Drugs administered to lower the intraocular pressure (IOP) include those that work by decreasing production of aqueous humor (AH), increasing drainage, or a combination of those mechanisms.

**ADRENERGIC AGENTS**

**β-BLOCKERS**

Currently, this class includes non-selective (timolol, levobunolol, metipranolol, carteolol) and β₁-specific (betaxolol) agents. How blockade of the β-receptors of the ciliary body (CB) epithelium leads to ocular hypotensive effects of these drugs is not known. It is suspected that the tonic sympathetic stimulation, provided by norepinephrine, is inhibited through β-blockade, resulting in decreased activation of adenylate cyclase, inhibited production of cAMP in the CB, and ultimately decreased AH production. Alternatively, these drugs may inhibit Na⁺,K⁺-ATPase activity, or may act via a vasoactive mechanism. Regardless of the mechanism, β-blockers are effective antihypotensive agents when administered topically.

The most significant factors to consider in the use of topical β-blockers are their effects on the cardiovascular and pulmonary systems, both of which are heavily dependent upon adrenergic stimulation. Cardiac rate, rhythm, and force are controlled primarily by β₁-receptors, while pulmonary function is dependent upon β₂-receptors. The vasculature of both the cardiac and the pulmonary systems are innervated by a combination of β₁ and β₂ receptors however, making the relative effects of different drugs somewhat variable. Regardless, β-blockers should be administered with EXTREME CAUTION (or not at all) in patients with signs of β-blockade, particularly those with heart block, bradycardia, heart failure, asthma, chronic bronchitis, or other cardiopulmonary conditions. It is recommended that, when available, a lower concentration of drug should be used in cats or small dogs (i.e., <20 lbs).¹

An additional effect that may occur with topical β-blocker therapy relates to their membrane stabilizing activity. This action is similar to that of local anesthetics, and can in fact produce topical ocular anesthesia. Preparations approved for ophthalmic use experience little clinical effect from this ability, however superficial punctate keratitis or epitheliopathies have been reported in humans with chronic use.

**Timolol**

Timolol is a nonselective β-blocker supplied as 0.25 or 5% maleate salts, 0.25 or 0.5% hemihydrate salts, 0.47% potassium sorbate, or 0.25 or 5% gel-forming solutions.² The 0.25% and 5% solutions have comparable efficacy in humans, while the potassium sorbate formulation has increased lipophilicity, resulting in greater anterior chamber relative to plasma concentrations (and therefore potentially fewer systemic side effects).² Regardless of the formulation, timolol is very effective in humans with primary open angle glaucoma or ocular hypertension, and is often used on a once-daily dosing regimen, decreasing IOP from 17 – 48%.²,³

**Levobunolol**

Levobunolol is also a non-selective β-blocker, supplied as a 0.25% and 0.5% HCl salt. The clinical administration, efficacy, and side effects in humans are similar to those of timolol. A study comparing 0.5% levobunolol with 0.5% timolol – 2.0% dorzolamide in normal dogs found levobunolol to be less effective than the combination on a twice-daily dosing schedule.⁴

**Metipranolol**
Metipranolol is a non-selective β-blocker, available as 0.3% metipranolol HCl. Its clinical administration, efficacy, and side effects in humans are similar to those of timolol and levobunolol. No published evaluations of ophthalmic metipranolol in veterinary patients exist.

Carteolol
Carteolol is a non-selective β-blocker, supplied as 1.0% carteolol HCl. While its clinical administration, efficacy, and side effects are similar to those of the other non-selective β-blockers, it also possesses intrinsic sympathomimetic activity (ISA). ISA can be considered to be a ‘partial agonism’ for adrenoceptors, meaning that the drug has intrinsic ability to stimulate, rather than solely block, β-adrenoceptor activity. This may be advantageous in individuals with low sympathetic tone, as the ISA capability of a drug may limit bradycardia occurring secondary to β-blockade. The true clinical implications of ISA associated with topical ophthalmic β-blockers are unknown, however. Studies involving carteolol in veterinary ophthalmology have not been published.

Betaxolol
Betaxolol is a β1-selective antagonist, available as 0.25% betaxolol HCl. It’s β1-selectivity theoretically reduces its negative pulmonary effects, as β2 receptors predominate within pulmonary function, however its cardiac effects are similar to those of the other drugs listed. It may also protect retinal tissue from ischemic insults, in part by inhibiting glutamate-induced increases in intracellular calcium. A study utilizing 0.5% betaxolol twice daily as prophylaxis in the normotensive eye of dogs with unilateral glaucoma documented an increased duration of development of glaucoma in the normotensive eye of dogs receiving therapy relative to dogs not receiving prophylactic therapy (31 months versus 8 months, respectively).

α2-AGONISTS
The mechanism of IOP reduction produced by this class of drugs is most likely related to activation of both the presynaptic and postsynaptic α2-receptors, inducing a reduction in AH production (α2-receptors are inhibitory for adenylate cyclase, while β-receptors are stimulatory). Activation of the presynaptic (adrenergic nerve terminal) receptors inhibits the release of endogenous norepinephrine, blocking the tonic adrenergic stimulation of the CB epithelium. Activation of the postsynaptic receptors on the CB suppresses G-protein-related activation of adenylate cyclase, which decreases intracellular cAMP in the CB epithelium. While the initial cause of the IOP reduction is due to decreased AH production, these drugs also appear to increase uveoscleral outflow following more chronic use (i.e., days).

Apraclonidine
Apraclonidine is available as 0.5% or 1.0% apraclonidine HCl. It is used in humans primarily to achieve IOP reduction before and after surgical procedures for treatment of glaucoma, i.e., prior to filtering procedures or following anterior segment laser surgery. When administered three times daily over a period of 3 months, its efficacy in humans is comparable to that of 0.5% timolol, achieving a 30 – 40% reduction in IOP. The primary ocular side effects noted include conjunctival blanching, eyelid elevation, and mydriasis, associated with activation of α2-receptors. While its systemic side effects are relatively mild compared to those of the B-blockers, apraclonidine can induce sensation of a dry nose or mouth, as well as mild elevations in resting heart rate, blood pressure, and respiration. The main problem associated with the use of apraclonidine is its tendency to induce tachyphylaxis, or a decreased response, with chronic use. Ocular allergic reactions may also occur.

Brimonidine tartrate
Brimonidine tartrate, with a greater specificity for α2-receptors than that of apraclonidine, is available as 0.10%, 0.15%, and 0.25% solutions. It binds to melanin, which therefore serves as a slow-release reservoir for the drug. Brimonidine may also be neuroprotective to retinal ganglion cells and the optic nerve, however the extent of this effect clinically is not known. Although there is variation in efficacy relative to the
concentration and preservative of specific formulations of brimonidine, in humans, twice daily administration produces IOP reductions comparable to that of 0.5% timolol and 2.0% dorzolamide. It is additive with 0.5% timolol, as well as with latanoprost, reducing IOP by 3 mmHg more than what is achieved with latanoprost alone. When used as monotherapy, it is recommended that brimonidine be administered three times daily, while as part of combination therapy, twice daily administration is sufficient. Brimonidine also induces miosis, which may improve vision function under scotopic conditions in patients who have had refractive surgery and are suffering from glare, halos, or other night vision problems.

Ocular side effects are similar to those of apraclonidine, including stinging, hyperemia, and a foreign body sensation, along with allergic reactions. Systemic side effects include dry mouth, headache, and fatigue, as well as clinically insignificant alterations in heart rate and blood pressure.

**Epinephrine and Dipivefrin (dipivalyl epinephrine)**

Epinephrine is an α- and β-receptor agonist (norepinephrine is primarily α-receptor agonist), and dipivefrin is the more lipophilic prodrug of epinephrine. The increased lipophilicity allows greater penetration through the corneal epithelium into the stroma, where esterases convert dipivefrin to epinephrine. As with other α₂-agonists, epinephrine is believed to reduce AH production, primarily through vasoconstriction of CB vasculature, and to increase AH drainage, potentially through stimulation of cAMP production in the trabecular meshwork. While both drugs have reasonable efficacy in people (decrease IOP in glaucomatous patients by approximately 23%,⁷ the considerable local (burning, hyperemia, allergy, conjunctival and corneal pigmentation [adrenochrome deposits]) as well as systemic (tachycardia, faintness, palpitations) side effects have led both drugs to be largely replaced with the previously mentioned α₂-agonists.

It is surmised that immediate stimulation of post-synaptic β₂-adrenergic receptors leads to an increase in AH production, following which that pathway is desensitized (wang). Subsequently, activation of presynaptic α₂-adrenergic receptors, which reduce endogenous norepinephrine, decreases AH production, and thus IOP.⁸

**CHOLINERGIC AGONISTS (MIOTICS)**

The parasympathetic nervous system utilizes acetylcholine (ACh) as its pre- and post-synaptic neurotransmitter, stimulating either muscarinic (smooth muscle and glands) or nicotinic (skeletal muscle and autonomic ganglia) receptors. Following utilization by the post-synaptic nerve terminal, ACh is destroyed by acetylcholinesterase and recycled back to the presynaptic terminal. Drugs which stimulate the parasympathetic nervous system (parasympathomimetics) may be either direct-acting (stimulate cholinergic receptors at the postsynaptic junction directly by mimicking ACh) or indirect-acting (inhibit breakdown of ACh by acetylcholinesterase at the post-synaptic junction). Indirect-acting parasympathomimetics may in turn be carbamate inhibitors (bind acetylcholinesterase in a reversible manner) or organophosphorous inhibitors (irreversibly complex with the enzyme).

**Pilocarpine**

Pilocarpine is a direct-acting parasympathomimetic, available as a topical solution or gel in various concentrations, ranging from 0.25% to 10%, often with a low (and potentially quite irritating) pH of 4.5 to 5.5 (necessary for drug stability). Pilocarpine mimics the muscarinic (but not the nicotinic) action of ACh, resulting in contraction of intraocular smooth muscle, which is clinically apparent as miosis, ciliary body muscle spasm, and ocular hypotony. In humans, this reduction in IOP is proposed to occur when contraction of the longitudinal muscle fibers of the ciliary body alters the position of the scleral spur, which in turn widens the trabecular spaces and increases AH outflow. Owing to different ocular anatomy, the mechanism of action in canine patients is likely different as well, however canine ciliary body muscle has been documented to have cholinergic activity, indicating that drugs affecting the cholinergic system are likely to have some effect on AH outflow.⁹ An additional finding is the appearance of giant vacuoles in the endothelium of Schlemm’s canal, indicating increased AH uptake likely contributes to the decreased IOP. It should be noted that cholinergic agonists reduce uveoscleral outflow, making them potentially less effective in species that are heavily dependent upon uveoscleral outflow (i.e., horses).
In humans, pilocarpine is utilized in the management of primary open-angle glaucoma, acute angle-closure glaucoma, and many secondary glaucomas. It is generally administered four times daily (solution) or once daily (gel). Side effects may be significant however, potentially necessitating discontinuation of the drug. The ciliary body muscle accommodative spasm may last 2 – 3 hours following administration, with a less pronounced effect in older patients due to decreased contractile responses in general. Additionally, miosis is profound and may result in significantly decreased visual ability, particularly in patients with nuclear sclerosis or cataract. With long-term use, miosis may be irreversible due to both dilator muscle atrophy and sphincter muscle fibrosis. Pilocarpine may also induce angle-closure glaucoma, due to thickening of forward displacement of the lens associated with administration, or pupillary block glaucoma due to miosis. Systemic side effects may be attributable to the mechanism of pilocarpine, such as salivation, lacrimation, vomiting, and diarrhea. Bronchiolar spasm and pulmonary edema may also occur.

Carbachol
Carbachol, available as 0.75% to 3% solutions, is a direct-acting parasympathomimetic, which may also have indirect action by inhibition of acetylcholinesterase. It does not penetrate the intact epithelium, and when selected for topical administration (for which it is rarely used), must be combined with a surfactant to enhance its penetration. In humans, carbachol administered three times daily has been shown to be as effective as 2% pilocarpine administered four times daily, and produces more profound miosis. It also produces more severe headaches and accommodative muscle spasms, however.

Demecarium Bromide
Demecarium bromide, with limited to no commercial availability currently, may be compounded as a 0.125% or 0.25% solution. It is a long-acting carbamate inhibitor (reversible), which has been shown to decrease the IOP in normal human eyes by 3 to 11 mmHg within 24 hours, and in glaucomatous eyes by an average of 48%, in association with significant miosis. Its mechanism involves increasing the facility of outflow by an average of 121% in glaucomatous eyes. Side effects include ciliary body muscle spasm, producing a browache and blurred vision, as well as nausea, vomiting, diarrhea, salivation, sweating, and bradycardia.

Echthiophate (Phospholine)
Echthiophate is an organophosphate that irreversibly inhibits acetylcholinesterase. It is available in 0.03%, 0.125%, and 0.25% solutions. It increases the facility of outflow by an average of 127%, producing an IOP-lowering effect in glaucomatous human eyes, which is not additive (and is in fact potentially toxic) when administered in combination with pilocarpine. Systemic toxicity is potentially high with echthiophate, producing symptoms such as diarrhea, nausea, abdominal cramps, fatigue, and weakness.

CARBONIC ANHYDRASE INHIBITORS (CAI)
This class of medications includes both topical (dorzolamide, brinzolamide) and systemic (acetazolamide, methazolamide, dichlorphenamide) agents. Seven isoenzymes of carbonic anhydrase (CA) exist, with CA I, CA II, and CA III found within the cytosol, CA IV membrane-bound, CA V within mitochondria, and CA VI and CA VII within salivary glands. CA catalyzes step one in the conversion of carbon dioxide and water to carbonic acid and free hydrogen molecules. Bicarbonate ions and sodium cations are then transported into the posterior chamber, with water following due to the resulting osmotic gradient. CAIs are sulfonamide compounds with a preference for the sulfonamide-sensitive isoenzyme CA II, which is
the predominant form within human ciliary processes. Inhibition of this isoenzyme results in decreased production of AH, with the degree of reduction achieved varying among individual agents. As most tissues within the body have an excess of carbonic anhydrase relative to that necessary to maintain physiologic functions, at least 99% of enzyme activity must be inhibited to produce a clinical effect.

CAIs are indicated in the treatment of primary open-angle glaucoma and secondary glaucomas in humans. While systemically administered agents are useful in both the management of acute episode and maintenance therapy, their use has been largely supplanted by the development of topically administered agents.

**SYSTEMICALLY ADMINISTERED CAIs**

**Acetazolamide**

Acetazolamide is an orally-administered CAI, available as tablets (125 or 250 mg), sustained-release capsules (500 mg), and an injectable formulation (500 mg/vial). In humans, a significant reduction in IOP occurs within 2 hours following administration and is maintained for 6 to 24 hours, depending upon formulation, due to suppression of AH production by 24%. Acetazolamide is highly protein-bound in humans, which necessitates relatively large doses to result in sufficient levels of the unbound, un-ionized, active form of the drug – this in turn results in intolerable side effects in 30 to 80% of patients. A significant systemic side effect is metabolic acidosis, resulting from excessive urinary excretion of bicarbonate. Other systemic side effects include numbness and tingling of the fingers, toes, and perioral region; a metallic taste; fatigue, weight loss, depression, and anorexia; and gastrointestinal irritation. Potentially severe blood dyscrasias may also occur, including thrombocytopenia, agranulocytosis, and aplastic anemia. Transient myopia has also been reported, potentially due to CB edema producing a forward shift in the lens-iris diaphragm. Systemic CAIs are contraindicated in patients with preexisting renal dysfunction, patients taking potassium-depleting diuretics (CAIs lead to increased urinary potassium loss) or digitalis (hypokalemia increases the risk of digitalis toxicity), patients with liver disease or chronic obstructive pulmonary disease (inability to compensate for metabolic acidosis with increase ventilation), or those with preexisting hematologic disease.

**Methazolamide**

Methazolamide is available in 25 and 50 mg tablets. The molecular structure of methazolamide is modified relative to that of acetazolamide, conferring greater water and lipid solubility, and thus greater plasma half-life and concentrations, with lower protein-binding (55% versus 90-95% for acetazolamide). This allows lower doses to be administered to achieve similar clinical effect and results in less severe (but still potentially significant) systemic side effects.

**Dichlorphenamide**

Dichlorphenamide has variable availability in the United States, but has greater potency than acetazolamide, reducing AH formation by an average of 40%. In contrast to other CAIs, dichlorphenamide increases the renal excretion of chloride, in addition to sodium, potassium, and bicarbonate. This results in less frequent metabolic acidosis, however diuresis persists over the duration of therapy (the diuretic effect of other systemic CAIs generally decreases with prolonged use). It is rapidly absorbed following oral administration in humans, and results in a measurable IOP reduction within 30 minutes, which is maximal at 2 – 4 hours and persists for 6 to 12 hours.

**TOPICALLY ADMINISTERED CAIs**

**Dorzolamide**

Dorzolamide 2.0% was the first effective topical CAI introduced. It has a pH of 5.6 and contains the preservative BAC (0.0075%). Its molecular structure allows it to alternate between acidic and basic forms, which increases both its lipid and water solubility and enables greater corneal and scleral penetration. While its major mechanism of action is believed to be inhibition of CA II isoenzyme, it also inhibits the membrane-bound form CA IV, which may also play a role in its IOP-reducing ability. It is generally administered every 8 to 12 hours, resulting in an IOP reduction of 22-26% in humans. The maximal effect is achieved 2 hours following
administration, and residual effect from twice-daily dosing may effectively decrease IOP over a 24-hour period, however three-times daily dosing is generally recommended. No additive effect is achieved with topical dorzolamide and oral acetazolamide in humans, therefore combined use is not indicated in the management of glaucoma.

Ocular side effects related to irritation and discomfort may occur in association with the relatively low pH of dorzolamide. Additionally, superficial punctate keratitis or local hypersensitivity reactions may occur. Dorzolamide also inhibits CA II in the corneal endothelium, posing a threat of endothelial cell dysfunction manifesting as corneal edema, however this risk appears to be minimal unless a patient has preexisting endothelial cell compromise. Systemic side effects are generally not appreciated with topical administration.

**Brinzolamide**

Brinzolamide is available as a 1% solution with a pH of 7.5 and BAC 0.01% added as a preservative. It is reported to cause less ocular discomfort than dorzolamide (3% versus 16.4% of patients, respectively), although complaints of blurred vision are greater with brinzolamide (5 – 6% prevalence). It has high affinity for the CA II isoenzyme, allowing it to be dosed on a twice-daily schedule in humans, with efficacy comparable to three-times daily dorzolamide and slightly less than twice-daily timolol.

**PROSTAGLANDIN ANALOGUES**

The prostaglandins (PG) are a class of inflammatory mediators, with chemically modified versions of the endogenous PG, PGF$_{2\alpha}$, developed for use as ocular hypotensive agents. The chemical modifications create prodrug forms with improved lipid solubility, and therefore epithelial penetration. Passage through the epithelium exposes the prodrug to corneal esterases, which hydrolyze the agent to its active form for delivery into the eye, with the major active metabolite depending on the drug administered -- 17-phenyl-PGF$_{2\alpha}$ for latanoprost, bimatoprost, travoprost, or a free acid of isopropyl unoprostone for unoprostone.

The active metabolite of each drug has IOP-lowering effects via action on prostanoid FP receptors, which are known to be present in humans and monkeys, and are presumed to be present in dogs. Exact cellular localization has not been determined, however they have been identified in ciliary and iris sphincter muscles and in trabecular meshwork cells of humans. Action on the FP receptors increases uveoscleral outflow through extensive remodeling of the ciliary muscle extracellular matrix. Such remodeling is believed to be due to increased levels of matrix metalloproteinases degrading the collagen within the extracellular matrix, thus reducing the resistance to outflow. It is possible that conventional (pressure-dependent) outflow is also increased with long-term FP receptor activation through similar remodeling of the trabecular meshwork. Additionally, suppression of AH formation has been suggested due to a reduction in the AH flow rate in following administration of latanoprost, however this has not been supported in other studies.

**Latanoprost**

Latanoprost is available as a 0.005% solution with 0.02% BAC as a preservative, used for once-daily dosing. Greater long-term control of IOP in humans is achieved with once-daily latanoprost versus twice-daily 0.5% timolol (30% IOP reduction versus 20%, respectively). These IOP-lowering effects are more consistent throughout diurnal variation (versus β-blockers, which have greater efficacy during the day), with greatest effect in the 12- to 24-hours following administration. For these reasons, latanoprost is generally administered once daily in the evenings, to provide greater IOP control during the subsequent day. Twice daily dosing appears to provide less consistent control of IOP, and long-term administration does not appear to induce tolerance with consequent loss of effect. Although monotherapy with latanoprost is advocated, when it is administered as part of combination therapy, the effect is additive due to the unique mechanism of action of PG analogues.

Side effects noted in people include irreversible darkening of the iris in individuals with mixed-color irises (due to increased melanin within existing melanocytes), increased eyelid pigmentation (reversible), hypertrichosis, conjunctival hyperemia, allergy, cystoid macular edema, anterior uveitis, or punctate corneal erosions. Contraindications include a history of uveitis or a predisposition to cystoid macular edema or herpes virus keratitis.
**Travoprost**
Travoprost is a PGF$_{2\alpha}$ analogue available as a 0.004% solution in 0.015% BAC as a preservative, as well as a BAC-free formulation with zinc, sorbitol, and borate buffers meant to provide the preservative activity without the toxic epithelial effects commonly noted with BAC-containing solutions. This BAC-free formulation has demonstrated identical efficacy with the BAC-containing solution in humans. As with latanoprost, travoprost is dosed once daily and produces mean IOP reductions of 7-8 mmHg. Similar ocular side effects as occur with latanoprost may occur with travoprost.

**Bimatoprost**
Although grouped in the PG-analogue drug class, bimatoprost is actually a synthetic prostamide. Whereas endogenous PGs are derived from arachidonic acid through the actions of COX-1 and COX-2, prostamides are derived from anandamide, a fatty acid precursor. They do not interact, or interact only weakly, with PG receptors, and therefore their true mechanism of action remains unknown. Bimatoprost is available as a 0.03% buffered solution with a pH of 6.8 to 7.8. While it does contain BAC, its concentration is lower (0.005%) than that of travoprost, and therefore may cause less ocular discomfort. Compared to twice daily timolol, which reduced IOP in glaucomatous humans by 23%, bimatoprost reduced IOP by 33%, indicating comparable efficacy to that achieved with latanoprost and travoprost, with similar side effects reported.

**Unoprostone Isopropyl**
Unoprostone isopropyl is a PG analogue, available as 0.15% solution which is no longer commercially available in the US. Its active metabolite is a free acid of isopropyl unoprostone (versus 17-phenyl-PGF$_{2\alpha}$ for the other PG-analogues).

**OSMOTIC AGENTS**
Osmotic (or hyperosmotic) agents increase the osmotic pressure of the plasma to levels greater than those of the aqueous or vitreous, creating an osmotic gradient in which the plasma is hypertonic to the intraocular environment. This gradient both decreases the ultrafiltration component of AH formation and draws water from the vitreous humor, ultimately decreasing the intraocular fluid volume and thus, IOP. Additionally, reduction in the volume of the vitreous creates a posterior shift in the iris-lens diaphragm, which in turn opens the ICA and allows better drainage of AH. For an osmotic agent to be effective at reducing the IOP, it should be nontoxic, have a low molecular weight, and have relatively poor intraocular penetration. If these conditions are not met, or if intraocular inflammation allows entrance of constituents within the plasma into the eye, IOP may actually increase. These agents are frequently administered in concert with temporary water deprivation (i.e., 4-6 hours), to maintain a lower extracellular fluid volume with greater hypertonicity, and thus potentially greater clinical effect. It should be emphasized that these agents are only indicated for the management of acute congestive glaucoma, not for maintenance therapy. Also, considering the efficacy and availability of topically administered antiglaucoma medications, use of osmotic agents is less common.

**Mannitol**
Mannitol is a six-carbon sugar for IV administration, with a 20% solution most commonly employed in ophthalmology. It is a large molecule that concentrates within extracellular fluid compartments, rather than diffusing throughout total body water, and therefore imparts beneficial clinical effect. It is minimally metabolized and is excreted by the kidneys, with 80% excretion within 3 hours associated with marked diuresis. Its IOP-lowering effect in humans occurs within 30 to 60 minutes of administration and may persist for 6 hours.

**Glycerin/Glycerol**
Glycerin is a trihydric alcohol which is rapidly absorbed following oral administration. In humans, it produces a reduction in IOP within 10 minutes which is maximum at 30 minutes, and persists for 5 hours. The magnitude of the IOP reduction is less than that achieved with mannitol. It is metabolized to glucose, and thus may produce hyperglycemia and glucosuria.
**Isosorbide**

Isosorbide is a dihydric alcohol for oral administration and does not produce hyperglycemia or glucosuria. Administration of 1.5 to 2 g/kg results in IOP reduction in humans, however this drug has not been evaluated in veterinary ophthalmology.

**References**