PDR®

52 EDITION

1998

PHYSICIANS' DESK REFERENCE®

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Printed on recycled paper

ISBN: 1-56363-251-9

Store at controlled room temperature 15–30°C (59–86°F) with protection from light. CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
U.S. Patent Nos. 4,089,969; 4,454,151; 5,110,493
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ALLERGAN

Irvine, CA 92612

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ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

DESCRIPTION
ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white, pale yellow to pale pink powder. In solution, ALPHAGAN® has a clear, greenish-yellow color. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL). The molecular formula is $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$.
ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% is a sterile ophthalmic solution. Each mL of ALPHAGAN® Solution contains:
ACTIVE: brimonidine tartrate 2 mg (equivalent to 1.32 mg as brimonidine free base).
PRESERVATIVE: benzalkonium chloride (0.05 mg)
INACTIVES: polyvinyl alcohol; sodium chloride; sodium citrate; citric acid; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.3–6.5).

CLINICAL PHARMACOLOGY
Mechanism of Action
ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.
Pharmacokinetics
After ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 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 with 120 hours, with 74% found in the urine.
Clinical Studies
Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. ALPHAGAN® has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.
In comparative clinical studies with timolol 0.5%, lasting up to one year, the IOP lowering effect of ALPHAGAN® was approximately 4–6 mm Hg compared with approximately 6 mm Hg for timolol. In these studies, both patient groups were dosed BID, however, due to the duration of action of ALPHAGAN®, it is recommended that ALPHAGAN® be dosed TID. Eight percent of the subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

INDICATIONS AND USAGE
ALPHAGAN® is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of ALPHAGAN® Ophthalmic Solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS
ALPHAGAN® 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.

PRECAUTIONS
General: Although ALPHAGAN® had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.
ALPHAGAN® has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.
ALPHAGAN® should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.
During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with ALPHAGAN® Ophthalmic Solution during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication be routinely monitored for IOP.
Information for Patients: The preservative in ALPHAGAN®, 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 ALPHAGAN® to insert soft contact lenses.
As with other drugs in this class, ALPHAGAN® may 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.
Drug Interactions: Although specific drug interaction studies have not been conducted with ALPHAGAN®, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbituates, opiates, sedatives, or anesthetics) should be considered. ALPHAGAN® did not have significant effects on pulse and blood pressure in clinical studies. However, since alpha-agonists, as a class, may reduce pulse and blood pressure, caution in using concomitant drugs such as beta-blockers (ophthalmic and 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 ALPHAGAN® can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after ALPHAGAN® is instilled are available. 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/kg/day (as the free base) and 1.0 mg/kg/day, respectively (~77 and 118 times, respectively, the human plasma drug concentration following the recommended ophthalmic dose).
ALPHAGAN® 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.
Pregnancy: Teratogenic Effects: Pregnancy Category B.
Reproduction 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 ALPHAGAN®. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.
There are no studies of ALPHAGAN® in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ALPHAGAN® 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 ALPHAGAN® is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Adverse events occurring in approximately 10–30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.
Events occurring in approximately 3–9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.
The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations, nasal dryness and syncope.

OVERDOSAGE
No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION
The recommended dose is one drop of ALPHAGAN® in the affected eye(s) three times daily, approximately 8 hours apart.

HOW SUPPLIED
ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% is supplied sterile in white opaque plastic dropper bottles as follows:
5 mL NDC 0023-8665-05
10 mL NDC 0023-8665-10
15 mL NDC 0023-8665-15
NOTE: Store at or below 25° C (77° F).
CAUTION: Federal (U.S.A.) law prohobits dispensing without prescription.
ALLERGAN

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AZELEX®
(azelaic acid cream) 20%
For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION
AZELEX® (azelaic acid cream) 20% contains azelaic acid, a naturally occurring saturated dicarboxylic acid.
Structural Formula: $HOOC-(CH_2)_7-COOH$. Chemical Name: 1,7-heptanedicarboxylic acid. Empirical Formula: $C_9H_{16}O_4$. Molecular Weight: 188.22.
Active Ingredient: Each gram of AZELEX® contains azelaic acid ..... 0.2 gm (20% w/w).
Inactive Ingredients: cetearyl octanoate, glycerin, glyceryl stearate and cetearyl alcohol and cetyl palmitate and cocoglycerides, PEG-5 glyceryl stearate, propylene glycol and purified water. Benzoic acid is present as a preservative.

CLINICAL PHARMACOLOGY
The exact mechanism of action of azelaic acid is not known. The following *in vitro* data are available, but their clinical significance is unknown. Azelaic acid has been shown to possess antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. The antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis.
A normalization of keratinization leading to an anticomedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohistochemical evaluation of skin biopsies from human subjects treated with AZELEX® demonstrated a reduction in the thickness of the stratum corneum, a reduction in number and size of keratohyalin granules, and a reduction in the amount and distribution of filaggrin (a protein component of keratohyalin) in epidermal layers. This is suggestive of the ability to decrease microcomedo formation.
Pharmacokinetics: Following a single application of AZELEX® to human skin *in vitro*, azelaic acid penetrates into the stratum corneum (approximately 3 to 5% of the applied dose) and other viable skin layers (up to 10% of the dose is found in the epidermis and dermis). Negligible cutaneous metabolism occurs after topical application. Approximately 4% of the topically applied azelaic acid is systemically absorbed. Azelaic acid is mainly excreted unchanged in the urine but undergoes some β-oxidation to shorter chain dicarboxylic acids. The observed half-lives in healthy subjects are approximately 45 minutes after oral dosing and 12 hours after topical dosing, indicating percutaneous absorption rate-limited kinetics.
Azelaic acid is a dietary constituent (whole grain cereals and animal products), and can be formed endogenously from longer-chain dicarboxylic acids, metabolism of oleic acid, and ω-oxidation of monocarboxylic acids. Endogenous plasma concentration (20 to 80 ng/mL) and daily urinary excretion (4 to 28 mg) of azelaic acid are highly dependent on dietary intake. After topical treatment with AZELEX® in humans, plasma concentration and urinary excretion of azelaic acid are not significantly different from baseline levels.

INDICATIONS AND USAGE
AZELEX® is indicated for the topical treatment of mild-to-moderate inflammatory acne vulgaris.

CONTRAINDICATIONS
AZELEX® is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS
AZELEX® is for dermatologic use only and not for ophthalmic use.

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