CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-770

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:	21-770
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	04/06/04
PRODUCT:	Brimonidine tartrate ophthalmic solution, 0.1%
INTENDED CLINICAL POPULATION:	Glaucoma and ocular hypertension
SPONSOR:	Allergan Pharmaceuticals
DOCUMENTS REVIEWED:	Electronic NDA
REVIEW DIVISION:	Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
PHARM/TOX REVIEWER:	Asoke Mukherjee, Ph.D.
PHARM/TOX SUPERVISOR:	Josie Yang, Ph.D.
DIVISION DIRECTOR:	Brian Harvey, Ph.D., M.D.
PROJECT MANAGER:	Michael Puglisi

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: [redacted]

C. Recommendations on labeling:

Suggested labeling by the reviewer:

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 [redacted] and **120** times, respectively, the plasma drug concentration (C_{max}) estimated in humans treated with one drop of Tradename into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of in vivo and in vivo studies including 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 in rats **and rabbits** with oral doses of 0.66 mg base/kg revealed No evidence of harm to the fetus due to Tradename. Dosing at this level produced an exposure in rats **and rabbits** that is [redacted]

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. Tradename 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; although 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.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

The sponsor studied the IOP lowering effect of 0.1% brimonidine tartrate ophthalmic solution in New Zealand rabbit eyes. The drug solution reduced the IOP up to 4 hours. The 0.15% ophthalmic solution of brimonidine slightly increased the IOP above the baseline immediately after the dose. However, 0.1% brimonidine ophthalmic solution did not increase the IOP above the baseline. Bioavailability of 0.1% brimonidine solution in the aqueous humor was similar to that observed for 0.15% ophthalmic solution of brimonidine. It appears that an increase in the pH from 7.2 to 7.7 improved the bioavailability of brimonidine in the aqueous humor. Plasma levels of brimonidine from one drop of 0.1% solution were lower than 0.15% solution. An impurity designated as [redacted] did not show ocular toxicity in rabbits.

The clinical pharmacology section of the package insert indicated increased permeability of brimonidine ophthalmic solution at higher pH. However, only nonclinical data were provided in the NDA to support the claim. The clinical reviewer needs to determine if the nonclinical data were sufficient to claim that the penetrability of the drug across the cornea is dependent on the pH of the solution.

B. Pharmacologic activity: One drop of 0.1% Brimonidine ophthalmic solution reduced the IOP in normotensive rabbit eyes that lasted for 4 hours.

C. Nonclinical safety issues relevant to clinical use: Plasma levels of glucose increased after the treatment with brimonidine 0.15% ophthalmic solution as reviewed for NDA 21-262 submitted by Allergan Pharmaceuticals. However, the sponsor did not investigate the effect of 0.1% brimonidine ophthalmic solution for this NDA.

[Please limit to 1-3 pages]

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-770
Review number: One
Sequence number/date/type of submission: 000, 505 (b)(1)
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Allergan Pharmaceuticals, California
Manufacturer for drug substance: Ash Stevens, Riverview, MI 48192 and Torean Chemicals Ltd., Ontario, Canada.

Reviewer name: Asoke Mukherjee, Ph.D.
Division name: Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products
HFD #: 550
Review completion date: Sept 20, 2004

Drug:

Trade name: Brimonidine tartrate ophthalmic solution 0.1%
Generic name. [redacted]
Code name: AGN 190342-LF
Chemical name: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate

CAS registry number: 70359-46-5
Molecular formula/molecular weight: $C_{11}H_{10}BrN_5.C_4H_6O_6$; 442.24
Structure:

Relevant INDs/NDAs/DMFs: NDA 21-764, NDA 20-613, NDA 21-262, NDA 21-770, IND 32,292 and DMF [redacted]

Drug class: α_2-adrenergic agonist

Intended clinical population: Patients with glaucoma and ocular hypertension

Clinical formulation:

Ingredient	Content (% w/v)
Brimonidine tartrate	0.1%
Purite	0.005%
Sodium carboxymethyl cellulose	[redacted]
Boric acid	
Sodium borate [redacted]	

Ingredient	(	)
Sodium chloride		
Potassium chloride		
Calcium chloride, [redacted]		
Magnesium chloride, [redacted]		
Hydrochloric acid		
Sodium hydroxide		
Purified water		

Route of administration: Ophthalmic drops

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

Studies reviewed within this submission:

1. IOP lowering in rabbits by Alphagan-P upgrade 0.1% and other formulations of brimonidine, M4 vol 1, p 008.
2. IOP lowering in rabbits by brimonidine Purite 0.1% (pH 7.7), M4 vol 1, p019.
3. Comparison of ocular and systemic bioavailability of three 0.1% brimonidine Purite formulations to that of 0.15% Alphagan in albino rabbits, M4 vol 1, p 029.
4. Alphagan P upgrade, 1-month ocular toxicity study of Alphagan P upgrade with impurity [redacted] in rabbits, M4 vol 1, p 112.

Studies <u>not</u> reviewed within this submission:

1. Relative ocular bioavailability of 0.2% Alphagan and 0.15% brimonidine-BAK to that of 0.15% Alphagan P in female albino rabbits, M4 vol 1, p 064.

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:

1. IOP lowering in rabbits by Alphagan P upgrade 0.1% and other formulations of brimonidine. Module 4, vol 1, page 008, report # Bio-03-401.

The study was conducted in male albino New Zealand rabbits weighing 2-3 kg. The sponsor stated that 6-9 rabbits were used per group. The following formulations were used in the study:

Solution #	1	2	3	4
Formulation #	9329X	7831X	9174X	9541X
% Brimonidine (AGN342)	0	0.2	0.15	0.10
Solution Description	Refresh tears, Placebo	Alphagan, 0.2%	Alphagan-P	Alphagan-P 0.1%
Preservative	Purite,	Bak,	Purite	Purite
Viscosity agent	CMC,	PVA	CMC	CMC
Buffer	Borate	Citrat	Borate	Borate
Tonicity agent	NaCl,	NaCl,	NaCl,	NaCl,
Other excipients	KCl, $CaCl_2$, $MgCl_2$	N/A	KCl, $CaCl_2$, $MgCl_2$	KCl, $CaCl_2$, $MgCl_2$
Target pH	7.2	6.4	7.2	7.7
Viscosity	3	~3	3	3
Storage conditions	Protect from light	Room Temp	Protect from light	Protect from light

A 35 μL of each test solution was applied to one eye and IOP was measured immediately before the treatment and at 0.5, 1, 2, 3, 4, 5 and 6 hour post dose by a pneumatonometer. A slight increase in the IOP was noted immediately after dosing followed by a reduction of IOP by 29% at the end of 3 hours after treatment with 0.1% Alphagan. Alphagan P showed a maximum 19% reduction at the end of 2 hours of the treatment and the effect continued up to 4 hours. Data suggest that 0.1% brimonidine solution showed a better ocular hypotensive effect than that of 0.15% solution of brimonidine. Mean percent increase or decrease of IOP from the base line is shown in the table below.

Preparation	Brimonidine %	N	Baseline IOP, mm Hg	Time following instillation						
				0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Refresh Tear, placebo	0	8	18	-4	2	-3	3	1	7	6
Alphagan	0.2	8	18	20	15	-26	-30	-8	7	8
Alphagan-P	0.15	6	18	22	14	-19	-16	-3	6	11
Alphagan-P 0.1%	0.1	9	19	12	9	-23	-29	-20	-4	-1

2. IOP lowering in rabbits by brimonidine Purite 0.1% (pH 7.7), Module 4, vol 1, page 019, report # Bio-03-408.

Above study was repeated in male albino rabbits weighing 2 to 3 kg. A drop of 35 µL of brimonidine solution or placebo was instilled into one eye. IOP was measured before the treatment and 0.5, 1, 2, 3, 4 and 6 hours after the treatment with Refresh Tears as a placebo control or Alphagan-P at pH 7.2 or brimonidine Purite 0.1% at pH 7.7. A slight elevation of IOP was noted during first hour, which could be due to α_1-adrenergic effect of the drug. However, both formulations showed a decrease in the IOP that lasted about 4 hours. Brimonidine Purite 0.1% showed a slightly better effect than that of 0.15% solution of brimonidine. IOP decreasing effect as % of the mean is shown in the table below.

Preparation	Brimonidine %	N	Baseline, IOP mm Hg	0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr

Preparation	Brimonidine %	N	Baseline, IOP mm Hg	0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Placebo	0	6	19	2	11	12	14	15	17	5
Alphagan P	0.15%	6	19	30	5	-29	-27	-18	2	7
Alphagan P upgrade	0.1%	6	19	22	9	-31	-35	-19	-4	5

Data suggest that brimonidine Purite 0.1% was equally effective as brimonidine Purite 0.15% ophthalmic solution.

Summary of pharmacology data:

Both Alphagan P (pH 7.2) and brimonidine Purite 0.1% ophthalmic solutions (pH 7.7) reduced the IOP in normal rabbit eyes that lasted almost 4 hours. Data suggest that pharmacodynamic effect of the drug in rabbit eyes improved by increasing the pH of the ophthalmic solution so that both 0.15% and 0.1% brimonidine were pharmacodynamically equivalent for lowering IOP. Data suggest that pH plays an important role in the bioavailability of the drug in eyes.

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 the inhibition of aqueous humor formation and increased aqueous humor outflow.

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

No secondary pharmacology data were submitted in the NDA.

2.6.2.4 Safety pharmacology

No safety pharmacology data were submitted in the NDA.

2.6.2.5 Pharmacodynamic drug interactions:

No data for drug-drug interactions were 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]

Tabulated summary of two pivotal pharmacology studies is shown in the table below.

Study	Species	Route	Dose	Gender, #	Finding	GLP	Study

Type							Location
Effect on IOP	NZW rabbits	Ocular drop	1 drop, 35 μL	M, 6-9	1% brimonidine had IOP lowering effect like Alphagan and Alphagan P	No	M4,vol 1, page 008, #BIO-03-401
Effect on IOP	NZW rabbits	Ocular drop	1 drop, 35 μL	M, 6	IOP lowering effect of 1% and 1.5% brimonidine was similar. Slight increase in the pH improved the IOP lowering effect	No	M4, vol 1, page 019, #BIO-03-408

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: Brimonidine 0.1% and 0.15% ophthalmic solutions were bioequivalent in the aqueous humor in the rabbit eye. Plasma levels of brimonidine from 0.1% ophthalmic solution was lower than those of 0.15% following instillation of one drop into the eye in rabbits.

2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

1. Comparison of ocular and systemic bioavailability of three 0.1% brimonidine Purite formulations to that of 0.15% Alphagan Purite in albino rabbits. Module 4, vol 1, page 029, study # PK-02-229.

Objective of the study was to compare ocular and systemic bioavailability of brimonidine tartrate from 0.15% Alphagan P to that of 0.1% brimonidine Purite, 0.1% [redacted] and 0.1% [redacted] at pH 7.8. About 35 μL of each formulation was instilled into each eye. The study was conducted in female New Zealand white rabbits with approximately 2-3 kg body weight. However, table 1 on page 049 stated that male rabbits were used in the study. Three rabbits were dosed with each formulation for each time point. One ml blood was collected from the ear artery and 100 μL. Aqueous humor was collected from each eye. Sampling time was predose, 10, 20, 40 min and 1, 1.5, 2 and 3 hours after the dose.

The study design suggests that same rabbits were used for another formulation after 3 days of washout period in accordance to a cross-over design. Rabbits were anesthetized by ketamine and xylazine before collection of samples. One or two drops of Ocuflox were applied after the collection of aqueous humor samples. Brimonidine content of the aqueous humor samples was determined by the LC-MS method at a limit of detection of [redacted]. Plasma samples were analyzed by the GC-MS and the limit of detection was 0.05 ng/ml.

Results:

Pharmacokinetic parameters for brimonidine formulations in aqueous humor are shown in the table below.

Parameter	0.15% Alphagan P	0.10% Alphagan P	0.10% [redacted]	0.10% [redacted]
C_{max} (μg/ml)	0.629	0.644	0.551	0.684
T_{max} (hr)	0.667	0.667	0.667	0.667
$T_{½}$ (hr)	0.822	0.565	1.03	0.606
$AUC_{0\text{-}3\ hr}$ (μg.hr/ml)	0.759	0.802	0.733	0.901
$AUC_{0\text{-}\infty}$ ((μg.hr/ml)	0.831	0.835	0.857	0.945

Above data suggest that both 0.15% and 1.0% brimonidine was equally bioavailable in the aqueous humor.

Plasma brimonidine kinetics following a single ophthalmic dose of brimonidine formulations are shown in the table below.

Parameter	0.15% Alphagan P	0.1% Alphagan P	0.1% [redacted]	0.1% [redacted]
C_{max} (ng/ml)	3.09	2.58	1.62	1.78
T_{max} (hr)	0.167	0.167	0.167	0.167
$T_{½}$ (hr)	0.689	0.550	0.570	0.403
$AUC_{0\text{-}tlast}$ (ng.hr/ml)	2.36	1.72*	1.44*	1.28*
$AUC_{0\text{-}\infty}$ (ng.hr/ml)	2.44	1.76	1.48	1.32

* Statistically significant compared to 0.15% brimonidine solution

Above data show that systemic bioavailability of brimonidine from 0.10% ophthalmic formulations was lower than that of 0.15% solution.

2.6.4.4 Distribution

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

2.6.4.6 Excretion: The sponsor did not submit any data on the excretion 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:** No other pharmacokinetic studies were submitted in the NDA.

2.6.4.9 Discussion and Conclusions: Bioavailability of 0.1% brimonidine ophthalmic solution was similar to that of 0.15% ophthalmic solution in rabbits. However, plasma levels of brimonidine from 0.1% solution was lower than the plasma levels achieved from 0.15% brimonidine ophthalmic solution.

2.6.4.10 Tables and figures to include comparative TK summary

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]

Tabulated summary of absorption after a single ocular administration. Report # PK-02-229 located on page 029, vol 1 and module 4.

List of item	Information
Species	rabbit
Gender (M/F), # animals	3 male/time point
Feeding condition	Fed
Vehicle/Formulation/concentration	Refresh Purite vehicle, 0.1% brimonidine solution
Method of administration/drop size	Ophthalmic drop, 35 μL/eye
Dose (μg salt/eye)	70
Sample	Aqueous humor and plasma
Sampling time (hours post dose)	0.17, 0.33, 0.67, 1, 1.5, 2 and 3 hr
Analyte	Brimonidine
Assay	LC-MS and GC-MS
PK parameters	
C_{max} (μg/ml or μg/g)	0.644 (aqueous humor) and 0.00258 (plasma)
T_{max} (hr)	0.67 (aqueous humor) and 0.17 (plasma)
AUC (μ.hr/ml)	0.80 (aqueous humor) , NA (plasma)
$T_{½}$ (hr)	NA

NA=not available

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary:

An impurity identified as [redacted] did not show ocular toxicity in the rabbit eye at [redacted] ophthalmic solution.

2.6.6.2 Single-dose toxicity: No single dose toxicity data were submitted in the NDA.

2.6.6.3 Repeat-dose toxicity

Study title: Alphagan P Upgrade: 1-month ocular toxicity study of Alphagan P upgrade with impurity [redacted] in rabbits.

Key study findings: [redacted] did not show any ocular toxicity

Study no.: TX 03017
Volume #, and page #: 112
Conducting laboratory and location: Allergan, Irvine CA 92612
Date of study initiation: May 5, 2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot # 12187A1, and % purity: Brimonidine tartrate [redacted] containing [redacted] as one of the impurities. The ophthalmic solution contains [redacted] of the label strength. Brimonidine tartrate 0.1% solution (Alphagan P upgrade) lot # 12139A1 containing [redacted].

Methods

Doses: The study design is shown in the table below.

Group	Animal	Formulation	Dose
1	6	Brimonidine tartrate 0.1% ophthalmic solution	One drop three times a day in the left eye
2	6	Brimonidine tartrate 0.1% ophthalmic solution with [redacted]	One drop three times a day in the left eye

Species/strain: Female New Zealand white (Hra-NZW) SPF rabbits
Number/sex/group or time point (main study): 6
Route, formulation, volume, and infusion rate: About 40 μL ophthalmic drop
Satellite groups used for toxicokinetics or recovery: Nil
Age: Approximately 6 months
Weight: 3.37-3.67 kg
Sampling times: Nil
Unique study design or methodology (if any): Nil

Observations and times:

Mortality: Twice daily
Clinical signs: Twice daily. Gross ocular observations were made once prior to the treatment (pretest), prior to the first dose and after the last daily dose during the treatment period.
Body weights: Individual body weight was recorded prior to randomization on day 1 and once weekly.
Food consumption: Food consumption was not recorded in the experiment.
Ophthalmoscopy: Slit lamp and indirect ophthalmoscopic examinations were performed before the dosing and at the end of dosing period during last week of the treatment.
EKG: EKG was not recorded.
Hematology: Hematological changes were not determined.
Clinical chemistry: Clinical chemistry was not conducted.
Urinalysis: Urine analysis was not conducted in the study.
Gross pathology: Rabbits were euthanized on day 29 of the study by IV injections of pentobarbital and gross changes in the eye were examined. Eyes lids, nictitating membrane, Harder's and lacrimal glands, optic nerve and extra-ocular muscles were collected from both eyes and preserved in 10% neutral buffered formalin.
Organ weights (specify organs weighed if not in histopath table): Organ weight was not recorded.
Histopathology: No histopathological examination was conducted in the study.

Results

Mortality: No mortality was recorded.

Clinical signs: No drug related clinical observation was recorded. Gross ocular observation was unrelated to the treatment since these changes were noted in the treated and untreated eyes. These changes were mild ocular discharge and congestion.

Body weights: There was no treatment related changes in the body weight.

Ophthalmoscopy: Slit lamp examination showed mild conjunctival congestion in both eyes in the brimonidin[redacted] and Alphagan upgrade formulations. These changes were considered to be unrelated to the treatment. Indirect ophthalmoscopic examination did not show any treatment related changes.

Gross pathology: No treatment related gross pathological changes in the eye were observed.

Organ weights (specify organs weighed if not in histopath table): Organ weight was not recorded.
Histopathology: Histopathology was not conducted on the eye tissues due to a lack of macroscopic and ophthalmological changes.

Toxicokinetics: Nil

It was concluded that brimonidine tartrate 0.1% ophthalmic solution and brimonidine 0.1% ophthalmic solution with [redacted] an impurity did not show any treatment related changes in the eye when one drop was instilled in the left eye three times a day for 28 days in New Zealand White rabbits.

Summary of toxicity data:

The sponsor did not submit any new toxicity study reports for brimonidine tartrate ophthalmic solution except a one-month study of the ocular toxicity of a 0.1% brimonidine solution that also contains [redacted] impurity designated a[redacted]. However, no differences in the ocular safety of 0.1% brimonidine tartrate ophthalmic solution with or without [redacted] were noted in the rabbit eye. Data suggest that contamination of the ophthalmic solution with [redacted] had no safety concern based on the non-clinical study.

2.6.6.4 Genetic toxicology

No genetic toxicity data were submitted in the NDA.

2.6.6.5 Carcinogenicity:

No carcinogenicity data were submitted in the NDA.

2.6.6.6 Reproductive and developmental toxicology:

No reproductive safety data were submitted in the NDA.

2.6.6.7 Local tolerance:

No study reports for local tolerance were submitted in the NDA.

2.6.6.8 Special toxicology studies:

No special study reports were submitted in the NDA.

2.6.6.9 Discussion and Conclusions: Nil

2.6.6.10 Tables and Figures: Nil

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	Species, strain	Formulation	Duration	Dose	GLP	Observation	Location
Toxicity of impurity [redacted]	NZW rabbits, Female	Ophthalmic solution of 0.1% brimonidine Purite with [redacted] impurity	28 days	1 drop, 3x/day in one eye, 35 μL	Yes	Presence of [redacted] did not show ocular toxicity	M4, vol 1, page 112, #TX03017

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The NDA is submitted for the approval of brimonidine Purite 0.1% ophthalmic solution for the reduction of IOP in glaucoma and ocular hypertensive patients. A similar formulation containing 0.15% brimonidine ophthalmic solution was already approved for lowering IOP. The sponsor conducted a comparative study in rabbit eyes for IOP lowering effect of Alphagan, Alphagan P (0.15%) and brimonidine tartrate 0.1% solution.

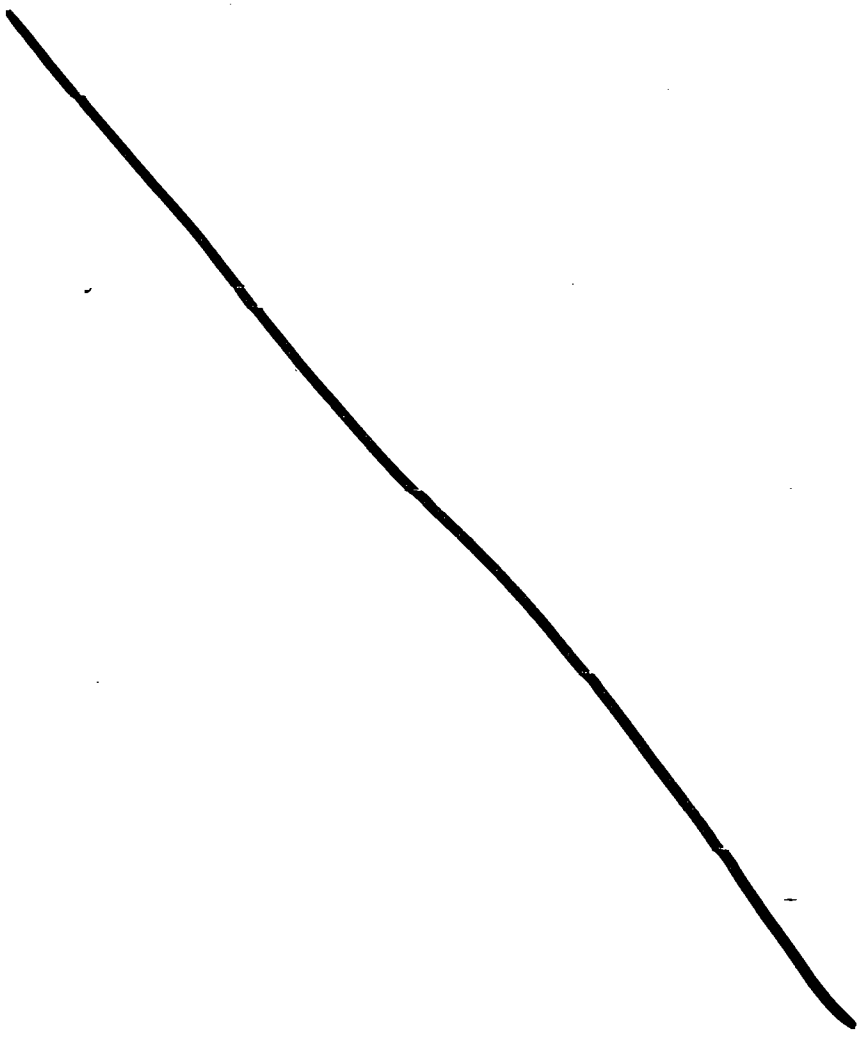
Data suggest that 0.1% ophthalmic solution showed IOP lowering effect up to 4 hours after a single drop in the eye by about 20% from the baseline data. In another study, aqueous humor and plasma bioavailability of 0.15 and 0.10% brimonidine tartrate was compared after application of a single drop into rabbit eyes. Data suggested that the level of 0.15% and 0.1% brimonidine was equivalent in the aqueous humor and its plasma bioavailability from 0.1% ophthalmic solution was less than that seen with 0.15% ophthalmic solution. The bioavailability data also suggest that an increase in the pH of the ophthalmic solution from 7.2 to 7.7 increased the exposure of brimonidine in the aqueous humor. Therefore, pharmacodynamic and ocular pharmacokinetics of the formulation is pH dependant in the rabbit model. Moreover, chances of systemic side effects from the 0.1% brimonidine ophthalmic solution would be lesser than that of 0.15% brimonidine ophthalmic solution without compromising the efficacy. The sponsor also submitted an ocular safety report of a formulation of 0.1% brimonidine tartrate containing [redacted] of an impurity designated as [redacted] Brimonidine tartrate 0.1% solution with [redacted] did not show an adverse effect in the rabbit eye in a one-month ocular safety study. The proposed human dose is one drop three times a day in the affected eye. The drop size is considered to be 35 μL and daily dose will be 3.5 μg/kg for a 60 kg subject.

It is concluded that nonclinical data support the IOP lowering effect of 0.1% brimonidine tartrate in rabbit eyes and its bioavailability in aqueous humor is comparable to that of 0.15% ophthalmic solution of brimonidine in the rabbit model.

Unresolved toxicology issues (if any): Nil

Recommendations: Brimonidine tartrate 0.1% ophthalmic solution is approvable on the basis of the nonclinical data and previous clinical experience with 0.15% brimonidine ophthalmic solution.

Proposed final draft label by the sponsor:



Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

C.C LIST:

NDA 21-770 Div File

HFD/550/ PM / M. Puglisi
HFD-550/Pharmacologist/A. Mukherjee
HFD-550/Team Leader/J.Yang
HFD-550/Medical Officer/ Martin Nevitt
HFD-550/Chemist/ Li Rodriguez

Revised on Oct 14, 2004 and OCT 18, 2004

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