagan.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Brimonidine is an α_2 -adrenergic agonist for the treatment of ocular hypertension and increased intraocular pressure in glaucoma patients. Brimonidine ophthalmic solutions

reduced intraocular pressure of the normal eyes and laser induced hypertensive eyes in several experimental studies. Brimonidine reversed prostaglandin DP receptor agonist induced hyperemia in the guinea-pig model. Data suggest that it has both pre synaptic and post synaptic effects.

The NDA is a 505 (b) (2) application of brimonidine tartrate 0.15% ophthalmic solution with Polyquad as a preservative. The recommended dose is one drop in the affected eye three times a day. Total dose for each patient will be 6 drops per day. Each drop contained $41.8 \pm 4.3 \mu\text{L}$ and $63 \mu\text{g}$ brimonidine tartrate. The total dose will be $378 \mu\text{g/day}$ or $6.3 \mu\text{g/kg}$ for a 60 kg patient. A similar dose was approved for brimonidine 0.15% ophthalmic solution with Purite as preservative.

The sponsor conducted a three-month ocular and systemic toxicity of 0.15 and 0.2 % brimonidine P ophthalmic solutions in the rabbit model. No ocular or systemic toxicity was noted except transient hyperglycemia after about one month of the treatment and slight reduction in the cholesterol levels. However, clinical significance of the finding is unknown. The drug is bioavailable in the ocular tissues and systemic circulation following ocular administration into rabbit eyes.

The preservative, Polyquad is approved for the use in contact lens cleansing solutions at 0.001% and for diclofenac ophthalmic solution. A one-year ocular toxicity was conducted for Polyquad up to 0.05% solution. A slight change in the cornea was noted at 0.05%. However, no Polyquad related effect was noted at 0.001% solution.

Unresolved toxicology issues (if any): Nil

Recommendations: Based on the nonclinical toxicity data for brimonidine and Polyquad, brimonidine tartrate 0.15% ophthalmic solution with Polyquad is approvable for the lowering of IOP in glaucoma patients.

Suggested labeling:

The proposed label:

┌

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✓

✓

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

C.C. LIST

NDA 21-764 Div File

- HFD-550/ PM/Raphael Rodriguez
- HFD-550/Pharmacologist/ A. Mukherjee
- HFD-550/ Team Leader/J. Yang
- HFD-550/ Medical Officer/ Rhea Lloyd
- HFD-550/Chemist/Lin Qi

Revised on Nov 29, 2004

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PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 21-764

Applicant: Alcon

Stamp Date: April 30, 2004

Drug Name: Brimonidine
Tartrate Ophthalmic Solution
0.15%

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? (Yes or No) yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL the required and requested IND studies completed and submitted in this NDA?	x		
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	x		A 3-month repeat dose study was conducted in rabbit eyes using the new formulation.
6	Are the proposed labeling sections relative to animal Pharmacology/Toxicology appropriate (including human dose multiples based on comparative serum/plasma levels or expressed in mg/m ²) and in accordance with CFR21, part 201.57?	x		
7	Has the sponsor submitted all special studies/data requested by the Division during pre-NDA meeting?	x		

Reviewing Pharmacologist:

Asoke Mukherjee

Date:

Team Leader:

Josie W.C. Yang

Date:

cc:
Original NDA 21-764
HFD-550/Division File
HFD-550/Pharm-Tox/A. Mukherjee
HFD-550/Pharm-Tox TL/JYang
HFD-550/CSO/N. Halonen

NDA21764checklistMay262004.doc

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