PRODUCT MONOGRAPH

^{Pr}BRIMONIDINE

(Brimonidine Tartrate Ophthalmic Solution)

0.2%

Relatively selective α_2-adrenoceptor Agonist

Elevated Intraocular Pressure Therapy

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Control #: 075060

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PrBRIMONIDINE

(Brimonidine Tartrate Ophthalmic Solution)

0.2%

THERAPEUTIC CLASSIFICATION

Relatively selective α_2-adrenoceptor Agonist

Elevated Intraocular Pressure Therapy

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Brimonidine tartrate is a relatively selective alpha adrenergic receptor agonist that in radioligand binding assays and in functional assays, is approximately 1000 times more selective for the alpha-2 adrenoceptor than the alpha-l adrenoceptor. This selectivity results in the absence of vasoconstriction in micro vessels associated with human retinal xenografts.

Topical administration of brimonidine decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine tartrate ophthalmic solution 0.2% reduces elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine tartrate ophthalmic solution 0.2% has a rapid onset of action, with the peak ocular hypotensive effect occurring at approximately two hours post-dosing. The duration of effect is 12 hours or greater.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. Brimonidine tartrate ophthalmic solution 0.2% lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacodynamics

Brimonidine tartrate ophthalmic solution 0.2% has no effect on pulmonary function or exercise-induced tachycardia. The cardiovascular effects of brimonidine tartrate ophthalmic solution 0.2% during exercise in normal volunteers were found to be limited to a slight suppression of systolic blood pressure, which was clinically insignificant, during the recovery period following a treadmill test.

Pharmacokinetics

After ocular administration of brimonidine tartrate ophthalmic solution 0.2% twice daily (both eyes) in humans for 10 days, plasma concentrations were low (mean C_{max}=0.06 ng/mL).

Plasma brimonidine levels peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

In humans, brimonidine is eliminated rapidly via extensive systemic metabolism; there is no marked systemic accumulation after multiple dosing. 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 in the first 96 hours.

Clinical Studies

Brimonidine tartrate ophthalmic solution 0.2% lowers intraocular pressure with minimal effect on cardiovascular parameters (heart rate, systolic and diastolic blood pressure) and no apparent effect on pulmonary parameters (spirometry, respiratory rate).

The long term efficacy of brimonidine tartrate ophthalmic solution 0.2% dosed b.i.d. was demonstrated in two one-year multicentre studies in subjects with open angle glaucoma or ocular hypertension. In these trials brimonidine tartrate ophthalmic solution 0.2% lowered IOP by mean values of 4.3 mm Hg at trough and 6.7 mm Hg at peak. IOP decreases were maintained for the duration of the studies in the majority of patients; no tachyphylaxis was observed. Nine percent of subjects were discontinued from the studies due to inadequately controlled intraocular pressure.

INDICATIONS AND CLINICAL USE

BRIMONIDINE (brimonidine tartrate) ophthalmic solution 0.2% is indicated for the control of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Brimonidine tartrate ophthalmic solution 0.2% is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY

The use of brimonidine tartrate ophthalmic solution 0.2% in pediatric patients is currently not recommended. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% to infants in the age range of 28 days to 3 months. **(See Adverse Reaction sections).**

PRECAUTIONS

General

Brimonidine tartrate ophthalmic solution 0.2% should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists.

Although brimonidine tartrate ophthalmic solution 0.2% had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Brimonidine tartrate ophthalmic solution 0.2% has not been studied in patients with hepatic or renal impairment; caution should be exercised in treating such patients.

Brimonidine tartrate ophthalmic solution 0.2% should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Drug Interactions

Although specific drug interaction studies have not been conducted with brimonidine tartrate ophthalmic solution 0.2%, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Brimonidine tartrate ophthalmic solution 0.2% did not have clinically significant effects on pulse and blood pressure in chronic clinical studies. However, since alpha-agonists, as a class, may reduce pulse and blood pressure, caution in the concomitant use of drugs such as beta-blockers (ophthalmic and/or systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with brimonidine tartrate ophthalmic solution 0.2% can lead to an interference in IOP lowering effect. No data are available on the level of circulating catecholamines after brimonidine tartrate ophthalmic solution 0.2% is instilled. Caution, however, is advised in patients taking tricyclic antidepressants, which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No compound-related carcinogenic effects were observed in 21 month and 2 year studies in mice and rats given oral doses of 2.5 mg base/kg/day and 1.0 mg base/kg/day, respectively. These oral doses are approximately 830 and 330 times greater, respectively, than the maximum recommended human daily ophthalmic dosage for brimonidine tartrate ophthalmic solution 0.2% (0.003 mg base/kg/day), based on a 60 kg human..

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

Use in Pregnancy

Teratogenicity studies showed no adverse effects in rats and rabbits when oral doses (1.65 mg base/kg/day and 3.33 mg base/kg/day) were administered at approximately 550 and 1110 times,

respectively, the maximum recommended human daily ophthalmic dosage for brimonidine tartrate ophthalmic solution 0.2% based on a 60 kg human.

There are no studies of brimonidine tartrate ophthalmic solution 0.2% in pregnant women, however in animal studies, brimonidine tartrate ophthalmic solution 0.2% crossed the placenta and entered into the fetal circulation to a limited extent (ratio of drug-related material in fetal: maternal blood = 0.1 - 0.3). Drug-derived material was eliminated from fetal tissues by 24 hours post-dose. Brimonidine tartrate ophthalmic solution 0.2% should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether brimonidine is excreted in human milk, although in animal studies, brimonidine has been shown to be excreted in breast milk. During treatment with brimonidine tartrate ophthalmic solution 0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Pediatrics

The use of brimonidine tartrate ophthalmic solution 0.2% in paediatric patients is currently not recommended. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% to infants in the age range of 28 days to 3 months. **(See Adverse Reaction sections).**

Information to be Provided to the Patient by the Physician

BRIMONIDINE (Brimonidine Tartrate) ophthalmic solution 0.2%, as with other similar medications, can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

The preservative in BRIMONIDINE, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling BRIMONIDINE to insert soft contact lenses.

ADVERSE REACTIONS

In clinical studies including 717 patients on brimonidine tartrate ophthalmic solution 0.2%, the most frequently reported adverse events were oral dryness [25.8%], ocular hyperemia [24.8%], burning and stinging [22.5%], blurring [17.3%], headache [16.3%], foreign body sensation [15.5%], fatigue/drowsiness [15.2%], corneal staining/erosion [10.0%], ocular allergic reactions [9.9%], and ocular pruritus [9.8%], and conjunctival follicles [9.6%].

Events occurring less frequently included photophobia [7.4%], ocular dryness [7.0%], eyelid erythema [6.1%], ocular ache/pain [6.0%], upper respiratory symptoms [6.0%], tearing [5.6%], conjunctival edema [5.3%], eyelid edema [4.9%], dizziness [4.2%], conjunctival blanching [3.8%], blepharitis [3.6%], ocular irritation [3.1%], gastrointestinal symptoms [3.1%], asthenia [2.8%], abnormal vision [2.6%], abnormal taste [1.4%], conjunctival discharge [1.4%] conjunctival papillae [1.0%], and nasal dryness [1.0%].

The following adverse reactions were reported infrequently (<l%): depression [0.8%], systemic allergic reactions [0.8%], and palpitations [0.4%].

Serious Reports of Adverse Reactions in Paediatric Patients:

Several serious Adverse Reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0.2% to infants in the age range of 28 days to 3 months. These reactions included: bradycardia, hypotension, hypothermia, hypotonia, apnea, dyspnoea, hypoventilation, cyanosis and lethargy resulting in hospitalisation. Upon discontinuation of brimonidine tartrate ophthalmic solution 0.2% the infants recovered without sequelae.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No data are available on over dosage of brimonidine tartrate ophthalmic solution 0.2% in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained. Evacuation of the stomach should be considered during the first few hours after an overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of BRIMONIDINE (brimonidine tartrate) ophthalmic solution 0.2% in the affected eye(s) twice daily (doses taken approximately 12 hours apart).

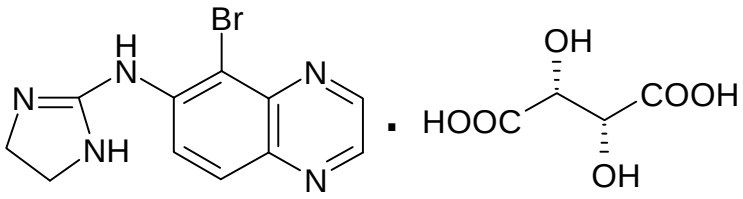
PHARMACEUTICAL INFORMATION

Drug Substance:

Common name: Brimonidine tartrate

Chemical name: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L- tartrate

Structural formula:



Molecular formula: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$

Molecular weight: 442.22

Description: Brimonidine tartrate is an off-white, pale yellow to pale pink powder, with a melting point range of 202.0 to 210.0˚C. It is water soluble (34 mg/mL) and soluble in DMSO (>60 mg/mL), slightly soluble in propylene glycol (-1.0 mg/mL, and very slightly soluble in ethanol (0.6 mg/mL) and acetone (<0.2 mg/mL). The pH of a 1 % solution of brimonidine tartrate in water is 3.5 at room temperature. A pK_a value of 7.78±-.05 has been determined.

Composition:

Each mL of BRIMONIDINE ophthalmic solution 0.2% contains Brimonidine Tartrate 2.0 mg with the following non-medicinal ingredients (alphabetically): 0.005% Benzalkonium Chloride as preservative, Citric Acid, Polyvinyl Alcohol, Purified Water, Sodium Chloride and Sodium Citrate (Dihydrate). Sodium Hydroxide may be added to adjust pH.

Stability and Storage Recommendations:

BRIMONIDINE should be stored between 15˚ to 30˚C. Product should be discarded 28 days after initial opening.

AVAILABILITY OF DOSAGE FORMS

BRIMONIDINE (brimonidine tartrate) ophthalmic solution 0.2% is supplied in white plastic dropper bottles. Each dropper bottle is sealed with a white plastic dropper tip and a white plastic threaded dropper tip cap with a clear plastic tamper-proof seal containing 5 mL (partial fill) and 10 mL (full fill).

INFORMATION TO THE CONSUMER

BRIMONDINE

(Brimonidine Tartrate Ophthalmic Solution 0.2%)

Do not allow the dropper tip of the bottle to touch the eye or other surrounding structures, because this could contaminate the tip with common bacteria known to cause eye infections. Serious damage to the eye with subsequent loss of vision may result if you use eye drop solutions that have become contaminated. If you experience any type of eye condition or have surgery, immediately seek your doctor's advice concerning the continued use of the bottle you are using.

NOTE: If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.** Product should be discarded 28 days after initial opening.

Patients Wearing Soft Contact Lenses:

Lenses should be removed prior to application of BRIMONIDINE (brimonidine tartrate) ophthalmic solution 0.2% and not re-inserted earlier than 15 minutes after use.

SIDE EFFECTS:

BRIMONIDINE may cause drowsiness and fatigue in some patients. Caution should be exercised when engaged in activities where mental alertness is required. Some common side effects that may occur include dry mouth, burning/stinging eyes, itchy eyes, blurring of vision and headache. If these persist or cause you concern, consult your doctor.

PHARMACOLOGY

Animal Pharmacology

Receptor binding and functional studies have characterized brimonidine as a potent and selective alpha-2-adrenoceptor agonist. As indicated in **Table 1**, brimonidine is notably more alpha-2 adrenoceptor selective than clonidine and *p*-aminoclonidine in both radioligand binding and functional assays.

Table 1: Receptor Pharmacology of Brimonidine, Clonidine and p-Aminoclonidine

Radioligand Binding; Ki (nM)*			***Functional; EC_{50} (nM)****	
Compound	**Alpha-1[a]**	**Alpha-2[b]**	**Alpha-1[c]**	**Alpha-2[d]**
Brimonidine	1850 ± 322 (5)	1.9 ± 0.5 (6)	1490 ± 214 (12)	1.0 ± 0.1 (24)
Clonidine	513 ± 108 (4)	3.4 ± 0.4 (6)	293 ± 47 (4)	4.4 ± 0.4 (11)
p-Aminoclonidine	181 ± 18 (4)	7.8 ± 1.2 (2)	180 ± 10 (8)	1.9 ± 0.2 (9)

[*] Mean ± SEM; "N" is noted in parentheses.
[a] [^{3}H] Prazosin in human cerebral cortex.
[b] [^{3}H] Rauwolscine binding in HT-29 cells.
[c] Contraction of isolated rabbit aorta.
[d] Inhibition of electrically induced contractions in the isolated rabbit vas deferens.

The ocular hypotensive effect of brimonidine has been demonstrated in normotensive rabbits, cats, and monkeys, as well as ocular hypertensive rabbits and monkeys. This effect is maintained following six months of chronic administration to albino rabbits (**Table 2**).

Table 2: The IOP Response to Chronic Administration of Brimonidine (b.i.d for 6 months) in Rabbits

Concentration (%)[a]	**Acute**	**Three Months**	**Six Months**
0.08	4.3[b]*	5.1*	3.8*
0.2	4.0*	6.0*	5.1*
0.8	1.0	6.5*	7.1*

[a] Concentration based on the bitartrate salt.
[b] Mean decrease in treated eye IOP (mm Hg) from vehicle-treated control at 2 hr following the AM dose.
* Significantly different from vehicle-treated animals ($p<0.05$) for treated eye.

Twenty-eight days of b.i.d. dosing of brimonidine tartrate 0.5% to rabbits and monkeys

demonstrated that monkeys experience a significantly diminished trough ocular hypotensive effect on chronic dosing. In rabbits, the trough IOP effect was unaltered, however, the peak effect significantly increased with this dosing regimen (confirmed also by 6 month experiments - see Table 2).

The mechanism of action for the ocular hypotensive effect of brimonidine in rabbits and monkeys is predominantly the suppression of aqueous humor production. Trabecular outflow was not found to be affected in monkeys. In rabbits, a secondary mechanism of action includes an enhancement of uveoscleral outflow.

Investigational studies have demonstrated that topically administered brimonidine stimulates a peripheral alpha-2 adrenoceptor to lower IOP in rabbits. SKF 104078, the selective postjunctional alpha-2 receptor antagonist, did not block the ocular hypotensive effects of brimonidine in rabbits, suggesting that the vascular postjunctional alpha-2 adrenoceptor is not involved in the IOP response in this species. The data in monkeys suggest that the IOP and cardiovascular responses to brimonidine are mediated by an imidazoline receptor located in the central nervous system (CNS). The miotic response to brimonidine, which occurs in monkeys is mediated by an alpha-2 adrenoceptor.

When the action of brimonidine as a neuroprotective agent was evaluated in *in vitro* and *in vivo* pharmacological studies in rats, [14,15]no deleterious effects on the optic nerve were observed.

Human Pharmacology

Mechanism of Action

The effect of brimonidine on aqueous humour dynamics was determined in 21 ocular hypertensive patients. Measurements were made at baseline and following one week (Day 8) of twice daily application of one drop of brimonidine tartrate 0.2% to one eye and vehicle to the fellow eye, in a double-blind fashion. Aqueous flow (Fa, μL/min) and outflow capacity (C_{fl}, μL/min/mmHg) were determined using a fluorophotometric technique. Intraocular pressure (IOP, mmHg), tonographic

outflow facility (C_{ton}, μL/min/mmHg), and episcleral venous pressure (Pev, mmHg) were also measured. Uveoscleral outflow (μLmin) by fluorophotometry (Fu_{fl}) or tonography (Fu_{ton}) was calculated from C_{fl} or C_{ton} values, respectively.

The results of this study (mean±SEM) are reported in **Table 3**. They indicate that brimonidine reduces IOP in humans by decreasing aqueous inflow and increasing uveoscleral outflow.

Table 3: Effects of Brimonidine on Aqueous Humour Dynamics

	Control Eye		**Treated Eye**	
	Baseline	**Day 8**	**Baseline**	**Day 8**
IOP	21.3 ± 1.0	20.0±0.6*	20.6±0.8	15.9±0.6*†
Fa	2.6 ± 0.2	2.3±0.1*	2.5±0.2	2.0±0.1*
Fu_{fl}	0.35 ± 0.20	0.50±0.17	0.12±0.28	0.65±0.16*
Fu_{ton}	0.28 ± 0.31	0.08±0.35	0.25±0.37	1.02±0.11*†
C_{fl}	0.22±0.03	0.16±0.02*	0.22±0.03	0.21±0.03
C_{ton}	0.17±0.01	0.19±0.02	0.19±0.03	0.16±0.02
Pev	8.9±0.5	8.5±04	8.8±0.5	9.2±0.3

*p≤0.05 vs baseline
†p≤0.05 vs control

Pharmacodynamics

In short-term studies (up to four days) in normal healthy volunteers, brimonidine tartrate ophthalmic solution lowered IOP (intraocular pressure) significantly better than vehicle at concentration tested (0.02 to 0.5%) and was found to be safe and comfortable. At these concentrations, the peak effect on IOP was observed between one and four hours post-instillation. The greatest reduction in IOP was dose-related, reaching a maximal decrease from baseline of up to 40% with brimonidine tartrate 0.5%. In the morning (12 hours after the evening instillation), the 0.08 % and 0.2 % concentrations reached a maximal IOP lowering effect following two days of b.i.d dosing. This was observed with the 0.5% concentration, however, 12 hours after the first installation. Conjunctival blanching was observed primarily at the 0.35 % and 0.5% concentrations, and was generally mild or moderate in nature. There was a significantly greater incidence of dry eye seen only with bromonidine 0.5% as compared to vehicle, although this finding was also reported at the lower concentrations. The

overall mean decrease in pupil size and systolic blood pressure was generally greater with brimonidine 0.2% and 0.5% than with vehicle. This change in systolic blood pressure was not judged to be clinically significant. Heart rate, diastolic blood pressure, visual acuity and cup-disc ratio did not appear to be significantly affected by brimonidine treatment (as compared to vehicle). Additionally, at the concentrations tested in these healthy volunteer studies, a contralateral effect of brimonidine was not observed.

When evaluated in open-angle glaucoma and ocular hypertensive patients at concentrations of 0.08%, 0.2% for one month (b.i.d), brimonidine tartrate was found to be both efficacious and safe. All concentrations tested were significantly more effective than vehicle in lowering elevated IOP. The two higher concentrations of brimonidine tartrate were also more effective than the 0.08% concentration. Bromonidine tartrate 0.5%, however, was not any more effective that 0.2% for long-term treatment.

The peak effect on IOP occurred at two hours for brimonidine tartrate 0.08%,0.2%, and 0.5%. The greatest decrease in IOP was dose-related, with a maximum reduction of 27 % from baseline with brimonidine tartrate 0.2 %, and 31% from baseline with brimonidine tartrate 0.5%. Brimonidine tartrate 0.5% was associated with a greater incidence of side effects than brimonidine tartrate 0.2% and 0.08%, including blurring, foreign body sensations, fatigue and drowsiness.

Dry mouth was seen more often in all active treatment groups than in the vehicle group. This event was also seen at a higher incidence with brimonidine tartrate 0.5% than with brimonidine tartrate 0.08%. Although heart rate did not appear to be significantly affected by brimonidine treatment, diurnal measurements of blood pressure indicated that brimonidine tartrate 0.5% was associated with a greater decrease than was vehicle or the lower brimonidine strengths. The mean blood pressure decreases were not considered to be clinically significant.

Systemic Pharmacokinetics

Systemic absorption of brimonidine after ocular administration of a single dose (both eyes) of brimonidine tartrate 0.08%, 0.2% and 0.5% to healthy volunteers, produced dose-dependent

increases in C_{max} and AUC. AUC increased proportionally with dose between the 0.08% and 0.2% doses; the increase in AUC of the 0.5% dose was less than proportional with the increase in dose. Following the 0.5% dose, plasma C_{max} and $AUC_{0\infty}$ were approximately 0.1 ng/mL and 0.5 ng·hr/mL, respectively. The mean T_{max} was 2-3 hours for all concentrations tested in this study. In general, plasma concentrations declined to undetectable levels by 12 hours post-dose. The apparent plasma $T_{1/2}$ ranged from 2 to 5 hours (mean=3.3 hours).

Plasma concentration-time profiles were similar for both young and elderly healthy volunteers following ocular instillation of a single dose of brimonidine tartrate 0.2%, although the elderly subjects showed a tendency to have a slightly greater systemic exposure to brimonidine. Steady state concentrations were reached by day 7 of multiple dosing (both eyes, b.i.d) in young (23-39 years) subjects. Twice daily ocular dosing for 10 days did not change the systemic absorption and disposition parameters of brimonidine in young subjects. The mean C_{max} was 0.0585 ng/mL and mean AUC_{0-12} was 0.309 ng•hr/mL after multiple dosing. There was a slight systemic drug accumulation after repeated dosing (accumulation factor: 1.4), consistent with an apparent half-life of 3 hours. Beyond 12 hours after the final dose, plasma concentrations were undetectable or approached the limit of quantitation. Systolic and diastolic blood pressures were generally lowered by brimonidine tartrate administration. These decreases in blood pressure tended to be slightly greater among the elderly subjects than among the young subjects.

TOXICOLOGY

Acute Toxicity

The acute median lethal dose (LD_{50}) or minimum lethal dose (MLD) values of brimonidine were evaluated in mice, rats, rabbits, and dogs by oral and intravenous (i.v.) administration. The LD_{50} or MLD values for each study are listed below:

Species	***Route***	***LD_{50} (mg/kg)****	***MLD (mg/kg)****
Mouse	Oral i.v.*	50 50	>8** Not performed
Rat	Oral i.v.	100 100-150	>8** Not performed
Rabbit	Oral i.v.	Not performed Not performed	>6 20-50
Dog	Oral i.v.	Not performed Not performed	0.5 0.05

* The doses are expressed as the base except in the mouse and rat MLD data, where they are expressed as brimonidine tartrate.

** The data from additional single dose oral studies of 0.2% solutions of brimonidine tartrate in mice and rats showed that the oral MLD is greater than 10 mg/kg.

The most frequently observed clinical signs in the acute/single dose toxicity studies were primarily due to the exaggerated pharmacological hypotensive effect of the compound. These signs included: sedation, ataxia, prostration, ptosis, reduced/loss of blink reflex, opacification of the cornea, hypotension, bradycardia, hypothermia, respiratory depression, respiratory arrest and circulatory collapse. The ocular changes were seen only after doses at or above the minimum lethal dose.

Long-term Toxicity

Brimonidine was administered in repeated oral doses to mice (3 studies - 12 to 13 weeks), rats (6 studies 6 days to 1 year), dogs (2 studies - 4 to 14 weeks) and monkeys (2 studies - 1 year each). It was also administered ocularly to rabbits (2 studies - 1 and 6 months) and dogs (1 study - 4 weeks) and monkeys (1 study - 1 year). There were no observable adverse effects in oral dosing of mice at approximately 165 times the recommended ocular human dose, rats at approximately 80 times the

recommended ocular human dose, rabbits at approximately 25 times the recommended ocular human dose, dogs at approximately 55 times the recommended ocular human dose, and monkeys at 33 times the recommended ocular human dose. Dosage levels of approximately 330 times greater than those recommended for human ocular use showed toxic effects that were consistent with the pharmacological class of the compound.

Chronic oral dosing studies were performed at extreme levels of approximately 3000 times the recommended human ocular dose. At these extreme doses, mice showed goblet cell hyperplasia and depletion in the rectum and colon, hypertrophy of the tunica muscularis of small and large intestine, and hyperplasia of the non-glandular epithelium of the stomach. Rats dosed orally at approximately 1500 times the human ocular dose, showed thickening of muscularis mucosa of small intestine, and a dose related incidence of illeal intussusception was observed in all rats, but no associated lesions or morphological changes were observed. Evidence of toxicity characterised by decreased body weight gain and/or decreased food consumption was often seen at the higher oral doses in the mouse, rat and monkey. The most notable effects seen in the subacute studies was an exaggerated pharmacological effect characterised by sedation, ataxia, hypoactivity, ptosis, decreased muscle tone, hypotension and bradycardia.

There were no observable adverse effects in ocular dosing of rabbits up to approximately 120 times the recommended ocular human dose, dogs up to approximately 20 times the recommended ocular human dose, and monkeys up to approximately 40 times the recommended ocular human dose.

Carcinogenicity

There was no compound-related oncogenic effect observed in either mice or rats studies.

The maximal brimonidine plasma concentrations after oral administration of 2.5 mg base/kg/day to mice for 21 months correspond to approximately 77 times the human systemic exposure to brimonidine tartrate ophthalmic solution 0.2% instilled in each eye (one drop) twice daily for 10 days.

After two years of oral administration at 1.0 mg base/kg/day to rats, plasma concentrations were approximately 118 times greater than those seen in humans receiving one drop of brimonidine tartrate ophthalmic solution 0.2% in each eye b.i.d for 10 days.

There were no observable tumorigenic effects seen in mice or rats dosed at 2.5 mg base/kg/day (approximately 830 times the recommended human ocular dose), for up to 24 months.

Mutagenicity

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

Reproduction and Teratology

Reproductive toxicology studies conducted with brimonidine in rats and rabbits showed that brimonidine had no adverse effects on fertility and general reproductive performance, and showed no evidence of embryolethal or teratogenic activity at the dosages administered.

The mean maximal plasma brimonidine concentrations measured during the rat teratogenicity study (1.65 mg base/kg/day, orally) were approximately 333 times the human systemic exposure to brimonidine tartrate ophthalmic solution 0.2% instilled in each eye (one drop) twice daily for 10 days.

Mean maximal plasma brimonidine concentrations in the rabbit teratogenicity study (3.33 mg base/kg/day, orally) were approximately 24 times greater than plasma concentrations seen in humans receiving one drop of brimonidine tartrate ophthalmic solution 0.2% in each eye b.i.d for 10 days.

There were no treatment-related reproductive and teratological effects observed in the F1 rat pup group, although a reduction in body weight was observed at a dose level of 1.65 mg base/kg/day after 14 days. Dose related reduction in body weight gains were observed in rat dams at dose levels of 0.66 and 1.65 mg base/kg/day after 15 days.

In 1 rabbit study, body weight gain and food consumption in the low and mid-dose groups was comparable to the control group throughout the study. Spontaneous abortions occurred in 2 of 8 rabbits at the 3.3 mg base/kg/day level (gestation day 21 or 23), and may have been the result of the exaggerated pharmacological effects observed at this level. No abortions occurred at the 0.165 or 0.66 mg base/kg/day level. Maternal necropsy was generally unremarkable. There was no evidence of treatment-related embryotoxicity, fetal toxicity, or teratogenicity at dosage levels up to 3.3 mg base/kg/day (approximately 1100 times the recommended human ocular dose). In another study involving 20 rabbit dams, dosed orally up to 2.64 mg base/kg/day, no adverse effects were observed other than a decrease in weight gain during the dosing period, and no treatment related embryolethal or teratogenic effects were observed.

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