CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-262

PHARMACOLOGY REVIEW

DFS a 14/32/c.

Review and Evaluation of Pharmacology/Toxicology Data

Key words: Ocular hypertension, glaucoma and α_2 adrenergic agonist

Reviewer Name: Asoke Mukherjee
Division Name: Division of Analgesic, Anti-inflammatory and Ophthalmic drugs
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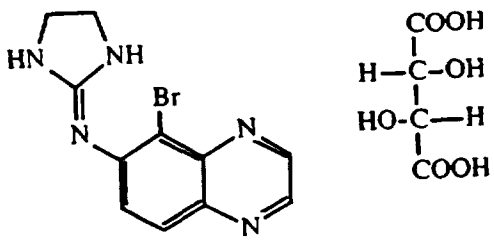
NDA Number: 21-262
Serial Number, date, type of submission: # 000; June 29, 2000; 505 (b) (1)
Information to the sponsor: Yes () No (x)
Sponsor or agent: Allergan Inc. 2525 DuPont Drive, Irvine, CA 92623
Manufacturer for drug substance: [redacted]

Drug Code Name: AGN 190342, UK-14, 304-18
Generic Name: Brimonidine Tartrate 0.15% ophthalmic solution with Purite preservative
Trade Name: Not given
Chemical Name: 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate
CAS registry number: 59803-98-4
Molecular formula/Molecular weight: $C_{11}H_{10}BrN_5$, $C_4H_6O_6$ and molecular weight 292.14 as base.
Structure:



Relevant IND/NDA/DMFs: NDA 20-613, [redacted]

Drug class: α_2- adrenergic agonist
Indication: Treatment of ocular hypertension and increased IOP in glaucoma.

Clinical formulation (mg/ml):

Brimonidine Tartrate 1.5
Purite 0.05
Sodium carboxymethyl cellulose [redacted]
Boric acid [redacted]
Sodium borate [redacted]
Sodium chloride [redacted]
Potassium chloride [redacted]
Calcium chloride dihydrate [redacted]
Magnesium chloride [redacted]
Hydrochloric acid adjust pH to [redacted]
Purified water [redacted]

Route of administration: Ophthalmic drops

Proposed clinical use: The product will be used for the treatment of ocular hypertension and increased intraocular pressure in patients with open angle glaucoma.

Previous clinical experience:

Brimonidine tartrate is approved as 0.2% ophthalmic solution (Alphagan) for the treatment of ocular hypertension and increased IOP in glaucoma patients. The approved product contains benzylalkonium chloride as the preservative. In the present NDA, the sponsor proposed the use of a reformulated ophthalmic solution of brimonidine that contains purite. The sponsor stated that the new formulation would improve efficacy and safety of the brimonidine ophthalmic solution. Clinical efficacy of brimonidine for the above indications has been demonstrated for the approval of NDA 20-613.

Introduction and drug history:

α_2 adrenergic agonists are used for the treatment of systemic and ocular hypertension. The mode of action of α_2 adrenergic agonist is to reduce the release of adrenergic neurotransmitter from the nerve endings. In addition to this mechanism that prevails for the systemic and ocular hypertensive therapy, brinomidine is suggested to increase the out flow of aqueous humor fluid in the eye. The product is already approved for the treatment for the reduction of IOP in ocular hypertension and glaucoma. There are reports that α_2 adrenergic agonist can bind with its receptors at the postjunctional sites. In that case, the sponsor indicated that vasoconstriction of the afferent arterioles of the ciliary process would result in lowering production of aqueous humor by lowering its secretion.

Since the product will be delivered topically, its involvement at the CNS site (solitary tract of medulla) does not appear to contribute to the mode of action of the drug unless it is highly bioavailable to the systemic circulation.

Brimonidine is a clonidine-like drug; clonidine is also approved for the treatment of hypertension.

The approved brimonidine eye drops contain benzylalkonium chloride. The formulation used in this NDA contains another preservative Purite that is also used in approved ophthalmic products up to 150 ppm. The

sponsor suggested that 0.15% brimonidine –Purite formulation is more efficacious than 0.2% brimonidine ophthalmic solution.

The disinfectant or preservative used in the formulation, chlorine dioxide, was approved for the use in Lens Plus in Oct 89, Refresh Contact in Oct 99 and Refresh Tear (over the counter). The sponsor stated that as much as 150 ppm was used in these products.

Studies reviewed within the submission:

Cardiovascular effects of α_2 adrenoceptors, [redacted] Anesthetics Pharmacology Review, 1, 246-262, 1993, page 170, vol 21.

Blood pressure and heart rate changes in cynomolgus monkeys after ocular administration of brimonidine tartrate formulated as Alphagan 0.2% or as 0.1 or 0.2% solution in refresh purite. Page 99, vol 15.

Further validation of in vivo and in vitro pharmacological procedures for assessing the α_2/α_1 selectivity of test compounds by Megens et al. Europ. J. Pharmacol. 129, 57-64, 1986, page 195, vol 22.

Brimonidine purite formulation (in purite) 0.2%: A one-week glucose evaluation study in New Zealand white rabbits. Study # TX98007, page 103, vol 15.

0.2% brimonidine reformulation (in purite), a four day ocular safety study in New Zealand white rabbits. Page 226, vol 15.

0.2% brimonidine reformulation in purite, A three-day ocular safety study in New Zealand white rabbits. Page 251, vol 15.

Pharmacological characterization of the hyperglycemia induced by α_2 adrenoceptor agonists by Angel et al. JPET 246, 1098-1103, 191988. Page 137, vol 21.

Involvement of α_2 adrenergic receptor subtypes in hyperglycemia by Angel et al. JPET 254, 877-882, 1989, page 143, vol 21.

Relative ocular bioavailability of 0.2% brimonidine purite and 0.2% Alphagan PF to that of 0.2% Alphagan in albino rabbits. Page 87, vol 21, Report # PK-00-010

Comparison of four ophthalmic brimonidine tartrate reformulations to Alphagan in albino rabbits. Report # PK-98-013, page 75, vol 21.

Ocular effects of a relatively selective α_2 agonist (UK-14,304-18) in cats, rabbits and monkeys by Burke and Potter, Current Eye Res., 5, 665-676, 1986, Page 192, vol 21.

Toxicokinetic analysis of plasma concentrations for study TX97053 "Brimonidine reformulation in purite 0.1% and 0.2% a six-month ocular and systemic safety study in New Zealand white rabbits, page 31, vol 21.

Effects of brimonidine on aqueous humor dynamics in human eyes, Arch Ophthalmology, 113, 1514-1517, 1995, page 206, vol 95.

Apraclonidine and brimonidine effects on anterior ocular and cardiovascular physiology in normal and sympathectomized monkeys. Exp. Eye. Res. 59, 633-644, 1994, page 77, vol 22.

Time course of the effect of UK 14304-18 (brimonidine tartrate) on rabbit uveoscleral outflow by Lee, Serle and Podos et al, Invest. Ophthalmic, Vis. Sci., 33, 1118, 1992, page 142, vol 22.

Selective α_2-adrenergic agonists BHT 920 and UK 14304-18, effects on aqueous humor dynamics in monkeys, Arch Ophthalmol., 109, 1158-1162, 1991, page 137, vol 23.

Brimonidine reformulation (in purite) 0.1% and 0.2%, A six-month ocular and systemic safety study with a one month recovery, in New Zealand white rabbits. Study # TX97053, Page 87, vol 16.

A review of the uses, chemistry and health effects of chlorine dioxide and the chlorite ion. Page 1, vol 22.

Ames/Salmonella plate incorporation assay, chlorite solution (150 ppm), page 1, vol 21.

Interoffice memo, Seven day study of Refresh Tears in rabbit cornea, page 28, vol 21.

Reproductive effects in Long-Evans rats exposed to chlorine dioxide by Carlton et al. Environmental Res., 56, 170-177, 1991, page 204, vol 21.

Assessment of maternal toxicity, embryotoxicity and teratogenic potential of sodium chlorite in Sprague Dawley rats, page 63, vol 22.

Acute oral toxicity study in male and female rats by single oral intubation of chlorine dioxide solution No. 7723X. Page 338, vol 15.

Brimonidine purite [redacted]: A one – month ocular toxicity study in rabbits. Page 83, vol submitted on Oct 17, 2000 amendment.

Studies not reviewed within this submission:

Toxicity of chlorine dioxide in drinking water by Abdel-Rahman et al., J. Am. Col. Tox. 3, 277, 1984, page 129, vol 21.

Subchronic toxicity of chlorine dioxide and related compounds in drinking water in the non-human primate by Bercz et al., Environ. Health Persp., 46, 47, 1982, page 149, vol 21.

General pharmacology of α_2 adrenoceptor by Bloor, Anesth. Pharm. Rev. 1, 221, 1993, page 158, vol 21.

Effect of tear proteins on preservative toxicity to epithelial cells by Cheng et al. J. Toxicol. 14, 287, 1995, page 42, vol 22.

Effect of chlorine dioxide and metabolites on glutathione dependent system in rat, mouse and chicken blood by Couri, J. Environ. Path. Tox., 3, 451, 1980, page 53, vol 22.

Apraclonidine and brimonidine effects on anterior ocular and cardiovascular physiology in normal and sympathectomized monkeys by Gabelt et al., Expt. Eye. Res., 59, 633, 1994, page 77, vol 22.

Effects of chlorine dioxide on thyroid function in the African green monkey and the rat by Harrington, J. Tox., Environ., Health., 19, 235, 1986, page 88, vol 22.

Subchronic toxicity of sodium chloride in the rat by Harrington et al., J. Am. Col. Tox. 14, 21, 1995, page 93, vol 22.

Oxidative damage to the erythrocyte induced by sodium chlorite in vivo by Hefferman et al., J. Environ. Path. 2, 1487, 1979, page 106, vol 22.

Adrenergic factors involved in the control of crypt cell proliferation in jejunum and descending colon of mouse by Kennedy et al., Clin. Experiment., Pharmacol. Physiol. 10, 577, 1983, page 126, vol 22.

Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis by Kurokawa et al., Cancer Letters, 24, 299, 1984, page 136, vol 22.

The effect of chronic administration of chlorine dioxide, chlorite and chlorate to normal healthy adult male volunteers by Lubbers et al., page 143, vol 22. (Journal citation not available in the NDA).

The effects of chronic administration of chlorite to glucose-6-phosphate dehydrogenase deficient healthy adult male volunteers by Lubbers et al. Page 153, vol 22. (Journal citation not available in the NDA).

α_2 adrenoceptor agonists, defining the role in clinical anesthesia by Maze and Tranquilli, Anesthesiology, 74, 581, 1991, page 157, vol 22.

The effects of subchronic chlorate exposure in Sprague Dawley rats by McCauley et al., Drug and Chemical Toxicology, 18, 185-199, 1995, page 180, vol 22.

Chlorine dioxide water disinfection: A prospective epidemiology study by Michael et al., Arch. Environ. Health, 36, 20-27, page 203, vol 22.

The effects of chlorine dioxide and sodium chlorite on erythrocyte of A/J and C571/l mice by Moore et al., J. Environ. Path. Tox. 4, 513-524, 1980, page 211, vol 22.

Effects of chlorite exposure on conception rate and litters of A/J strain mice by Moore et al., Bull. Environ. Toxicol. 25, 689-696, 1980, page 218, vol 22.

Toxicological effects of chlorite in the mouse by Moore and Calabrese, Environ., Health Perspective 46, 31-37, 1982, page 226, vol 22.

The lack of nephrotoxicity in the rat by sodium chlorite, a possible by product of chlorite, possible byproduct of chlorine dioxide disinfection in drinking water by Moore et al., J. Environ. Sci., Health A19, 643-661, 1984, page 233, vol 22.

21-day subacute eye toxicity study on chlorine dioxide solution #7723X in conjunction with Bausch and Lomb soft contact lens cleaner (AECLC), lens plus daily. Page 282, vol 15.

Guinea-pig sensitization study on chlorine dioxide solution #7723X-A-7891 (test) and 0.1% 1-chloro-2,4,-dinitrobenzene (DNCB)-positive control. Page 349, vol 15.

One-day ocular toxicity and cytotoxicity study in rabbits on chlorine dioxide saline solution #7723X-A-7982 in conjunction with [redacted] contact lenses and multiple topical installations. Page 371, vol 15.

Six-month ocular and systemic toxicity study in rabbits on chlorite saline (150 ppm) solution no. 8199x activated with [redacted] Page 1, vol 16.

Six-month ocular and systemic toxicity study of chlorine dioxide, solution # 7723X in rabbits, page 51, vol 20.

Comparison of five ophthalmic brimonidine tartrate reformulations to Alphagan in albino rabbits. Page 53, vol 21.

α-Adrenergic receptors by Timmerman et al. Page 146, vol 23. (Journal citation not available in the NDA).

The influence of adrenoceptor activity on crypt cell proliferation in the rat jejunum by Tutton and Helme, Cell Tissue Kinet, 7, 125-136, 1974, page 199, vol 23.

Assessment of MK-467, a peripheral α_2-adrenergic receptor antagonist, with intravenous clonidine by Warren et al, Clin. Pharmacol. Therapy. 50, 71-77, 1991, page 211, vol 23.

Intestinal adaptation by Williamson and Chir, New England J. Med. June 22, 1978, page 219, vol 23.

Studies of carcinogenicity of sodium chlorite in B6C3F1 mice by Yokose et al, page 228, vol 23. Environmental Health Perspectives 76, 205-210, 1987.

Functions mediated by α-adrenoceptors by Nichols and Ruffolo, page 1 vol 23. Molecular Biology, Biochemistry and Pharmacology, Prog. Basic Clin Pharmacol. Basel, Karger, 1991, Vol 8, pp 115-179.

Pharmacological characterization of α_2-adrenergic receptor subtype involved in the release of insulin from isolated rat pancreatic islets by Niddam et al, JPET, 254, 883-887, 1990, page 66, vol 23.

Changes in plasma glucose and lactate evoked by α and β_2-adrenoceptor stimulation in conscious fasted rabbits by Reverte et al, Fundam. Clin., Pharmacol. 5, 663-676, 1991, page 71, vol 23.

The α_2-adrenergic receptors, Ed by Limbird Lee L, Humana Press, New Jersey, page 85, vol 23.

Pharmacology:

Brimonidine is structurally related to para-amino clonidine and an agonist to α_2 adrenergic receptor. It is considered to be a nonselective α_2 adrenergic agonist whereas oxymetazoline another α- adrenergic agonist is α_{2A} subtype. The sponsor submitted a summary of the pharmacological activity in page 10 vol 15. Based on the binding study and in vitro functional assay it is more than 750 times selective for α_2 site than α_1 site. The sponsor stated that brimonidine does not have mydriatic effects in rabbits and vasoconstrictatory effects in human retinal xenografts. Brimonidine is more selective to the α_2 adrenergic receptor compared to α_1 adrenergic receptor when similar selectivity is compared for clonidine and Para- amino clonidine.

Pharmacodynamic activity of brimonidine is investigated for lowering IOP in normal rabbits, cats and monkeys. The sponsor stated that 0.1% ophthalmic solution was effective in lowering IOP of normotensive eyes. A dose dependant lowering of IOP is demonstrated in the laser induced ocular hypertensive eye in monkey model. The pharmacodynamic effect was blocked by prior administration of rauwolscine (α_2 antagonist) topically.

The sponsor referenced several research reports and publications related to the effect of the drug for increasing uveoscleral outflow and decreasing flow (production) of aqueous humor in the eye. Fluorophotometric methods were used in the experiments. Uveoscleral outflow involves flow of aqueous humor through the ciliary muscle. Therefore, it suggests that the neural control of the ciliary muscle maintains the outflow of aqueous humor that is modulated by brimonidine. Otherwise, it should be assumed that the effect of brimonidine on ciliary muscle is due to hormonal postsynaptic α_2 adrenoceptor activation.

The sponsor attached publication (page 158, vol 21) that suggests there are distinct imidazoline receptors in the CNS, peripheral sites and modulates antihypertensive effects of imidazoline. The role of the receptor has not been fully characterized. Therefore, it is premature to consider other modes of action of brimonidine in addition to its effects on α_2 adrenergic receptors.

The sponsor submitted a published paper on the effect of brimonidine on the intraocular pressure as shown below.

1. Ocular effects of a relatively selective α_2 agonist (UK-14,304-18) in cats, rabbits and monkeys by Burke and Potter, Current Eye Res., 5, 665-676, 1986, Page 192, vol 21.

The effect of brimonidine in normal eyes of rabbits, cats and monkeys was investigated for lowering IOP and its effect on pupillary diameter. 0.05 mg dose of brimonidine to one eye showed immediate and short lasting decrease in IOP in the contralateral eye. The IOP lowering effect was delayed by 2 hours in the ipsilateral eye. The ipsilateral eye also showed transient elevation of IOP at 0.05 mg dose in male white rabbits. Miosis in the contralateral eye is reported.

In normal cats, ocular hypotensive effect to 0.05% brimonidine in the ipsilateral eye was delayed (3 hrs). The reduction of IOP in the contralateral eye was observed within 1 hr. Unilateral miosis in the ipsilateral eye in the cat was noted 1-2 hours after 0.05 mg ocular dose of brimonidine. The authors stated that miosis was observed unilaterally whereas ocular hypotension was observed bilaterally in cats. Cats also showed sedation, nausea, salivation and diarrhea at 0.5 mg ophthalmic dose.

0.5 mg brimonidine ophthalmic drop to one eye showed about 4 mm reduction in IOP in ipsilateral eye and 5 mm reduction in the contralateral eye in normal Cebus capella monkeys. The maximum decrease in IOP in both eyes was observed at 2 hours. Contralateral eye showed faster onset of IOP lowering effect than ipsilateral eye. 0.5 mg opthalmic dose also showed sedation and miosis bilaterally.

Rauwolscine, an α_2 adrenergic antagonist inhibited the ocular hypotensive effect and miosis in rabbits. Brimonidine 0.05 mg ocular doses did not reduce IOP in ganglionectomized rabbit eyes. Sympathectomized (unilateral) cats showed IOP elevation by 7 mm that lasted 2-3 hours. Brimonidine showed miotic response in normal eyes. However, mydriatic response was observed in sympathectomized eyes in cats.

Brimonidine increased the baseline tone, decreased the sympathetic neuron mediated contractions and increased norepinephrine-induced contractions of cat nictitating membrane preparations.

Brimonidine inhibited contraction of cat nictitating membrane to pre- and ganglionic stimulation at 1-3.3 µg i.a. dose suggesting that the drug has an action on the preganglionic site and post ganglionic synapses. Brimonidine also increased the norepinephrine-induced contractions of nictitating membrane in cats.

Brimonidine at 0.05 mg ocular dose reduced the elevated IOP induced by water load in the ipsilateral and contralateral eyes in rabbits. The reduction of IOP in the contralateral eye was faster than the ipsilateral eye as seen with the normal rabbits. However, the reduction of IOP in the ipsilateral eye persisted for a longer time.

The authors suggested that the reduction of IOP by brimonidine might be due to a reduction of the aqueous humor flow.

Conclusion of the report:

Brimonidine showed a reduction of IOP in ipsilateral and contralateral eyes in rabbits, cats and monkeys when applied topically and unilaterally to the normal eye at about 0.05 to 0.5 mg single dose. The IOP

lowering effect in the contralateral eye was faster and that of the ipsilateral eye was longer in duration. In addition to above effect on IOP, brimonidine showed miosis and sedation as side effects. The authors stated that the effect on IOP is related to presynaptic (prejunctional) α_2 adrenergic receptor activation based on the data in α_2 adrenergic antagonist pretreated animals and ganglionectomized animals. The authors also mentioned that postjunctional α_2 receptors might contribute to the IOP lowering effect of brimonidine. However, no direct experimental evidence on the post junctional α_2 adrenergic receptor activity related to IOP lowering effect of brimonidine has been shown in the report. Brimonidine increased the effect of norepinephrine in cat nictitating membrane. Authors suggested that the effect was due to α_1 stimulatory effect. The sponsor in page 10 vol 15 indicated that brimonidine is selective to α_2 receptor compared to α_1 adrenergic receptor effect. Based on the data on cat nictitating membrane on the augmentation of norepinephrine response (authors stated that norepinephrine response in nictitating membrane is due to α_1 adrenergic receptor) brimonidine has functional α_1 adrenergic activity in the eye also.

2. Apraclonidine and brimonidine effects on anterior ocular and cardiovascular physiology in normal and sympathectomized monkeys. Exp. Eye. Res. 59, 633-644, 1994, page 77, vol 22.

The authors stated that about 200 µg ophthalmic dose of brimonidine applied unilaterally to the normal eye of anesthetized monkey showed a reduction of IOP in both eyes. The ocular hypotensive effect was also shown in the sympathectomized animals. However, the reduction of IOP in the sympathectomized eye was less than the normal eye. Ocular hypotension did not appear to be dependent on sympathetic innervation of the eye but innervation played a role towards lowering of IOP. Fluorescein treated fluorophotometric measurement showed a dose dependent reduction of aqueous flow at 10-250 µg dose of brimonidine. This effect was also not dependent on the sympathetic innervation.

Brimonidine showed miosis in normal monkeys presumably due to α_2 adrenoceptor related attenuation of sympathetic tone. Miosis was dependent on sympathetic innervation. The sponsor stated that brimonidine has weak α_1 adrenergic activity.

Summary of the publication:

Brimonidine showed ocular hypotension in anesthetized monkeys. On the basis of the effect of the drug in sympathectomized animals, it appears that brimonidine has both pre and postsynaptic α_2 adrenergic effects. The sponsor stated that brimonidine has a weak α_1 adrenergic activity.

3. Time course of the effect of UK 14304-18 (brimonidine tartrate) on rabbit uveoscleral outflow by Lee, Serle and Podos et al, Invest. Ophthalmic, Vis. Sci., 33, 1118, 1992, page 142, vol 22.

Uveoscleral out flow was determined in the rabbits after treating one eye with 50µL 0.1% brimonidine unilaterally. IOP was measured and eyes were treated with fluorescein dye. At several time points, animals were sacrificed and uveoscleral outflow was determined from the quantity of fluorescein in the ocular tissue of the uveoscleral pathway. Data suggest that the decrease in the IOP in the ipsilateral eye is partly due to a increase in the uveoscleral outflow. The effect of brimonidine on the uveoscleral outflow in the untreated eye was insignificant in the rabbit model.

Summary of the published abstract:

Brimonidine reduced the uveoscleral outflow in rabbits in the treated eye only.

4. Selective α_2-adrenergic agonists BHT 920 and UK 14304-18, effects on aqueous humor dynamics in monkeys, Arch Ophthalmol., 109, 1158-1162, 1991, page 137, vol 23.

Female cynomolgus monkeys were anesthetized with IM injections of ketamine. Intraocular pressure was determined by pneumatonograph. Monkeys were treated unilaterally with 50 µl of 0.3, 0.5 and 1% solution of brimonidine in saline at pH 7. The contralateral eye was treated with equal volume of saline. IOP was lowered both in the brimonidine and saline treated eyes by about 8-10 mm of Hg. Brimonidine was also effective in lowering IOP in laser induced ocular hypertension at 0.5% single dose or twice daily application for 5 days.

Aqueous humor outflow was measured by an electronic indentation tonograph following unilateral application of 0.5% brimonidine. There was no effect on the outflow in treated and contralateral eyes.

Aqueous humor flow was measured by fluorophotometry in fluoresein treated eyes. The aqueous humor flow rate was reduced in the treated and untreated eyes at 0.5% brimonidine treatment unilaterally.

Systolic and diastolic blood pressure were reduced significantly following topical application of 0.5% brimonidine.

Summary of the published article:

Brimonidine 0.5% ophthalmic drops reduced IOP in anesthetized monkeys in the treated and control eyes. The effect in the control eye may be due to the systemic transfer of the drug and systemic hypotension following ocular administration. It has no effect on the aqueous humor outflow measured by electronic tonography. However, brimonidine ophthalmic treatments reduced aqueous humor flow as measured by fluorophotometry in the treated and control eyes. Brimonidine did not show tachyphylaxis to IOP lowering effect when multiple doses were used.

5. Effects of brimonidine on aqueous humor dynamics in human eyes, Arch Ophthalmology, 113, 1514-1517, 1995, page 206, vol 95

Brimonidine 0.2% ophthalmic drops were given twice daily for one week to patients with ocular hypertension. The treatment was given to one eye and the contralateral eye was treated with the vehicle. Fluorescein dye was given to the eye for fluorophotometirc outflow facility calculation of aqueous humor. For this purpose fluorophotometric scans of the cornea and anterior chamber were taken. Aqueous flow was calculated from these scans. Fluorophotometric outflow is calculated as the ratio of aqueous flow to the change in IOP from the baseline when the subjects were treated with timolol and acetazolamide as the IOP lowering agents. Tonographic outflow was determined using a pneumotonograph. Episcleral venous pressure was measured by a venomanometer. IOP was measured by pneumomanometer. Uveoscleral outflow was calculated from the anterior chamber aqueous flow, fluorophotometric outflow, episcleral venous pressure and IOP.

The treated eye showed a reduction of IOP by about 4.7 mm of Hg on day 8. A slight (1.2 mm) but significant reduction was noted in the untreated eye. The episcleral venous pressure was not changed significantly by the treatment. The aqueous flow was reduced significantly both in the treated and vehicle treated eyes. The treated eye showed statistically significant increase in the uveoscleral outflow. However, the vehicle treated eye did not show significant changes in the uveoscleral outflow.

Summary of the published article.

Brimonidine ophthalmic drops showed a reduction in the IOP in the brimonidine and vehicle treated eyes in ocular hypertensive patients. Animal studies also showed decreases in the IOP in the brimonidine treated and untreated eyes. Fluorophotometric methods showed an increase in the uveoscleral outflow in the brimonidine treated patients.

6. IOP response to brimonidine in monkeys: Mechanism of action and comparison with β blockers.

BIO-94-009, page 123, vol 13, NDA 20-613.

Female cynomolgus monkeys were used in the experiment for the evaluation of the effect of brimonidine in normotensive eyes. In another set of experiment, IOP was elevated in the right eye of the monkey by argon laser photocoagulation of trabecular meshwork. IOP was measured by pneumotonometer and a mm scale measured pupillary diameter. A single 50 µl of of brimonidine (0.3%) or β blockers was instilled into one eye for measuring its effect on IOP. Aqueous humor flow was measured by fluorophotometric method using fluorescein dye. The uveoscleral outflow was indirectly inferred from the interactions between pilocarpine and brimonidine. Results are shown below.

% Decrease of aqueous humor flow and IOP in normotensive and glaucomatous eyes in monkeys.

Compounds	Flow	IOP, normotensive	IOP. Glaucomatous
Saline treated	1.3	0.2	4.6
Contralateral	1.8	0.3	3.9 (Increased)
0.3% Brimonidine	40	30	30
Contralateral	36	27	21
0.5% betaxolol	32	0.6	25
Contralateral	27	1.3	4.8
0.5% Timolol	42	7.5	43
Contralateral	46	7.7	18
1% l-bunolol	47	4.3	36
Contralateral	45	5.1	3.9

Data suggest both brimonidine and β-blockers reduced aqueous humor flow in the treated eyes. Brimonidine showed greater effect on IOP reduction in the contralateral eye than β-blockers. Brimonidine showed higher IOP reduction than β-blockers in normotensive eyes. Brimonidine reduced IOP in the ocular hypertensive eyes. Both ipsilateral and contralateral eyes responded to brimonidine. β-Blockers also reduced the IOP of the ocular hypertensive eye greater than the normotensive eye.

Pilocarpine administration to one eye induced a reduction of IOP and pupillary diameter. Since pilocarpine contracts ciliary muscle and iris muscle, it is considered to reduce the uveoscleral aqueous humor outflow. Brimonidine does not have any advantage to increase the uveoscleral outflow in the monkey model. The sponsor suggested that in the monkey model a reduction of the episcleral venous pressure by brimonidine might be responsible for the IOP lowering effect.

Summary of the report:

Brimonidine at 50 µL 0.3% ophthalmic solution reduces the IOP of normal and hypertensive eyes. Both ipsilateral and contralateral eyes showed IOP reduction. The sponsor stated that reduction of episcleral venous pressure could be the mechanism of action of brimonidine for lowering IOP in monkeys.

7. Suppression of aqueous humor flow by brimonidine in pigmented rabbits.

BIO-94-012, page 196, vol 13, NDA 20-613.

Rate of aqueous humor flow was determined by measuring the rate of disappearance of fluorescein dye by the fluorophotometer scan. Mixed-bred pigmented (Dutch belted/New Zealand white) rabbits of either sex with the body weight 2-3 kg were used in the study. Brimonidine 0.1% solution in distilled water was

applied topically to one eye of each animal at 50 µL volume. Animals in the control group received distilled water in one eye. Contralateral eyes were untreated. pH of the solution was adjusted to 7. Above study was conducted in 1986.

The sponsor repeated the study in 1990. Hydroxymethylcellulose (HPMC) was used to increase the penetration and retention of fluoresecein. The method used for determination of the aqueous humor flow was similar to that used in the 1986 study. One eye of the treated animal received 50 µg (25 µl of 0.2% solution) of brimonidine solution in distilled water. The control animals were treated with equal volume of distilled water in one eye. The pH of the solution was adjusted to 6-6.5.

Results of the 1986 study show that brimonidine treatment reduced the aqueous humor flow (significantly) by about 25% in the treated and the contralateral eyes within 1 hour. The saline treated animals also showed a reduction of aqueous humor flow but it was not statistically significant. The sponsor has not presented the statistical comparison between the distilled water control and brimonidine treated eye for the reduction of the aqueous humor flow.

A similar observation was reported in the 1990 study.

Although the sponsor has not provided data, the results of the report state that IOP was reduced bilaterally. The onset of IOP reduction in the treated eye was delayed compared to the untreated eye. The treated eye showed an initial hypertension. The sponsor stated that the transient increase in IOP in the treated eye was due to its α_1-adrenoceptor activity.

Conclusion of the study:

Brimonidine bilaterally reduced the IOP and aqueous humor flow in normal pigmented rabbit model. The result explains that the reduction of aqueous humor flow is a possible mechanism of action for the IOP lowering effect of brimonidine. The sponsor also stated that brimonidine has α_1-adrenoceptor activity that resulted a transient increase in the IOP in the drug treated eye.

Summary of pharmacology:

On the basis of the preclinical pharmacodynamics, brimonidine is a α_2 adrenergic agonist (selective as an α-adrenergic but nonselective as a α_2 adrenergic agonist) and lowers intraocular pressure.

Brimonidine ophthalmic solution showed a reduction of IOP in rabbit, cat, monkey and human eyes. Side effects observed in the animal studies were miosis, sedation, nausea, salivation and diarrhea. In the rabbit model, transient elevation of IOP was noted before the onset of ocular hypotensive response. The sponsor suggested that the rise in the IOP is due to α_1 adrenoceptor activity. α_1 adrenergic activity was also noted in the cat nictitating membrane.

Brimonidine showed a reduction of aqueous humor flow and increase in the uveoscleral outflow in the rabbit model. Tonography studies did not show increase outflow of aqueous humor in the monkey model. The sponsor suggested that the reduction of IOP in monkey is due to a reduction of episcleral venous pressure.

The reduction in the IOP appears to be mediated by the presynaptic α_2 adrenergic receptor based on the data from ganglionectomized rabbit eyes. However, data on the sympathectomized eye in monkeys suggest the involvement of both pre and post sympathetic α_2-adrenoceptor activity.

Brimonidine showed ocular hypotensive effects in the untreated eye that may be due to the systemic transfer of the drug and due to systemic hypotensive effect (in monkeys). Human studies in ocular hypertensive subjects showed a reduction in the IOP associated with increased uveoscleral outflow and

decreased aqueous humor flow in the eyes. However, unlike the monkey, episcleral venous pressure was unchanged by the ophthalmic application of brimonidine.

Based on the preclinical pharmacodynamic studies it is concluded that brimonidine lowers IOP possibly by its effects on the pre and postsynaptic α_2 adrenergic receptor activity. It has α_1 adrenoceptor activity although it is a selective α-adrenergic agonist of α_2 subtype. Its mode of action related to lowering of aqueous humor flow and in some instances increased the uveoscleral outflow.

Safety Pharmacology:

Cardiovascular:

1. Cardiovascular effects of α_2 adrenoceptors, Bloor and Schmeling, Anesthetics Pharmacology Review, 1, 246-262, 1993, page 170, vol 21:

The publication showed hypertensive followed by hypotensive effects of dexmedetomidine (α_2 agonist) in man. The authors stated that α_2 adrenergic receptors are present both pre and post synaptically in the vascular smooth muscle. The authors also referred to the imidazoline receptors (distinct site) that are located in the central and peripheral sites. However, the role of imidazoline receptors in hypertension is not clear. Therefore, it is considered that clonidine-like compounds are α_2 agonist unless the effect of an imidazoline without α_2 effect is proven.

In general α_2 adrenergic agonists cause hypotension in preclinical and clinical studies.

2. Blood pressure and heart rate changes in cynomolgus monkeys after ocular administration of brimonidine tartrate formulated as Alphagan 0.2% or as 0.1 or 0.2% solution in refresh purite.

Page 99, vol 15.

Study BIO-98-278 describes the comparative effect of the drug. Alphagan or the purite formulation is used.

Blood pressure and heart rates of conscious monkeys were recorded over 8 hours. The test compounds were given as a single 35-µl drop to both eyes. A dose dependent decrease in the blood pressure and heart rate were noted up to 2 hours after dosing and recovered between 4-6 hours. The maximum decrease in the blood pressure was about 20% of the base line and that of the heart rate was about 30% of the base line. The approved Alphagan also showed similar effects on the cardiovascular system. However, the magnitude of the change was smaller than that of the purite formulation. The sponsor stated that brimonidine purite does not affect heart rate differently than Alphagan.

The mean blood pressure change (1hr) and heart rate (2 hr) as % of the base line are shown in the following table.

Formulation	% Change in blood pressure	% change in heart rate
Brimonidine-purite 0.1%	-9.4	-17.4
Brimonidine-purite 0.2%	-23.6	-25.9
Alphagan 0.2%	-16.1	-21.5

Other safety effects:

The sponsor stated that sedation was observed in mice at 75 mg/kg/ip dose. The sponsor provided data on the ophthalmic application of 0.2% brimonidine one drop three times a day for 4 days in New Zealand white rabbits using purite and Alphagan formulations. Both formulations showed sedation during three to

four days of the treatment (pages 226, 251 vol 15). The sedation lasted till three hours after the dosing. The sponsor stated that occasional sedation is observed clinically from the ophthalmic delivery of brimonidine (page 14, vol 15). A reduction of motor activity was also observed in rats at 77 µg/kg/IV dose. Antidiarrheal and diuretic effects were observed at 50 µg/kg/S.C dose in rats that is mediated by α_2 adrenoceptor effects (Megan et al. Europ. J. Pharmacol. 129, 57-64, 1986). The sponsor stated that diuresis and constipation induced by brimonidine ophthalmic drops are clinically insignificant (page 14, vol 15).

Hyperglycemia:

Brimonidine purite formulation (in purite) 0.2%: A one-week glucose evaluation study in New Zealand white rabbits. Study # TX98007, page 103, vol 15.

The study is conducted at Allergan, CA 92623 using New Zealand rabbits. The animals used in the study are 6-7 months old. Body weights varied from 3.08 kg to 3.8 kg. The drug product used in the study is 0.2% brimonidine purite reformulation (9115X) lot # 11203. [redacted] Drug product is a yellow solution. This is a non GLP study.

The protocol of the study divided into three stages referred as stage 1, 2 and 3. The dosing information is given as follows.

Step 1:

Group	#/sex	Treatment	Eye	µg/kg/dose	Frequency of dosing
1	3	Vehicle	Left	0	3/day
2	6	0.2% brimonidine in purite	Left	20	3/day

One drop (35µL) was instilled into the left eye three times daily at three-hour intervals for 6 days. On day 7, only one drop was administered. The sponsor stated that the daily dose is 60 µg/kg/day. The right eye served as the untreated control.

Mortality and clinical signs were observed daily. The body weight was recorded before the dosing and at the end of dosing period.

Prior to the dosing blood samples were collected from the ear vein from overnight fasted animals. The blood sample was collected on days 3 and 7 one hour after the first dose. On day 7, fasted blood samples were collected from 2 male rabbits. Subsequent samples were taken at 0.5, 2, 4 and 6 hours after a single dose. Serum glucose levels were determined.

Step 2:

The dosing schedule is shown in the following table.

Group	#/sex	Treatment	Eyes	µg/kg/dose	Frequency of dosing
1	5	Vehicle	Both	0	2
2	5	0.2% brimonidine in purite	Both	11	2

Each drop (10µl) was administered by a micropipette at 6 hour interval. The treatment was given for four days. The daily dose is 23 µg/kg. However, only one dose was given on day 4. Mortality and clinical signs were observed daily. Individual body weight was recorded at baseline before dosing and on day 5. Blood samples were collected prior to dosing on day 1 from the fasted animals. Blood samples were collected at 1.5 hour after the dose on day 4, animals were fasted overnight. Animals were fasted overnight and blood samples were taken 24 hours after the last dose on day 5. Serum glucose levels were determined.

Step 3:

The dosing schedule for the experiment is shown in the following table.

Group	#/sex	Treatment	Eye	µg/kg/dose	Frequency of dosing
1	5	0.2%brimonidine purite	Left	6	2/day

Animals were treated at 5 µl/drop at one drop twice a day for 3 days at 6 hour interval in the left eye. On day 4, only one drop was administered. The table in page 125 vol 15 showed 6 µg/kg/dose for a 3.5 kg animal. The calculated dose should be 2.8 µg/kg/dose. Also, if two drops are given to the left eye per day, the daily dose would be 5.7 µg/kg/day. The sponsor stated that the daily dose was 11 µg/kg. The sponsor also stated in page 126, vol 15 that both eyes were treated although the table showed that the left eye was treated.

Mortality and clinical signs were observed daily. Body weights were recorded before the treatment and on day 4.

Blood samples were collected from overnight fasted animals before dosing. Blood samples were collected one hour after the dose on day 4. Blood samples were divided for hematology and Serum chemistry.

Results:

Step 1:

Torticollis (contracted state of cervical muscle) was observed in one male in the vehicle and drug treated groups. There was no effect on the body weight. Serum glucose (mg/dl) levels on days 3 and 7 were elevated significantly as shown in the following table.

Vehicle	Baseline	Day 3	Day 7
Male	128	130	124
Female	121	129	127
0.2% brimonidine purite			
Male	127	265	289
Female	120	255	214

Data for the time course of glucose levels show that the peak glucose levels after the treatment was observed about 1-2 hour post dose. Thereafter, the serum glucose levels were declined to the basal level. Animals were treated at 60 µg/kg /day dose.

Step 2:

No death, abnormal clinical sign or changes in the body weight due to the treatment were reported.

The daily dose of brimonidine was 23 µg/kg and the glucose levels are shown in the following table.

Vehicle	Baseline	1.5 hr	24 hr
Male	133	134	115
Female	131	130	116
0.2%brimonidine			
Male	135	186	115
Female	127	142	113

Above data suggest that male animals showed higher serum glucose levels within 1.5 hr post dose. The sponsor stated that lower values in females could be due to the later sampling time than that mentioned in the table.

Step 3:

No mortality or abnormal clinical signs are reported. Treatment related weight changes were not observed. Hematology data did not show treatment-related changes. The serum glucose levels (mg/dl) did not change significantly as shown in the following table.

Sex	Baseline	Day 4
Male	127±2.2	143±9.8
Female	121±2.9	142±10.7

Data suggest that a dose of 5.7 µg/kg did not show changes in serum glucose in male and female animals.

Conclusion of the study:

Brimonidine at 0.2% ophthalmic solution two drops per eye/day (10µl per drop) for 4 days and higher doses showed an increase in the serum glucose levels. The literature reports suggest that the hyperglycemia is due to the inhibition of insulin release. The elevated levels of glucose were decreased to the normal level after about 2 hours. Therefore, brimonidine increased blood sugar levels possibly by the inhibition of insulin release due to its α_2 adrenergic activation in rabbits. However, insulin levels were not measured.

The sponsor stated that hyperglycemia due to brimonidine ophthalmic solution is clinically insignificant (page 14, vol 15).

The sponsor provided the following published literature on the effect of α_2 adrenergic agonist on insulin secretion.

1. Pharmacological characterization of the hyperglycemia induced by α_2 adrenoceptor agonists by Angel et al. JPET 246, 1098-1103, 191988. Page 137, vol 21.

The authors stated that α_2 adrenergic agonist induced hyperglycemia in mice is mediated by the direct activation of postsynaptic α_2 receptors located on the pancreatic beta cells that induces inhibition of insulin release.

2. Involvement of α_2 adrenergic receptor subtypes in hyperglycemia by Angel et al. JPET 254, 877-882, 1989, page 143, vol 21.

Hyperglycemia and inhibition of insulin release induced by the α_2 adrenoceptors is not mediated by the α_{2B}-adrenoceptor subtype but rather through a α_{2A} adrenoceptor.

Summary of the safety pharmacology:

Brimonidine ophthalmic drops showed hypotensive effects and bradycardia in conscious monkeys when given as Alphagan 0.2% or brimonidine purite 0.2% ophthalmic solution. Sedation was also observed in white rabbits when 0.2% brimonidine purite or Alphagan was given as ophthalmic drops for 3-4 days. A reduction of motor activity in rats (77 µg/kg/IV) and antidiarrheal effect in rats (50 µg/kg/SC) were observed.

Experimental study in rabbits showed that brimonidine purite 0.2% eye drops induced transient (1-2 hr duration) hyperglycemia. Several published papers suggest that hyperglycemic effect of brimonidine is mediated by the α_{2A} adrenergic receptor in the beta cells of the islet and reduces the release of insulin.

Pharmacokinetics/Toxicokinetics:

1. Relative ocular bioavailability of 0.2% brimonidine purite and 0.2% Alphagan PF to that of 0.2% Alphagan in albino rabbits. Page 87, vol 21, Report # PK-00-010

The study is conducted in accordance to GLP guidelines. The sponsor indicated in the report that brimonidine is an alpha$_{2B}$ adrenoceptor agonist. However, other published paper discussed in the review mentioned that brimonidine belongs to nonselective alpha$_2$ class of adrenergic agonist.

Brimonidine purite (9115X, lot #11523A) at pH 7.2 containing potassium chloride and magnesium chloride is used in the study. The comparator drug is Alphagan (7831X, lot # 11390) at pH 6.3 containing benzalkonium chloride. In order to assess the role of the preservative, Alphagan in the absence of preservative (Alphagan PF, 9251X) is included in the study.

Ocular bioavailability and aqueous humor kinetics of 0.2% brimonidine formulations is compared in the study. Three and a half year old female New Zealand rabbits were used in the experiment.

Eighteen rabbits were used in the study. Each rabbit was treated with each formulation at one drop (35 µL) per eye. Both eyes were treated. The washout period was about three days between the treatment. Both eyes were treated with each formulation in a crossover study. Two animals served as the untreated control at each experimental session. However, the sponsor has not stated whether the same animals were used as the untreated control at each session.

Aqueous humor samples were collected from both eyes of each animal before dosing and at 10, 20, 40 min, 1, 1.5, 2, 3, 5 and 8 hours after dosing. 100 µL aqueous humor sample was collected from the anterior chamber under isoflurane anesthesia. Aqueous humor samples were stored at –15C and assayed by Liquid chromatography-MS methods.

Aqueous humor kinetics of brimonidine in the eye were estimated.

Results:

Pharmacokinetic data for brimonidine for several formulations in the aqueous humor are shown in the following table:

Parameter	Brimonidine purite	Alphagan PF	Alphagan
C_{max} (µg/ml)	2.69 ±0.72	1.24 ± 0.22	1.74 ± 0.13
T_{max} (hr)	0.67	0.33	1
$T_{½}$ (hr)	0.75	0.75	0.92
Mean Residence Time (h)	1.45	1.51	1.44
AUC $_{0\text{-last}}$ (µg.h/ml)	3.78±0.38*	2.49±0.22	2.77±0.22
AUC $_{0\text{-}\infty}$ ((µg.h/ml)	3.83	2.53	2.83
AUC $_{0\text{-}t\,last}$ degrees of freedom	11.1	11.5	9.41

PF= preservative free

± Standard error of the mean

*$p<0.05$ compared to Alphagan

Above data suggest that the bioavailability of brimonidine in aqueous humor from purite formulation is higher than that from Alphagan. The sponsor also stated that brimonidine is detectable in the aqueous humor of New Zealand rabbits up to 3-5 hours.

It is concluded that brimonidine from purite formulation is bioavailable in the ocular tissues like Alphagan following ophthalmic delivery.

2. Comparison of four ophthalmic brimonidine tartrate reformulations to Alphagan in albino rabbits. Report # PK-98-013, page 75, vol 21.

Male New Zealand white rabbits were used in the study. The sponsor has not indicated the age or body weight of the animals. Thirty rabbits were divided into five groups of six rabbits in each group. Both eyes of each rabbit were dosed with one 35 µL drop of 70µg of brimonidine salt into each eye with one of the five formulations. Three animals from each group were sacrificed at one or four hours post dose by lethal injection of Eutha-6. Blood, tears and aqueous humor samples were collected immediately before or after the sacrifice. Plasma was separated and samples were stored at –15C. Tear fluid was collected immediately after euthanasia with a tared sponge and stored at –15C. Immediately after the collection of tear samples, aqueous humor was aspirated from each eye and stored at –15C or below. The dosing schedule and formulations are shown in the following table.

Group	Formulation	1 hour, # rabbits	4 hour, # rabbits
1	Alphagan brimonidine tartrate 0.2%	3	3
2	Brimonidine tartrate 0.2% in purite	3	3
3	Brimonidine tartrate 0.2% purite	3	3
4	Brimonidine tartrate 0.2%	3	3
5	Brimonidine tartrate 0.2%	3	3

Brimonidine concentration in the tear fluid (µg/g) is shown in the following table. Data in the parentheses represent the tear concentration normalized to 70 µg dose.

Formulation of brimonidine	Dose / eye (µg)	1 hour (µg/g)	4 hour (µg/g)

Data suggest that refresh purite formulation is similar to Alphagan in the tear fluid at 1 hour. However, the levels at 4 hour decreased more from the purite formulation than from the Alphagan formulation.

The aqueous humor levels of brimonidine (normalized value to 70 µg brimonidine) are presented in the following table.

Formulation of brimonidine	Dose/eye (µg)	1 hour (µg/g)	4 hour (µg/g)

The aqueous humor levels of brimonidine were higher from the purite formulation than that of Alphagan.

Plasma brimonidine levels normalized to 70 µg brimonidine per eye are shown in the following table.

Formulation of brimonidine	1 hour (ng/ml)	4 hour (ng/ml)

As shown in the above table that purite formulation showed better bioavailability in the plasma than the Alphagan formulation. However, systemic bioavailability from both ophthalmic formulations is minimal.

3. Toxicokinetic analysis of plasma concentrations for study TX97053 "Brimonidine reformulation in purite 0.1% and 0.2% a six-month ocular and systemic safety study in New Zealand white rabbits, page 31, vol 21.

New Zealand white rabbits weighed 2.5 to 3.5 kg and 5 months of age were used in the safety study. About 70 animals were treated with brimonidine for toxicokinetic purposes. A total of 90 rabbits were used in the safety study. These animals were allotted to three groups, each group had 15 male and 15 female rabbits. Animals were treated with one 35 µL drug product three times a day in the left eye for six months. The right eye served as the untreated control. Blood samples were collected from two groups that were treated at 0.1 and 0.2% brimonidine purite solution. Blood samples were collected on weeks 3 and 12. The sponsor stated that at each collection time one ml of blood was drawn from 5 animals/sex/group.

Blood samples were collected from brimonidine treated animals immediately before the first dose at week 3 and at 7 hours after the first dose. On week 12, blood samples were taken immediately before the first dose and at 1, 3, 4, 7, 9, 12 and 24 hours after the first dose. Plasma brimonidine levels were analyzed by GC/MS methods. The sponsor has not mentioned which vein or the procedure used for the collection of blood samples. Following pharmacokinetic parameters were calculated.

C_{max}, T_{max} and AUC_{0-24}

Results:

The plasma brimonidine levels (pg/ml) on week 3 and 13 are shown in the following table. The time of collection of the sample referred as the time after the first dose.

Formulation	Wk 3 Predose	Wk 3 7 hr	Wk 12 Predose	Wk 12 1 hr	Wk12 3 hr	Wk 12 4 hr	Wk 12 6 hr	Wk 12 7 hr	Wk 12 9 hr	Wk 12 12, 24 hr
0.1%,M	BLQ	456	BLQ	313	BLQ	358	BLQ	285	BLQ	BLQ
0.1%, F	BLQ	119	BLQ	425	BLQ	356	BLQ	251	BLQ	BLQ
0.2%,M	BLQ	769	BLQ	974	55.1	643	BLQ	543	BLQ	BLQ
0.2%,F	BLQ	546	BLQ	943	BLQ	653	BLQ	512	104	BLQ

BLQ= Below limit of quantitation

The pharmacokinetic data are shown in the following table.

Formulation	Sex	Week 3	Week 12	Week 12	Week 12
		C_{max} (pg/ml)	C_{max} (pg/ml)	T_{max} (hr)	AUC $_{0\text{-}24}$ (pg.hr/ml)
0.1%	M	456	358	4	1430
0.1%	F	119	425	1	1550
0.2%	M	769	974	1	3320
0.2%	F	546	943	1	3420

Above data show brimonidine is bioavailable in the systemic circulation dose dependently after chronic ophthalmic doses in rabbits. Maximum plasma levels were observed at about one hour after the dose in most cases. The exposure to brimonidine in male and female rabbits was similar. The limit of detection in the assay is 50 pg/ml.

The sponsor stated that the data point at BLQ is considered to be 0 ng/ml for the calculation of the AUC. The sponsor also stated that the AUC would be greater if 50 ng/ml is considered for levels referred as BLQ. However, use of 0 as the level that is below the limit of quantitation is considered to be a conservative estimate of the AUC in this case.

Conclusion of the Pharmacokinetic study:

Brimonidine is bioavailable in the aqueous humor in rabbits after the application of 70 μg/eye as Alphagan or purite formulation. The levels were 0.78 and 2.32 μg/g in the aqueous humor of rabbits from Alphagan and purite formulation, respectively. Plasma levels of brimonidine with single dose of 75 μg/eye into both eyes (150 μg) one-hour post dose were 1.29 and 2.10 ng/ml for Alphagan and purite, respectively. Plasma levels (C_{max}) of brimonidine in six month study in rabbits showed 391 and 958 pg/ml at 35 μl three times daily dose in one eye at 0.1 and 0.2% brimonidine purite, respectively. Page 341, vol 1 of the NDA showed human PK data at 0.1 and 0.2% at one drop TID in both eyes. The C_{max} on day 7 was 30.0 and 64.7 pg/ml at 0.1 and 0.2% brimonidine from the purite, respectively. These data suggest that human systemic exposure is more than 10 times lower than that in rabbit considering rabbits were treated in one eye only in the six-month safety study.

It is concluded that purite formulation of brimonidine has greater bioavailability in the aqueous humor than Alphagan. Brimonidine is also more bioavailable in the systemic circulation in rabbits after ophthalmic doses as purite formulation than Alphagan. Maximum levels were detected within one hour of dosing, thereafter, the plasma levels were reduced to below the limit of detection.

Toxicology:

1. Acute oral toxicity study in male and female rats by single oral intubation of chlorine dioxide (purite) solution No. 7723X. Page 338, vol 15.

Sponsor's ID: 1634-0839-9

Conducting Laboratory: Allergan Inc., Irvine, CA 92715
Date of study initiation: Nov 9, 1987
GLP compliance: Yes
QA report: Yes

Methods:

Animals were fasted overnight. The test substance was administered by oral gavage. Animals were observed immediately after dosing for dyspnea, hyperactivity and other signs of abnormal behavior. Thereafter, the animals were observed once daily for 14 days. Body weights were recorded on days 1, 7 and 14. Any animal that died during the test period was necropsied and gross changes of major organs were sought. At the end of 14 days, all surviving animals were sacrificed by carbon dioxide asphyxiation and gross pathological changes were examined for the following organs:

Adrenal glands, esophagus, heart, kidneys, liver, lungs, ovaries, pancreas, small and large intestines, salivary glands, spleen, stomach, thymus, testes, trachea, urinary bladder and uterus.

Species: Sprague Dawley rats

#/sex/group: 10

Age and weight: Young adult, male weighed 180-198 g and female weighed 160-185 g.

Route, form and volume: Oral, dose was 20 ml/kg, approximately 1000 µg/kg, test material formulation 7723X, Lot # 07633D

Formulation for 1000 L :

Sodium chloride: [redacted]
Boric acid: [redacted]
Hydrochloric acid, [redacted]
Sodium hydroxide to pH [redacted]
Purogene: [redacted]

Results:

No immediate clinical signs of toxicity were noted after the administration of chlorine dioxide formulation at about 1000 µg/kg per oral. No death was reported. Data suggest that 1000 µg/kg or 20 ml/kg dose of chlorine dioxide solution is safe after a single dose in rats.

2. Brimonidine reformulation (in purite) 0.1% and 0.2%, A six-month ocular and systemic safety study with a one month recovery, in New Zealand white rabbits. Study # TX97053, Page 87, vol 16.

Conducting Laboratory: Allergan, Irvine, Ca 92623-9534

Date of study Initiation: Nov 4, 1997

GLP compliance: Yes

QA report: Yes

Methods:

Dosing information:

Species: New Zealand white rabbits

#/sex/group: 15

Age: 5 months

Weight: 2.76-3.36 kg

Dosage groups in administered units:

Group	#/sex	Concentration	Volume/dose	Frequency of dosing
1	15	Vehicle	35µL	3 per day
2	15	0.1%	35µL	3 per day
3	15	0.2%	35µL	3 per day

The sponsor stated that 5 animals/group/sex were continued without treatment beyond the dosing period for recovery.

Route, form and volume:

One-drop (35 µL) was administered three times a day for six months in the left eye at 3 hour intervals. The right eye served as the untreated control.

Drug Lot:

[redacted]

Brimonidine 0.1% solution reformulated in purite lot # 11206, formulation # 9118X.

Brimonidine 0.2% solution reformulated in purite lot # 11203 and 11261B, formulation # 9115X.

Formulation [redacted]

Ingredients	0.2% Brimonidine	0.1% Brimonidine	Vehicle
Brimonidine Tartrate	[redacted]	[redacted]	[redacted]
Purite [redacted]			
Sodium carboxymethyl cellulose			
Boric acid			
Sodium borate [redacted]			
Sodium chloride			
Potassium chloride			
Calcium chloride			
Magnesium chloride			
Sodium hydroxide			
Purified water			

Times at which clinical observations were made:

Clinical signs:

Animals were watched daily for mortality. Clinical signs were also noted daily at the time of dosing.

Gross ocular examinations:

Gross examinations of the eye were conducted on first and last instillation for one week. Thereafter, eyes were examined once weekly for gross changes. Ocular discomfort, severity of conjunctival hyperemia, discharge and swelling were scored. However, the sponsor has not mentioned the scoring criteria in the protocol.

Slit lamp examinations:

Both eyes were examined at pretest, 1, 3 months, 6 months of dosing and at the end of recovery periods. Conjunctiva, corneal damage, anterior chamber and iris were examined. The sponsor stated that numerical scores were used. However, the scoring systems were not mentioned in the protocol.

Ophthalmoscopic examinations:

Both eyes were examined by a direct ophthalmoscope at pretest and on months 1,3, 6 and at the end of recovery period. Mydriasis was induced by one drop of 1.0% tropicamide. Lens, vitreous and retina were examined.

Body weight:

Individual body weights were recorded on day 0, and once weekly during the first month of the treatment. Body weights were recorded biweekly during second month of the dosing.

Hematology and blood chemistry:

Fasting blood samples were collected at pretest and after the first daily dose on months 1, 3, 5 and 6. Blood samples were collected from the central ear artery. Samples for hematology were collected in the tube containing EDTA. Additional blood samples were collected after overnight fasting at the first post dose on month two. Also, post dose blood samples were collected at two days after two months of dosing. Plasma glucose levels from the blood samples will be compared to that collected after one month for determination of the effect of the drug on blood glucose levels. It is indicated in the literature that α_2 agonists have an effect on insulin secretion. Therefore, such data would verify the systemic adverse effect of brimonidine on glucose metabolism.

Blood samples were also collected for the pharmacokinetic study on weeks 3 and 12 from 5 animals/sex/group. Blood samples were collected before a daily dose and at 7 hours after the first dose on week 3. Sampling times on week 12 were 1, 3, 4, 6, 7, 9, 12 and 24 hours after the first dose. The sponsor has not indicated that a separate group of animals were used for the PK study.

Terminal sacrifice:

At the end of the treatment and recovery period all animals were euthanized by IV injections of sodium pentobarbital. Weights of following organs were recorded at necropsy:

Adrenal glands, brain, heart, kidney, liver, ovaries, pituitary gland, spleen and testes.

Histopathology of following organs were conducted from the control and high dose groups only.

Adrenal gland, aorta, bone marrow, brain, cervix, diaphragm, epididymides, eyes with optic nerve, gall bladder, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, heart, kidneys, liver, lungs, lymph nodes, mammary gland, ovaries, pancreas, pituitary gland, prostate, salivary gland, sciatic nerve, skeletal muscle, skin, spinal cord, spleen, testes, sternum, thymus, thyroid and parathyroid, tongue, trachea, urinary bladder, uterus and vagina.

Results:

Clinical signs:

The sponsor stated no death was observed in the study. Both at 0.1 and 0.2% signs of sedation were observed for about 1.5 hr on the day when gross ocular examinations were performed.

However, slight irritation and discomfort were observed in the vehicle and drug treated animals. It appears from the data that these side effects are possibly related to the vehicle.

Slit lamp and ophthalmoscopy:

There was no adverse effect due to the treatment reported in the cornea, iris and anterior chamber, posterior chamber and retina of the eye following the slit lamp and ophthalmoscopic examinations.

Body weight:

There was no treatment-related change in the body weight of animals. Average body weight of animals on prestudy and on week 26 are shown in the following table:

Week	Group 1		Group 2		Group 3	
	Male	Female	Male	Female	Male	Female
Prestudy	3.02	3.07	3.03	3.07	3.02	3.07
Week 26	3.56	3.83	3.54	3.92	3.54	3.86

Hematology:

There was no change in the hematology values due to the treatment. Male and female animals showed statistically significant changes in the RBC, WBC and platelet counts during the treatment period. However, the values are within normal range and do not have any biological significance.
Blood chemistry:

Serum glucose levels were increased during the treatment period with 0.1% and 0.2% formulation in male animals from the first month. However, the increase in the serum glucose levels was mostly evident from the third month of the treatment in female rabbits at 0.2% formulation. The predose levels were within the basal limit. The sponsor indicated that hyperglycemia was observed within 1 to 3 hours after ophthalmic doses.

The predose levels of glucose (mg/dl) at baseline of the study, six months of the study and post dose levels on six months of the study are shown in the following table:

Group	Baseline	6 months predose	6 months post dose
Vehicle, Male	142	136	142
0.1% brimonidine, male	135	144	213
0.2% brimonidine, male	133	154	280
Vehicle, female	129	131	124
0.1% Brimonidine, Female	134	131	155
0.2% Brimonidine, Female	132	138	229

There was no other changes noted due to the treatment.

Toxicokinetic data are shown in the pharmacokinetic section of the review on page 18.

Necropsy:

There were no treatment related gross changes observed at necropsy. Also, no treatment related changes in the organ weight were noted at necropsy.

Histopathology:

Both upper and lower eyelids of the right and left eyes showed leukopedesis (migration of leukocytes from the blood vessels) as shown in the following table:

Site	Group 1		Group 2		Group 3	
	Male	Female	Male	Female	Male	Female
Upper eyelid, left	0	2	5	1	6	3
Lower eyelid, left	0	1	7	1	7	4
Upper eyelid, right	0	3	6	1	7	3
Lower eyelid, right	0	2	4	1	6	2

The incidences were reversible during the recovery. The grade of leukopedesis is mild. The incidences were higher in male than female rabbits treated with brimonidine. Also, there is a differential response between males and females in the vehicle group. The treated left eyes and untreated right eyes showed similar incidences within each group. On the basis of the nature of the responses, it is concluded that leukopedesis is not treatment related. The sponsor stated no other treatment related histopathological changes were observed in the study.

The sponsor inadvertently omitted some of the histology tables in the report. The sponsor submitted these tables on Sept 26, 2000. Some of the data (observed/total) other than leukopedesis are shown in the following table:

Organ	Group 1		Group 2		Group 3	
	M	F	M	F	M	F
Vasculitis of lungs, subacute	0	1/10 (mild)	1/10 (min)	1/10 (min)	2/10 (min)	2/10 (min- mild)
Kidney cortex, tubular mineralization	0	1/10 (min)	0	0	1/10 (mild)	4/10 (min, mild)
Pancreas, accessory splenic nodule	0		0		2/10	

The data suggest that some of the histological changes were incidental and observed in control animals also. Accessory splenic nodule in the pancreas was not observed in male rabbits at high dose. Considering the low amount of systemic exposure and absence of the lesion in males, splenic nodule in pancreases is probably unrelated to the treatment.

Key study observations:

The data suggest that ophthalmic treatments up to 210 μg of brimonidine and 5.25 μg of purite per day (0.2% brimonidine) for six months in rabbits were associated with slight ocular discomfort, sedation and hyperglycemia. The minimal dose studied, 0.1% brimonidine ophthalmic solution also showed similar effects. The 0.1% ophthalmic dose at which ocular discomfort, sedation and hyperglycemia were observed corresponds to 35 μg/kg of brimonidine (420 μg/m^2) and 1.75 μg/kg or 21 μg/m^2 for purite in rabbits. The no effect dose is not established.

2. Brimonidine-purite [redacted] a one month ocular toxicity study in rabbits. Study # TX00022, page 83, vol submitted on Oct 17, 2000.

Conducting laboratory: Allergan, Irvine, CA 92612
Date of study initiation: April 3, 2000
GLP compliance: Yes
QA report: Yes

Methods:

Dosing information:

Species: New Zealand White rabbit (Hra(NZW) SPF1).
#/sex/group: 6 females/group
Age: 4-6 months, 2.90 to 3.63 kg body weight.
Satellite group: Nil.
Dosage groups in administered units:

Group	Test/Control article	Frequency	Dose mg/day
1	[redacted]	TID, Left Eye	0
2	0.2% brimonidine purite [redacted] Lot#11523a	TID, Left Eye	0.21
3	0.2% brimonidine purite [redacted] Lot# 11717	TID, Left eye	0.21

Route, form and volume:

One drop (35 μL) instilled into lower conjunctiva of the left eye three times a day for 28 days. The right eye served as the untreated control.
Formulation/Vehicle:

The sponsor has not provided the composition in the report. However, following formulation numbers have been provided.

Vehicle, 9117X; [redacted] 0.2% brimonidine, 9115X; 1.5% [redacted] 0.2% brimonidine, 9115X.

Observations:

Clinical observations:

Each rabbit was observed at pretest and daily throughout the study for treatment related clinical signs.

Body weight:

Body weights were recorded at pretest and once weekly thereafter.

Gross ocular examinations:

Animals were observed for discomfort and irritation on day 1 and weekly immediately following the first dose and last dose. Numerical scores were given to reflect severity of ocular discomfort (0-4 severity scale, duration 1-4 score), conjunctival hyperemia (0-3 score), discharge (0-3 score) and swelling (0-4).

Slit lamp biomicroscopy:

Both eyes were examined at pretest and on week 4. Conjunctiva, cornea, iris and anterior chamber were evaluated.

Ophthalmoscopy:

Both eyes were evaluated at pre test and on week 4 following dilatation by Mydriacyl. Lens, vitreous humor, fundus and optic disc were evaluated.

Terminal sacrifice:

Animals were euthanized by sodium pentobarbital. Rabbits were examined externally. Eyes with optic nerve and surrounding tissues were fixed in 10% formalin. Ocular tissues were processed and stained in hematoxylin and eosin for microscopic examinations.

Statistics:

Statistical analysis was conducted using analysis of variance [redacted] range test for significance.

Results:

No mortality was reported.

Clinical observation:

No treatment related clinical signs were reported.

Body weight:

The treatment had no effect on the body weight.

Gross ocular observations:

No treatment related changes in the gross observations e.g. discomfort, hyperemia, discharge and swelling were reported.

Slit lamp biomicroscopy:

No treatment related changes were reported for conjunctiva, anterior chamber and cornea for both eyes.

Ophthalmoscopic examinations:

No treatment related changes were observed in the posterior chamber of the eye.

Gross pathological findings:

No treatment related gross changes were observed in the study.

Histopathological changes:

Activated lymphoid tissues in the conjunctival mucosa were observed in the histopathological examinations as shown in the following table:

Site	Vehicle Control		0.2% Brimonidine [redacted]		0.2% Brimonidine [redacted]	
	Incidence	Severity	Incidence	Severity	Incidence	Severity
Upper lid, Left	0/6	0	1/6	1	0/6	0
Lower Lid, Left	1/6	1	4/6	1.25	3/6	1.33
Upper Lid, Right	0/6	0	1/6	1	2/6	1
Lower Lid, Right	0/6	0	2/6	1.5	2/6	1.5

Severity, 1=minimal, 2=mild, 3= moderate

The data suggest that changes were observed at the left lower and right lower lids. However, brimonidine formulation that had [redacted] did not show additional safety concerns when compared to that of [redacted] in the study. Based on the data on activation of lymphoid tissues of the conjunctiva in the 28-day study, the sponsor suggested that brimonidine ophthalmic solution induced mild antigenic response. The reviewer could not confirm the finding on the basis of the six-month safety data. Presence [redacted] did not exaggerate toxicity to eyes in the rabbits.

Key study observations:

Stability study of ophthalmic brimonidine purite showed the presence of brimonidine [redacted] that is the limit of impurity of the drug product according to the ICH guideline (Q3b). The sponsor has conducted a 28 day safety study of the ophthalmic formulation that contains [redacted] of the impurity. No toxicological changes due to higher limit of [redacted] are evident from the results of the study. However, activation of lymphoid tissues of the conjunctival mucosa was observed in the rabbits. According to the sponsor, the effect may be due to allergic response to brimonidine itself. The reviewer could not confirm the finding from the results of the six-month study.

4. Summary of the safety of purite.

A review of the uses, chemistry and health effects of chlorine dioxide and the chlorite ion. Page 1, vol 22.

Chlorine dioxide is a disinfectant and approved for cleaning and disinfecting contact lens. About 50 ppm of purite will be used in the present formulation. Considering the maximum recommended dose of 6 drops per day to a 70 kg individual, the anticipated human dose will be about 0.2 µg/kg of purite per day.

The sponsor stated in page 311, vol 1 that Purite consists of an equilibrium mixture of [redacted]

Chlorine dioxide is used extensively to disinfect drinking water (about 1 ppm is used in drinking water) due to its ability to kill bacteria, algae and viruses rapidly. It is also preferred because of its inability to form chlorinated hydrocarbons in the water that has carcinogenic potential. It is a strong oxidant and

forms ClO_2^-, Cl^- and ClO_3^- ions in water. The sponsor stated that the possible health effect of purite is a decrease in the red cell counts and hemoglobin levels in the blood due to the oxidative effect of chlorine dioxide. The disinfecting property of chlorine dioxide is due to nonspecific oxidative changes to the cell membrane and loss of ionic gradient across the membrane.

Chlorine dioxide tested positive in Ames test without metabolic activation and positive in the mouse micronucleus assay. Carcinogenicity studies were conducted in rats and mice according to the list of tests referred in the material handling data sheet. The sponsor stated in page 5, vol 22 that it is not carcinogenic in the bioassays. The attached review from the Center for Devices suggests that the carcinogenicity studies were reported in the material handling data sheet. These data were not reviewed in the submission for PMA supplement [redacted] The sponsor attached a published report for the mouse carcinogenicity study in page 228, vol 23. The published report lacks detail information that is necessary for a complete review. Therefore, carcinogenicity aspects of purite should not be included in the package label of brimonidine purite.

Reproductive safety summary:

The sponsor stated that at 100 ppm and above doses, a decrease in implants and an increase in stillbirth were observed in rats. Up to 24 ppm in the drinking water did not show systemic toxicity in healthy volunteers. According to the sponsor, the no observed dose level of chlorine dioxide is about 10 to 100 ppm. However, no data have been provided to support the conclusion. The reviewer reviewed literature reports on the reproductive safety in the next page of the review.

The sponsor's summary on mutagenicity studies is provided as follows:

The sponsor stated that chlorine dioxide at 20 ppm and $NaClO_2$ up to 400 ppm showed positive response in TA 100 strain of S. typhimurium without S-9 mixtures. The sponsor stated that the cell membrane of the bacteria would have been damaged in the culture dishes due to the disinfectant property of purite. The sponsor indicated that the genotoxicity of chlorine dioxide and sodium chlorite were tested in mouse micronucleus test following IP injections at 3.2 to 25 mg/kg for chlorine dioxide and 7.5-60 mg/kg for sodium chlorite. Increase in the micronucleated polychromatic erythrocytes was investigated. Both chlorine dioxide and sodium chlorite showed a positive response. However, oral doses of sodium chlorite did not show a positive response in the mouse micronucleus test. The sponsor has not indicated the oral dose used in the micronucleus test in the summary provided for a review.

Effect of Refresh Tears on corneal surface in rabbits

Page 28, vol 21.

Refresh Tears is available as an OTC product that contains Purite. The sponsor conducted a seven day topical ocular evaluation of Refresh Tears in the rabbit eye. Rabbits were dosed four times a day for 7 days. At the end of the study, electron microscopic evaluation of the cornea did not show superficial erosion of the cornea.

Reproductive Toxicology:

1. Reproductive effects in long Evans rats exposed to chlorine dioxide, Environmental research, 56, 170-177, 1991. Page 204, vol 21.

The publication reports the study according to the following design and no GLP compliance statement is included in the report.

Species: Long Evans rats, 4-6 weeks of age

Doses: 2.5, 5.0 and 10 mg/kg dose of ClO_2 administered by oral gavage in deionized water.

Study design:

Male rats were treated once per day for 56 days before mating and throughout the 10 day breeding period. Female rats were given same doses for 14 days prior to breeding, throughout the breeding, gestation and lactation and weaning day 21 for the offspring. Day of parturition is designated as lactation day 0. After the breeding period, blood samples were collected from the male animals for hematology and thyroid hormone levels. Male rats were sacrificed by pentobarbital overdose. Male rats were examined for gross changes at necropsy. Weights of testes, epididymis, prostate and seminal vesicles were recorded. These organs were preserved in formalin for histological evaluations. Sperm motility and morphology from the epididymis washings were examined.

Dams were observed for fertility, gestation period, body weight gain and maternal behavior. The sponsor has not indicated what were the behavioral parameters examined. Female rats were sacrificed on lactation day 21. Blood samples were collected before the sacrifice for hematological examinations. Animals were necropsied for gross changes. The reproductive tract was weighed and preserved for histological examinations.

Viability, size of the litter, body weight gain, day of eye opening and gross external appearance were examined for the F_1 pups. F_1 pups were sacrificed on day 21. Hematology and thyroid hormone levels were determined from 10 pups/sex /group at necropsy. Blood samples were collected for the hormone levels in the blood from rest of the pups on days 28, 34 and 40.

Number of animals/sex/dosing group: 12 male rats per dose group and 24 female rats per dose group.

Statistical evaluation: Statistical evaluation of sperm counts and morphology were made using one way analysis of variance. Statistical analyses of other data were performed according to Bartlett's, Dunnett's and Student's t- tests.

Results:

There were no treatment-related changes in the clinical signs or body weight gains during the treatment. Fertility rate and gestation period were unaffected by the treatment. The sperm motility and morphology were not affected due to the treatment. No treatment related gross lesions were observed in the male and female animals.

Among the F_1 pups, day of eye opening was decreased from 16.70 days in the control to 15.95 days at the high dose. However, biological significance of the reduction is not known. The absolute vaginal weight in the group 4 F_1 pups was reduced significantly (control = 0.036 g, gr 4=0.022 g). Body weight of the surviving pups during the weaning period was unaffected by the treatment. Survival and mortality of the F_1 pups during day 1, 4 and 21 is shown in the following table:

Group	Day 1		Day 4		Day 21	
	Live	Dead	Live	Dead	Live	Dead
Control	207	23	205	2	181	4
2.5 mg/kg	238	4	217	21	190	7
5.0 mg/kg	246	11	243	3	199	26
10 mg/kg	240	18	237	3	204	15

T_4 levels:

Male F_0 animals showed statistically significant decrease in the blood levels of T_4 thyroid hormone. F_1 male pups showed statistically significant increase in the T_4 levels in the blood only on postnatal day 17. However, these changes were small in magnitude and considered to be unrelated to the treatment. Data for T_4 (μg/dl) are shown in the following table.

Group	0 mg/kg ClO_2	10 mg/kg ClO_2
Adult Males (F_0)	4.2	3.5*
Male F_1, day 17	4.8	5.6*
Male F_1, day 28	2.6	2.5
Male F_1, day 40	3.4	3.8

*Statistically significant

No other treatment related adverse reactions are reported.

Summary of the report:

Fertility and reproductive performance of chlorine dioxide given through deionized water by oral gavage at 2.5, 5.0 and 10 mg/kg doses were evaluated in rats. The treatment did not show any adverse effect on the male and female reproductive performance. The treatment also did not show any effect on gestation period, body weight gain and thyroid hormone levels. Survival of pups in the F_1 generation was not affected by the treatment compared to the control.

3. Assessment of maternal toxicity, embryotoxicity and teratogenic potential of sodium chlorite in Sprague Dawley rats, page 63, vol 22.

The report published in Environmental Health Perspective, 46, 25-29, 1982. No GLP statement is presented in the report.

Species: Sprague Dawley rats, body weights 300-320 g male and 268-303 g female.

Doses and route of administration:

1. 10, 20 and 50 mg/kg IP daily during days 8-15 of gestation.
2. 200 mg/kg daily during gestation days 8-10.
3. 0.1, 0.5 and 2% sodium chlorite solutions given as drinking water. The sponsor stated that the solution was changed three times during the treatment on days 1, 3 and 5. The duration of treatment was 8-15 days. Considering 300 g body weight, the doses calculated in mg/kg/rat/day were 113, 543 and 706 mg/kg for 0.1, 0.5 and 2% $NaClO_2$, respectively, in drinking water based on the water consumption.

Study design:

Four female rats were cohabited for mating with one male rat per cage. Pregnancy was established on the basis of the presence of sperm in the vaginal smears. Body weight, water and food consumption of pregnant rats were monitored on days 8, 15 and 22 of gestation. The control group received double distilled water until delivery. The treated animals received sodium chlorite ($NaClO_2$) during gestation days 8-15. General health and toxic signs of the dams were noted. The sponsor stated that some animals were allowed to deliver pups at term. Litter size, birth weights of pups and crowns to rump measurements were recorded. The offspring was examined for gross malformation and sacrificed by overdose of ether inhalation. Pups in one group were fixed in Bouin's solution for examination of organ malformations.

Pups in the other group were fixed in 95% ethyl alcohol for skeletal examination following [redacted] red staining.

Another group of dams was subjected to cesarean section before parturition on day 22. Live, dead and resorbed fetuses were counted. Reflex of live fetuses to touch was examined. Body weight of fetuses and crown to rump distance were recorded. Gross, soft tissue and skeletal malformations were examined using methods described above. Postnatal body weight up to 29 days was recorded for six pups selected randomly from each litter.

Number of animals/sex/dose:

For IP doses, 7-13 female rats were allotted per group. For 200 mg/kg oral gavage group only 4 female rats were used. Ten female rats were allotted for each group that received 0.5 or 2% sodium chlorite in drinking water. The sponsor has not indicated number of animals exposed to 0.1% sodium chlorite in the drinking water.

Statistical evaluations:

Significant changes were determined on the basis of Student's t test or chi square test.

Results:

Mortality and clinical signs of dams are shown in the following table:

Dose	Route	Clinical signs	Mortality
10 mg/kg	IP	Loss of weight	0
20 mg/kg	IP	Loss of weight (19.5%), Vaginal bleeding, ruptured and irregular RBC	5 out of 10
50 mg/kg	IP	Loss of body weight, Vaginal bleeding (7%)	7 out of 7
200 mg/kg	PO gavage	Loss of body weight, Vaginal bleeding	4 out of 4
0.5%	Drinking water ad lib.	Loss of body weight	0
2%	Drinking water ad lib.	Loss of body weight, irregular and ruptured RBC	0

Data suggest that highest tolerated dose without mortality is 10 mg/kg/IP and 2% in drinking water during gestation days 8-15. Loss of body weight was the major side effect. The no effect dose to the dams (no maternal toxicity) is 0.1% of sodium chlorite in the drinking water during gestation days 8-15.

Most of the treated groups that showed a decrease in the body weight also showed a decrease in the food and water consumption. When sodium chlorite was given in the drinking water, the reduced water consumption in some animals affected the intake of sodium chlorite.

The body weight, water and food consumption of dams during gestation days 8-15 are shown in the following table:

Treatment	BW change/rat	Food intake, g/rat	Water intake, ml/rat
Distilled water	27.2	166.20	353.60
0.1% in drinking water	71.1	168.5	237.5
0.5% in drinking water	-18.8	112.8	224.4
2% in drinking water	-72.5	54.5	63.2
10 mg/kg oral gavage	3.69	129.5	249.5
20 mg/kg oral gavage	-53.2	59.0	203.0

The effect of sodium chlorite on fetuses following delivery at term showed increased still birth at 2% solution in the drinking water and at 10 mg/kg IP injections during days 8-15 of gestation.
Pups delivered by caesarian Section on day 22 showed dead pups and resorptions at 10, 20 mg/kg IP and 2.0% in drinking water. Dead pups and resorption were also noted at 0.1% in the drinking water. The sponsor has not provided data for control animals at caesarian section. When data of the control dams from normal delivery group were compared, increased dead fetuses greater than the control were observed at 0.1% $NaClO_2$ in the drinking water. Data are shown in the following table:

Treatment	Fetuses alive	Fetuses dead	resorbed	Crown-rump length	Fetal weight, g
0.1%	40	1	4	3.66	4.14
0.5%	44	1	2	3.87	5.23
2%	37	2	21	3.37	4.59
10 mg/kg	58	3	7	4.06	5.35
20 mg/kg	15	0	34	-	-
		Term Delivery			
Control	9.8*	0		4.44	7.24
0.1%	9.8*	0.5*		4.22	6.85

*Average of 4-7 litters

Based on the observation it is suggested that treatment with 0.1% sodium chlorite in the drinking water during gestation days 8-15 showed fetotoxicity. The sponsor stated that weight of pups delivered by control and treated dams did not show differences in the body weight gain. Also incidences of malformation in the pups from the control and treated dams were comparable.

Summary of the study:

Maternal toxicity associated with loss of body weight, vaginal bleeding, mortality were observed in all IP and oral gavage doses. 0.1% in the drinking water is considered to be non toxic to dams when given during organogenesis. However, fetotoxicity (dead fetuses and resorption) was noted at 0.1% dose in the drinking water (113 mg/kg/day). The no effect dose is not established in the teratogenicity study. Based on the data, sodium chlorite is considered to be embryotoxic in rats.

Genetic Toxicology:

Ames Salmonella plate incorporation assay for chlorite solution (150 ppm). Page 1, vol 21.

Sponsor's IDPH-301-AN-002-89
Conducting Laboratory: [redacted]
Date of study initiation/completion: May 31, 1989/ June 4, 1989.
GLP Compliance: Yes
Drug Lot # 85-0796B (chlorite solution, 150ppm)
Study end point: increase in number of histidine revertant colonies

Methods:

Strains: Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 used in the assay.

Dose selection:

Toxicity of the test substance was determined in a preliminary assay on the basis of the growth inhibition. The test article was evaluated at 50, 167, 500, 1670 and 5000 μg/plate.

Metabolic activation system:

S-9 mixtures prepared from [redacted] induced male Sprague Dawley rat liver homogenates.

Positive and solvent Controls:

For TA 1535 and TA 100, sodium azide was used in the absence of S-9 mixtures. For TA 1537, 9-aminoacridine, for TA 1538 and TA 98, 2-nitrofluorene was used. In the presence of S-9 mixtures, 2-anthramine was used for all strains tested. Distilled water is used as the solvent control.

Mutation Assay:

Mutation experiments were conducted at 167, 500, 1670, 5000, 7500 and 10,000 μg/plate using 150 ppm chlorite solution in the presence and absence of S-9 mixtures. Positive and solvent controls were added in the experiment. The incubation of the test article or solvent, agar and tester strain was done for 48 hours at 37C. Following the incubation period, background lawn was scored for number of revertant colonies.

Results:

No toxicity was detected at 150-ppm chlorite solution up to 5000 μg/plate (approx 15 μg of chlorite per plate). Mean revertant colonies in the absence and presence of S-9 mixtures was comparable to the control. It is concluded that 150 ppm chlorite solution is devoid of a mutagenic effect in this bacterial system.

Overall summary and Evaluation:

Brimonidine is an approved drug for the treatment of ocular hypertension and increased IOP in patients with glaucoma as a 0.2% ophthalmic solution. In the present NDA, brimonidine will be used for similar indications as a 0.15% ophthalmic solution containing purite as the preservative instead of benzylalkonium chloride. Brimonidine is a α_2 adrenergic agonist. The sponsor stated that brimonidine reduces IOP by decreasing aqueous humor formation and increasing aqueous humor outflow.

Brimonidine is a selective agonist at α_2 adrenergic receptor than α_1 adrenergic receptor site. However, α_1 adrenergic receptor activity is shown in the cat nictitating membrane preparation and by the presence of a transient ocular hypertension in the animal model. Ocular antihypertensive effect of brimonidine may be due to both pre and post-sympathetic α_2 adrenergic activity. Brimonidine showed an ocular hypotensive effect in several animal species. It is interesting to note that ophthalmic delivery of brimonidine solution showed ocular hypotensive effect both in the treated and untreated eyes. The effect on the untreated eye was observed in experimental animals as well as in human eyes. The ocular hypotensive effect of brimonidine in the contralateral eye could be due to systemic transfer of the drug from the treated eye to the untreated eye. In the monkey model, systemic hypotension also played a role for the hypotensive effect

in treated and untreated eyes. Brimonidine purite 0.1% or 0.2% formulation showed systemic hypotension and bradycardia up to 1-2 hours after dosing into eyes of conscious monkeys.

Brimonidine showed miosis, sedation, nausea, salivation and diarrhea in the pharmacodynamic studies as side effects following ophthalmic delivery. Subcutaneous injections of brimonidine at 50 μg/kg showed antidiarrheal and diuretic effects in rats. The sponsor stated that diuresis and constipation were not significant in clinical studies. Brimonidine showed hyperglycemia at 23 μg/kg/day ophthalmic dose in rabbits (3-4kg) that lasted about 2 hours after the dose. The effect of brimonidine on blood sugar levels was due to the inhibition of insulin release by α_2 adrenergic agonist. However, the sponsor stated that hyperglycemia due to brimonidine is clinically not significant.

A single dose of [redacted] vehicle did not show acute toxicity in Sprague Dawley rats. Chronic administration of brimonidine at 105 μg and purite at 5.25 μg daily for six months in rabbits showed slight ocular discomfort, sedation and hyperglycemia. However, no pathological changes in the anterior and posterior chambers of the eye were reported. The no effect dose for the adverse effects for chronic ophthalmic uses in the rabbit is not established.

During the review process the sponsor submitted a study report on the effect of a dimer of brimonidine [redacted] level in the formulation. The purpose of the study is to examine its safety because it may reach a level higher than the recommended ICH level of 1%. The data did not show any safety concerns to [redacted] However, brimonidine related response to the conjunctiva was noted in rabbits characterized by the presence of activated mucosal lymphoid tissue. The sponsor stated that the activation of lymphoid tissue is an allergic reaction. Since allergic and hypersensitivity reactions to brimonidine is already addressed in the package insert, further action to the finding is not necessary. It should also be noted that the six-month safety data did not show activation of lymphoid tissue in the conjunctiva of rabbits. The reviewer could not confirm the sponsor's conclusion on the possible allergic reactions in conjunctiva in the rabbit model.

The recommended human dose of purite (0.005%) based on six 50 μL drops per day for a 70 kg subject is approximately 0.2 μg/kg per day. The human dose of purite is about 8 times lower than the dose used in the chronic safety study in the rabbits. Human dose of brimonidine (0.15%) based on six 50 μL drops per day in 70 kg subject is 6.42 μg/kg, that is about 10 times lower than 0.2% ophthalmic drops used in rabbits for six months.

Pharmacokinetic data suggest that brimonidine is bioavailable in the aqueous humor and plasma from the purite formulation. The levels of brimonidine in rabbits from 0.2% brimonidine purite was greater in the aqueous humor and plasma than Alphagan. Chronic administration of 0.1 and 0.2% brimonidine purite formulation at 35 μL (one drop) three times a day to the left eye for six months showed systemic bioavailability of brimonidine dose dependently in rabbits. The C_{max} was about 391 and 958 pg/ml in the plasma at 0.1 and 0.2% formulations, respectively on week 12.

Mutagenicity and reproductive safety of purite were investigated and provided in the NDA in the form of a published report and summary. Chlorite solution at 150 ppm did not show mutagenic effect in Ames assay. However, the sponsor stated that 400 ppm (0.04%) of sodium chlorite and 20 ppm (0.002%) of chlorine dioxide showed positive response in mutagenicity assay in TA 100 strain of S. typhimurium in the Ames test. Similarly, 3.2 mg/kg IP injections (16000 times human dose) of chlorine dioxide and 7.5 mg/kg (37500 times human dose) sodium chlorite increased micronucleated polychromatic erythrocytes in mice. Based on the data, purite is considered to be mutagenic. However, 50 ppm (50 μg/ml) of purite in the 0.15% brimonidine solution did not show any damage to the anterior and posterior chambers of the eye in rabbits when treated for six months.

It should be mentioned in this context that purite formulation showed higher levels of brimonidine in the aqueous humor fluid. It is not known if purite contributed to the change in permeability to the drug. If so, long term treatment with purite formulation may develop a change in the barrier function of the cornea that may show higher bioavailability and ocular toxicity to other ophthalmic products.

The sponsor stated that purite is not carcinogenic in rats and mice. However, the carcinogenicity studies were not reviewed in the CDER.

Fertility and reproductive safety of chlorine dioxide were investigated in rats. Oral dose up to 10 mg/kg of chlorine dioxide (50,000 times human dose) did not show any adverse effect in male and female fertility in rats. Dead fetuses were observed at 0.1% sodium chlorite (113 mg/kg/oral) in the teratogenicity study in rats that is more than 500,000 times higher than human ophthalmic doses.

The human dose of purite is almost negligible compared to the dose that showed reproductive toxicity and is considered to be safe upon ophthalmic delivery in humans.

Conclusion:

Brimonidine purite (0.15%) ophthalmic solution is safe on the basis of chronic safety evaluation in the rabbits for six months. No pathological changes were observed in the anterior or posterior chambers of the rabbit eye. However, discomfort to the eye, hyperglycemia, sedation, nausea, miosis and systemic hypotension was observed as the side effects of brimonidine ophthalmic solution in the animal models. These safety concerns need to be addressed in the package inserts if similar adverse experience are noted in the clinical database. It should be mentioned in this context that brimonidine ophthalmic solution 0.2% is already approved in the USA. The approved package insert indicated that brimonidine should be used with caution in patients with cardiovascular diseases. The package insert mentioned that brimonidine causes drowsiness.

Pharmacokinetic data in rabbits suggest that brimonidine from the purite formulation produces higher levels in the aqueous humor and blood as opposed to a no-purite formulation. Clinical pharmacology data for brimonidine purite in human plasma are given in Page 344, vol 1 of the NDA. Clinical PK data For Alphagan 0.2%, brimonidine –purite 0.15% and 0.2% were compared. Doses were given as TID. $AUC_{0\text{-}24}$ was 735 and 927 pg.hr/ml for 0.2% brimonidine purite TID and Alphagan 0.2% TID doses, respectively. Based on the data Alphagan showed higher bioavailability in humans than brimonidine purite opthalmic drops.

It is possible that purite based preservative has an effect on the permeability of drugs in the cornea that can enhance the level of brimonidine and other ophthalmic drugs. The sponsor has not addressed the issue in the preclinical database. The reviewer recommends that the medical reviewer address the issue with respect to the requirements of collection of appropriate data as a post approval phase IV basis.

Chlorine dioxide and sodium chlorite showed mutagenicity in the Ames test at 20 and 400 ppm, respectively in TA 100 strain of S. typhimurium. Mutagenicity was also observed in mouse micronucleus test in vivo at 3.2 mg/kg/ip dose of chlorine dioxide and 7.5 mg/kg/ip dose of sodium chlorite. However, these doses are several thousand folds higher than the intended doses of the purite formulation. The mutagenic effect is considered to be of no biological significance to the safety of the eye tissues on the basis of the animal safety data and clinical experience of the approved purite based products. The purite preservative at the recommended doses is not expected to have any effect on the reproductive performance and on the development of fetuses upon ophthalmic dosing.

On the basis of the available preclinical data, brimonidine purite (0.15%) ophthalmic solution is approvable for the recommended uses.

Recommendations:

Internal:

1. Brimonidine purite ophthalmic solution showed sedation, systemic hypotension, miosis, nausea, hyperglycemia and discomfort to the eye in animal studies. Some of these side effects are already addressed in Alphagan and brimonidine purite label e.g. hypotension and sedation. It is recommended that the medical reviewer's review the clinical safety database and indicate appropriate adverse events in the package insert.

2. Ophthalmic dosing of brimonidine in purite showed higher levels of brimonidine in the aqueous humor and plasma than that given as Alphagan without purite in rabbits. It is possible that purite contributes to the change in permeability to the cornea. In order to evaluate the effect of purite on corneal permeability of drugs, it is necessary to examine the onset of action and plasma levels of commonly used ophthalmic drugs at baseline and following chronic treatment with brimonidine purite in clinical studies. The data can be collected in the post approval Phase IV study.

External to the sponsor: Nil

Labeling Review:

3. The reviewer recommends that the reproductive safety portion of the label should be similar to Alphagan except a correction for the human exposure due to 0.15% brimonidine purite as mentioned in page 294, vol 1. The recommendation is based on the fact that no new study on the reproductive safety is added to this NDA. The label should read as follows:

Pregnancy: Teratogenic effects: Pregnancy Category B, Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to Tradename. Dosing at this level produced an exposure that is [redacted] times higher than the exposure seen in humans following multiple ophthalmic doses.

"There are no adequate and well controlled studies in women.....Tradename should be used in pregnancy only if clearly needed".

Nursing mothers:

Same as proposed by the sponsor.

/S/

Asoke Mukherjee, Ph.D
Pharmacologist

/S/ 11/28/01

Robert Osterberg, Ph.D.
Team Leader

Addendum to Review:

C.C List:

Orig. NDA #21-262
HFD-550/Div.File
HFD-550/Reviewer/A.Mukherjee
HFD-550/Medical Reviewer/J.Harris
HFD-550/Chemist/L.Rodriguez
HFD-550/CSO/L.Gorski
HFD-345
R/D Init by:
F/T by:
C:NDA21-262July2000

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-262 SUBMISSION DATE: 06/30/00

PRODUCT: Brimonidine Tartrate Ophthalmic Solution, 0.15% (Brimonidine-Purite™)

SPONSOR: Allegan
Irvine, CA

REVIEWER: Veneeta Tandon, Ph.D.

I. BACKGROUND

Drug Classification: 3S

Dosage Form: Ophthalmic solution, 0.15%

Indication: For the lowering of intraocular pressure (IOP) in patients with open angle glaucoma or hypertension.

Pharmacologic Class: Alpha adrenergic receptor agonist. Mechanism of action of lowering IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Clinical Endpoints: Lowering of IOP

Dosage and administration: One drop in the affected eye(s) three times daily, approximately 8 hours apart.

Foreign marketing history: Brimonidine-Purite™ has not been marketed in any country. However, the active ingredient, brimonidine tartrate, with benzalkonium chloride as the preservative (BAK) is marketed as ALPHAGAN® 0.2% in several countries including US (NDA 20-613).

Formulation: Brimonidine-Purite™ Ophthalmic Solution 0.15% is a new formulation of brimonidine tartrate with a unique preservative. Brimonidine-Purite™ 0.15% is preserved with Purite™ (0.005% w/v), where as ALPHAGAN®is preserved with benzalkonium chloride (BAK). The formulation of Brimonidine-Purite™ Ophthalmic Solution 0.15% is shown in the following table.

Ingredient	Concentration (% w/v)	Concentration mg/ml.	Amount (kg) for a 400 L batch
Brimonidine Tartrate	0.15	1.5	
Purite™	0.005	0.05	
Sodium Carboxymethylcellulose USP			
Boric Acid NF			
Sodium Borate			
Sodium Chloride USP			
Potassium Chloride USP			
Calcium Chloride			
Magnesium Chloride USP			
Hydrochloric Acid NF or Sodium Hydroxide NF			
Purified Water USP			

a The brimonidine tartrate quantity is corrected for "as is" purity.

b The Purite™ quantity is corrected for raw material assay.

c The sodium carboxymethylcellulose quantity is corrected for moisture content based on the loss-on-drying (LOD) assay

Brimonidine-Purite™ is similar to ALPHAGAN® except for the following compositional differences:

- Brimonidine-Purite™ is preserved with Purite™, which confers better local tolerance than does the BAK contained in ALPHAGAN® .
- Brimonidine-Purite™ has a pH of 7.1 to 7.3. ALPHAGAN® has a pH of 6.3 to 6.5. Since the pKa of brimonidine base is approximately 7.2, the higher pH of Brimonidine-Purite™ increases the concentration of unionized drug and may therefore enhance ocular brimonidine absorption.
- Brimonidine-Purite™ contains potassium chloride, calcium chloride, and magnesium chloride, which are constitutive components of human tears. ALPHAGAN® does not.

II. RECOMMENDATION

The clinical pharmacokinetics section of the NDA is acceptable. There are no comments for the sponsor.

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III. ANALYTICAL VALIDATION

Analytical Validation for brimonidine is complete and acceptable.

Methodology: [redacted]
LLOQ:

IV. PHARMACOKINETIC STUDIES

The pharmacokinetic section has been reviewed in a question based manner, with the repsonses to the question provided in the section following the question.

Is 0.15% Brimonidine-Purite™ opthalmic solution systemically absorbed after topical application to the eye?
If yes, what is the systemic exposure of brimonidine from this new formulation?

Yes, brimonidine is systemically absorbed after topical topical application of the Brimonidine-Purite™ ophthalmic solution to the eye, however the study has not been conducted with the 0.15% ophthalmic solution.

The sponsor has evaluated the systemic exposure of brimonidine from a 0.1% and 0.2% ophthalmic solution of Brimonidine-Purite™ compared it to historical data of 0.2% ALPHAGAN®. Based on the results of this study, the sponsor has extrapolated the predicted parameters for 0.15% ophthalmic solution of Brimonidine-Purite™, which is the to-be-marketed strength of the formulation.

Comparing similar strengths, Brimonidine-Purite™ 0.2% solution in healthy volunteers produces an t_{max} that is earlier and mean C_{max} and AUC_{0-24} that are slightly higher than after 0.2% ALPHAGAN® administration.

The results were obtained from study PK-98-130.

Study Population:	39 healthy volunteers 18 years of age or older (21M & 18F)
Dose:	One drop of Brimonidine-Purite™, 0.1% or 0.2% solution or [redacted] to each eye 3 times daily for 27 1/3 days in a parallel study design.
Blood Samples:	Blood samples up to 8 hours were taken from each volunteer after the first daily dose on Day 1 and Day 7. Additional samples at 1 hour post dose on Days 8 and 28.

Day 1 and day 7 mean plasma concentration-time profiles of brimonidine and the pharmacokinetic parameters during Brimonidine-Purite™ treatment are shown below.

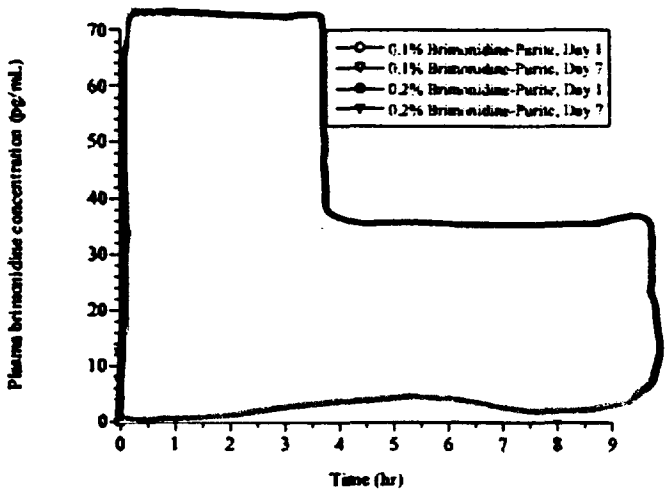


Table: Pharmacokinetic parameters of brimonidine in human plasma after 1 dose (day 1) or 19 doses (day 7) of Brimonidine-Purite 0.1% or 0.2% TID to each eye of healthy subjects. Parameters are expressed as mean ± SD (N).

Formulation	Day	C_{max} (pg/mL)	t_{max} (hr)	$AUC_{0-t_{last}}$ (pg·hr/mL)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{½}$ (hr)
0.1%	1	23.3 ± 14.1 (13)	1.54 ± 0.66 (13)	79.3 ± 47.8 (12)	NC[1]	NC[1]
	7	30.0 ± 17.8 (13)	1.50 ± 0.68 (13)	127 ± 87 (13)	136 ± 85 (12)	1.88 ± 0.81 (12)
0.2%	1	48.4 ± 35.1 (13)	1.77 ± 0.60 (13)	211 ± 147 (13)	NC[1]	NC[1]
	7	64.7 ± 37.8 (13)	1.35 ± 0.94 (13)	245 ± 124 (13)	245 ± 124 (13)	1.95 ± 0.63 (12)

1 Not calculated

There appears to be some degree of accumulation after 7 days of treatment as observed in the above figure and table. However, there were no statistical differences in brimonidine C_{max} at both dose levels. Similarly, there was no statistically significant difference in $AUC_{0\text{-}tlast}$ between days 1 and 7 in the 0.2% treatment group. In the 0.1% treatment group, the difference in $AUC_{0\text{-}tlast}$ was statistically significant but variability between individual subjects was large.

Dose proportionality was tested by two-sample t-test to test for mean differences between dose normalized parameters. The statistical analysis after dose and weight normalization gave the same results as mentioned above.
The plasma concentrations at one hour post dose on Days 1, 7, 8 and 28 are given below.

Table: Statistical Analysis Results for Hour 1 Plasma Concentration (Dose and weight normalized analysis)

Parameter	Units	Visit[a]	0.1% Brimonidine Purite[b]	0.2% Brimonidine Purite[b]	P-value[c]

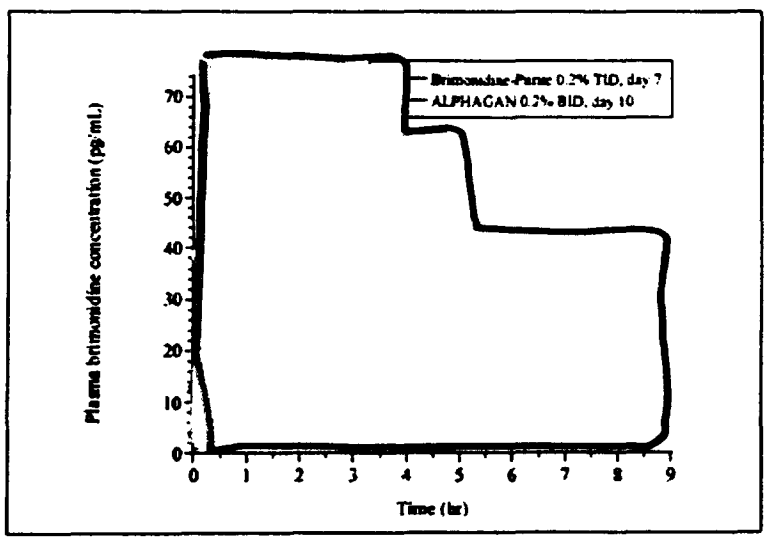
[a] Raw values were summarized at Days 1, 7, 8 and 28 visits.
[b] Mean values.
[c] P-Value for among-group comparison using two-sample t-test.

Observations/Conclusions:

- Brimonidine appeared rapidly in plasma following ocular administration with a mean tmax ranging from 1.35 to 1.77 hours.
- Brimonidine concentrations declined with a terminal half-life of about 2 hours.
- The inter-individual variability is very high.
- Steady state plasma concentrations during treatment with 0.1% and 0.2% Brimonidine-Purite™ appear to be dose proportional.
- Plasma brimonidine concentrations did not exceed 150 pg/mL in any individual subject.
- There was no statistically significant difference in brimonidine C_{max} between days 1 and 7 at either dose level.
- There was no statistically significant difference in $AUC_{0\text{-}tlast}$ between days 1 and 7 in the 0.2% treatment group. In the 0.1% treatment group, the difference in $AUC_{0\text{-}tlast}$ was statistically significant.

How does the exposure of brimonidine compare after the treatment of Brimonidine-Purite™ 0.2% and that after ALPHAGAN® 0.2%?

The sponsor has compared the brimonidine plasma concentrations during treatment with Brimonidine-Purite™ 0.2% TID for 6 1/3 days or ALPHAGAN® 0.2% BID for 9 1/2 days (from NDA 20-613) to both eyes of healthy subjects. The comparative plasma concentration time profiles are shown in the following figure.



Observations:

- T_{max} is earlier and mean C_{max} and $AUC_{0\text{-}24}$ are higher after Brimonidine-Purite™ administration. These could be due to the higher frequency of administration (TID with Brimonidine-Purite™ vs. BID with ALPHAGAN®)

Since the pharmacokinetic parameters are dose proportional, the sponsor has extrapolated the pharmacokinetic parameters for 0.15% Brimonidine-Purite™ from the data for 0.1% and 0.2% Brimonidine-Purite™ solutions, as shown in the following table.

Formulation	Day[1]	N	C_{max} (pg/mL)	$AUC_{interval}$[2] (pg•hr/mL)	AUC_{0-24}[3] (pg•hr/mL)
Brimonidine-Purite™ 0.2% TID	7	13 (7M + 6F)	64.7 ± 37.8	245 ± 124	735
ALPHAGAN® 0.2% BID	10	7 (3M + 4F)	58.5 ± 29.9	309 ± 142	618
Brimonidine-Purite™ 0.15% TID[4]	7	13 (7M + 6F)	47.4	191	572
ALPHAGAN® 0.2% TID[5]	10	7 (3M + 4F)	NE[6]	NE[6]	927

1 Samples were collected after the first dose on the day specified.

2 AUC during 1 dosing interval of 8 hours for Brimonidine-Purite™ or 12 hours for ALPHAGAN®.

3 AUC_{0-24} calculated as mean AUC_{0-8} • 3 (for Brimonidine-Purite™) or as mean AUC_{0-12} • 2 (for ALPHAGAN®).

4 Estimated by averaging plasma brimonidine parameters after ophthalmic 0.1% and 0.2% Brimonidine-Purite™ administration TID for 6½ days.

5 Estimated at steady state as AUC_{0-24} during BID treatment times 1.5.

6 Not estimated.

Observations/Conclusions:

- A comparison of brimonidine AUC_{0-24} during treatment with Brimonidine-Purite™ 0.15% TID and ALPHAGAN® 0.2% TID indicates that the expected daily systemic exposure to brimonidine during treatment with Brimonidine-Purite™ 0.15% TID is 38% lower than that estimated during approved treatment with ALPHAGAN® 0.2% TID.

V. OVERALL CONCLUSIONS

The systemic exposure of brimonidine from the Brimonidine-Purite™ formulation appears to be lower than the marketed formulation ALPHAGAN® formulation and the t_{max} appears to be faster as well.

VI. LABEL

The updated version of the Pharmacokinetics section of the label is acceptable, where information regarding study PK-98-130 have been incorporated in the first paragraph and the second paragraph is the same as the current label for ALPHAGAN®. The contents of the third paragraph will be reviewed by the Pharmacologist, although its place in the pharmacokinetics section seems inappropriate.

The label should read as:

Pharmacokinetics:
After ocular administration of either a 0.1% or 0.2% solution, plasma concentrations peaked within 0.5 to 2.5 hours and declined with a systemic half-life of approximately 2 hours.

In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

/S/ 11/22/00

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. /S/ 11/22/00

CC: NDA 21-262
HFD-550/Div File
HFD-550/CSO/Gorski
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy