

PRODUCT MONOGRAPH

Pr EMADINE®
Emedastine Difumarate Ophthalmic Solution
(0.05% as emedastine)

THERAPEUTIC CLASSIFICATION:
Anti-allergy Agent

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Emedastine Difumarate Ophthalmic Solution

(0.05% as emedastine)

THERAPEUTIC CLASSIFICATION:

Anti-allergy Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Emedastine is a potent, selective, and topically effective histamine H1 antagonist with a rapid onset of action. *In vitro* and *in vivo* examinations of emedastine's affinity for histamine receptors (H1, H2 and H3) demonstrate 10,000 fold selectivity for the H1 histamine receptor and concentration-dependent inhibition of histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. Emedastine is devoid of effects on adrenergic, dopaminergic and serotonin receptors.

As with other topically administered drugs, emedastine is absorbed systemically. In a study involving 10 normal volunteers dosed bilaterally twice daily for 15 days with Emedastine Ophthalmic Solution 0.05%, plasma concentrations of the parent compound were generally below the quantitation limit of the assay (<0.3 ng/mL). Samples in which emedastine was quantifiable ranged from 0.30 to 0.49 ng/mL. These plasma concentrations are at least 10-fold lower than those observed with well-tolerated multiple-dose oral regimens. The human oral bioavailability of emedastine is approximately 50% and maximum plasma concentrations are achieved within 1-2 hours post-dose. The elimination half-life of oral emedastine in plasma is 3-4 hours. Approximately 44% of the oral dose is recovered in the urine over 24 hours with only 3.6% of the dose excreted as parent drug. Two primary metabolites, 5- and 6-hydroxyemedastine, are excreted in the urine as both free and conjugated forms. The 5'-oxo analogs of 5- and 6-hydroxyemedastine and the N-oxide are also formed as minor metabolites.

INDICATIONS AND USAGE

EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) is indicated for the relief within minutes of the signs and symptoms of allergic conjunctivitis.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

WARNINGS

For topical use only. Not for injection. Patients should be instructed not to instill EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) while wearing contact lenses, but to wait 10 minutes after instillation before inserting contact lenses.

PRECAUTIONS

Information for Patients: To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Emedastine Difumarate demonstrated no carcinogenicity effects in lifetime studies in mice and rats at dietary doses up to 35,000 and 11,000 times the maximum recommended ocular human dose level, respectively. Higher dose levels were not tested. Emedastine Difumarate was determined to be nonmutagenic in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* modification of the Ames test, an *in vitro* mammalian chromosome aberration test, an *in vitro* mammalian forward mutation test, an *in vitro* mammalian DNA repair synthesis test, an *in vivo* mammalian sister chromatid exchange test and an *in vivo* mouse micronucleus test. There was no evidence of impaired fertility or reproductive capacity in rats at 6200 times the maximum recommended ocular human use level.

Pregnancy: Teratology and peri and post natal studies have been conducted with Emedastine Difumarate in rats and rabbits. At 6200 times the maximum recommended ocular human use level, Emedastine Difumarate was shown not to be teratogenic in rats and rabbits and no effects on peri/postnatal development were observed in rats. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers: Emedastine has been identified in breast milk in rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients between the ages of 3 and 16 have been established.

ADVERSE REACTIONS

In clinical studies of EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution), mild transient ocular discomfort (burning or stinging) was reported at an incidence of 2.5% and pruritis at 1.2%.

All other ocular and nonocular adverse reactions related to therapy were reported at an incidence equal to or less than 1.0%.

Ocular: hyperemia, dry eye, corneal staining, eye fatigue, foreign body sensation, blurred vision, tearing, infiltrate, irritation.

Nonocular: headache, asthenia, abnormal dreams, dermatitis, taste perversion.

SYMPTOMS AND TREATMENT OF OVERDOSE

A topical overdosage may be flushed from the eye(s) with warm tap water.

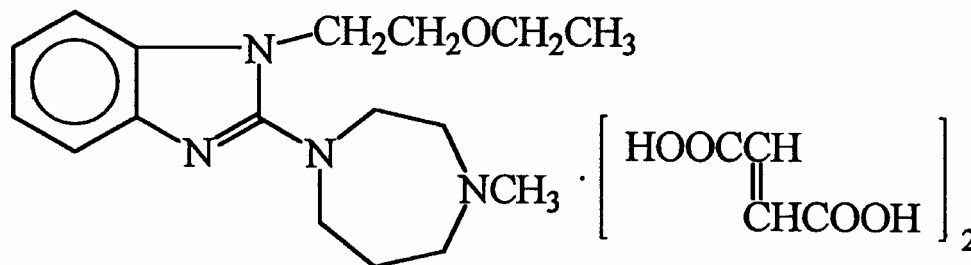
DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye twice daily. The dose may be increased to 1 drop 3 or 4 times daily.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Emedastine difumarate
 Chemical Name: 1H-Benzimidazole,1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl), (E)-2-butenedioate (1:2)
 Structural Formula:



Molecular Formula: $C_{25}H_{34}N_4O_9$
 Molecular Weight: 534.57
 Description: White, to faintly yellowish crystalline powder. Not hygroscopic.
 Solubility: Freely soluble in water, soluble in methanol, slightly soluble in acetone and very slightly soluble in diethyl ether.
 pH: Approx 3.6 (0.2% aqueous solution)
 pKa: pKa1 = 4.51; pKa2 = 8.48
 Melting Point: Approx 150°C
 Polymorphism: Two polymorphs have been identified by melting point, differential thermal analysis, and X-ray powder diffraction analyses. The polymorphs are easily distinguished by melting point: Polymorph I melts at about 139°C, Polymorph II at about 150°C. There was no difference in solubility due to the difference in crystal forms (both rapidly dissolved in water). Polymorph II is the more stable polymorph and is used for this drug product.

Composition: EMADINE 0.05% (Emedastine Difumarate) Ophthalmic Solution is a sterile ophthalmic solution containing emedastine, a potent, selective H₁-receptor antagonist for topical administration to the eyes.

Each mL of EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) contains:

Active: 0.884 mg emedastine difumarate equivalent to 0.5 mg emedastine.

Preservative: benzalkonium chloride 0.01%.

Inactives: Tromethamine, sodium chloride; hydroxypropyl methylcellulose; hydrochloric acid and/or sodium hydroxide (adjust pH); and purified water.

Stability & Storage Recommendations: Store at 4° - 30°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

Pr EMADINE® (Emedastine Difumarate) Ophthalmic Solution is available in plastic DROP-TAINER® dispensers containing 5 mL, 10 mL or 15 mL.

CLINICAL PHARMACOLOGY

Emedastine is a potent, selective, and topically effective histamine H1 antagonist with a rapid onset of action. *In vitro* and *in vivo* examinations of emedastine's affinity for histamine receptors (H1, H2 and H3) demonstrate 10,000 fold selectivity for the H1 histamine receptor and concentration-dependent inhibition of histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. Emedastine is devoid of effects on adrenergic, dopaminergic and serotonin receptors.

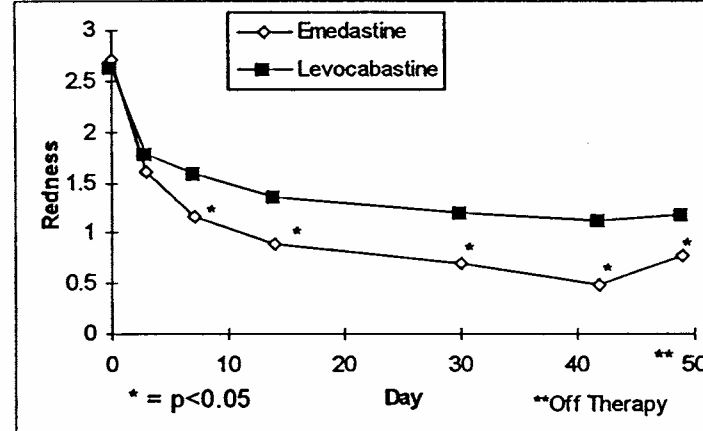
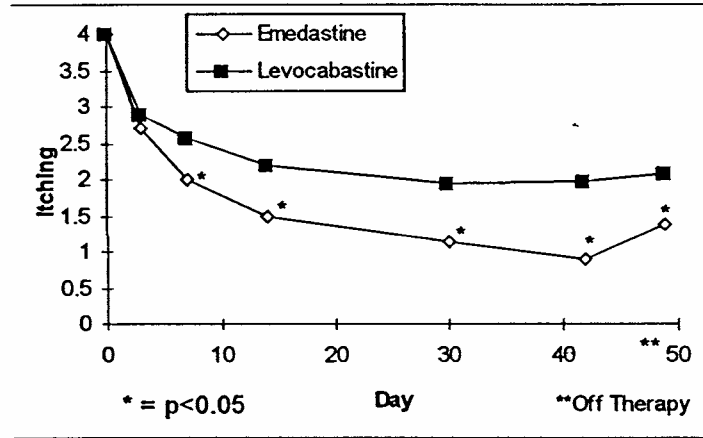
As with other topically administered drugs, emedastine is absorbed systemically. In a study involving 10 normal volunteers dosed bilaterally twice daily for 15 days with Emedastine Ophthalmic Solution 0.05%, plasma concentrations of the parent compound were generally below the quantitation limit of the assay (<0.3 ng/mL). Samples in which emedastine was quantifiable ranged from 0.30 to 0.49 ng/mL. These plasma concentrations are at least 10-fold lower than those observed with well-tolerated multiple-dose oral regimens. The human oral bioavailability of emedastine is approximately 50% and maximum plasma concentrations are achieved within 1-2 hours post-dose. The elimination half-life of oral emedastine in plasma is 3-4 hours. Approximately 44% of the oral dose is recovered in the urine over 24 hours with only 3.6% of the dose excreted as parent drug. Two primary metabolites, 5- and 6-hydroxyemedastine, are excreted in the urine as both free and conjugated forms. The 5'-oxo analogs of 5- and 6-hydroxyemedastine and the N-oxide are also formed as minor metabolites.

Results from conjunctival antigen challenge studies demonstrate that EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) when challenged with antigen both initially and up to four hours after dosing was significantly more effective than placebo in preventing ocular itching and redness associated with allergic conjunctivitis. In a placebo-controlled clinical study designed to evaluate safety, EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) administered four times a day for six weeks was shown to be safe and well-tolerated in subjects who were ages 3 years and older. In well controlled clinical studies, EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) produced significantly less ocular discomfort (burning and stinging) compared to Acular® (ketorolac tromethamine) 0.5% Sterile Ophthalmic Solution.

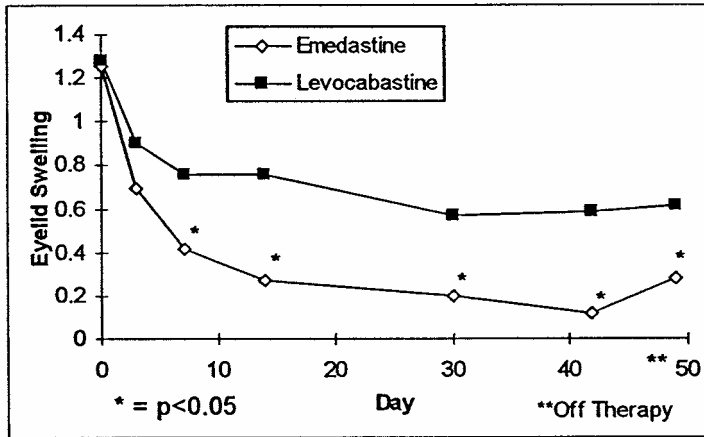
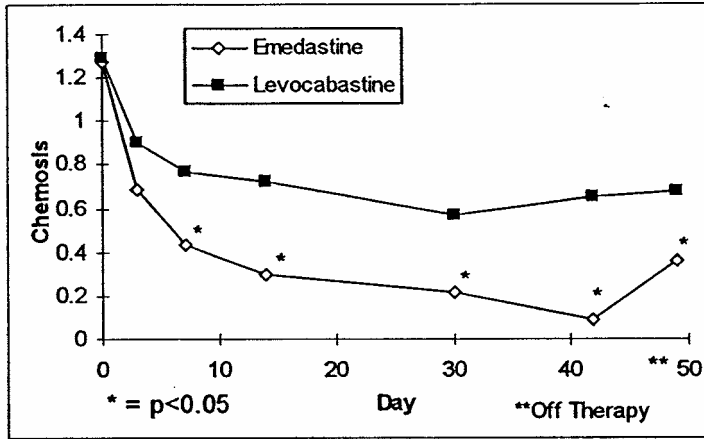
In a conjunctival antigen challenge study comparing EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) to LIVOSTIN™ 0.05% (Levocabastine Hydrochloride Ophthalmic Suspension), EMADINE 0.05% (Emedastine Difumarate Ophthalmic Solution) was superior to LIVOSTIN 0.05% (Levocabastine Hydrochloride Ophthalmic Suspension) in preventing the ocular itching and equivalent to LIVOSTIN 0.05% (Levocabastine Hydrochloride Ophthalmic Suspension) in preventing the ocular redness associated with allergic conjunctivitis.

In a six week, multicenter study (Protocol C-95-54; N=221), in the treatment of allergic conjunctivitis, patients were randomized to receive either EMADINE (Emedastine Difumarate) 0.05% Ophthalmic Solution or LIVOSTIN (Levocabastine) 0.05% Ophthalmic Suspension twice per day. Using a grading score from 0 to 4, the patients' eyes were graded by the physician, during office visits at days 3, 7, 14, 30, 42 following commencement of therapy. By Day 7 and through to Day 42, EMADINE solution was significantly more effective in alleviating the signs and symptoms of allergic conjunctivitis: redness, itching, chemosis, and eyelid swelling (see graphs). EMADINE solution produced progressive improvement in the ocular signs and symptoms over the 6 week treatment period.

Protocol C-95-54: Six Week Environmental Study (N=221)
Office Visit Scores - Ocular Itching and Redness



**Protocol C-95-54: Six Week Environmental Study
Office Visit - Chemosis and Eyelid Swelling**



TOXICOLOGY

The acute toxicity of emedastine difumarate has been investigated in mice, rats and dogs. Mice and rats demonstrated that emedastine difumarate was not an acute toxicity hazard with oral LD₅₀ values greater than 650 mg/kg, however, dogs were more sensitive to the toxic effects with an oral LD₅₀ value of 193 mg/kg. These levels are more than 14,000 times the maximum recommended ocular human use level of 2 drops per eye, QID.

Subchronic and chronic oral toxicity studies in rats and dogs demonstrated that emedastine difumarate has a low order of toxicity. Hepatocellular hypertrophy was the most common finding with some prostate gland toxicity being noted at higher doses in the studies. The prostate atrophy and decrease in prostate weight were observed in both rats and dogs, however attempts to repeat the effect in a second chronic dog study were unsuccessful. No effects were noted on LH, FSH, prolactin, or testosterone levels. Ocular evaluations were not remarkable. A no-effect level in rats was determined to be 10 mg/kg and a no adverse-effect level in dogs was 15 mg/kg, which are at least 2,000 and 3,000 times the maximum recommended ocular human use level, respectively.

Two topical ocular studies in rabbits of three-months and six-months duration have been completed. Rabbits were dosed QID with either 0.1%, 0.3%, or 1.0% Emedastine Difumarate Ophthalmic Solution, 330 times the maximum recommended ocular human use level. No signs of pharmacotoxicity were noted during the study periods. Slit-lamp and indirect ocular evaluations revealed no treatment-related findings and no gross lesions were noted at necropsy. Histopathologic evaluations for both studies demonstrated that emedastine difumarate treatment did not result in any treatment-related lesions.

Carcinogenesis: Emedastine Difumarate demonstrated no carcinogenicity effects in lifetime studies in mice and rats at dietary doses up to 35,000 and 11,000 times the maximum recommended ocular human dose level, respectively. Higher dose levels were not tested.

Mutagenesis: Emedastine Difumarate was determined to be nonmutagenic in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* modification of the Ames test, an *in vitro* mammalian chromosome aberration test, an *in vitro* mammalian forward mutation test, an *in vitro* mammalian DNA repair synthesis test, an *in vivo* mammalian sister chromatid exchange test and an *in vivo* mouse micronucleus test.

Reproduction & Teratology: There was no evidence of impaired fertility or reproductive capacity in rats at 6200 times the maximum recommended ocular human use level. Teratology and peri and post natal studies have been conducted with Emedastine Difumarate in rats and rabbits. At 6200 times the maximum recommended ocular human use level, Emedastine Difumarate was shown not to be teratogenic in rats and rabbits and no effects on peri/postnatal development were observed in rats.

BIBLIOGRAPHY

1. Lowry, GM, Abelson M, Rubin JM. Emedastine Ophthalmic Solution alleviates ocular itching and redness associated with allergic conjunctivitis. Invest Ophthalmol Vis Sci 37(3): S593, 1996.
2. Sharif, N. A., Xu, S.X., Yanni, J.M. Emedastine: A potent, high affinity histamine H₁-receptor-selective antagonist for ocular use: Receptor binding and second messenger studies. J Ocular Pharmacol 10 (4): 653-664, 1994a.
3. Sharif, N. A., Xu, S., Yanni, J.M. Histamine receptor-subtype affinities, selectivities, and potencies of emedastine, a novel H₁-selective antagonist, and other ocularly employed antihistamines. Drug Devel Res 33:448-453, 1994b.
4. Yanni, J. M., Stephens, D. J., Parnell, D. W., Spellman, J. M. Preclinical efficacy of emedastine, a potent, selective histamine H₁ antagonist for topical ocular use. J Ocular Pharmacol 10 (4): 665-675, 1994.