

NDA 20-706/S-011

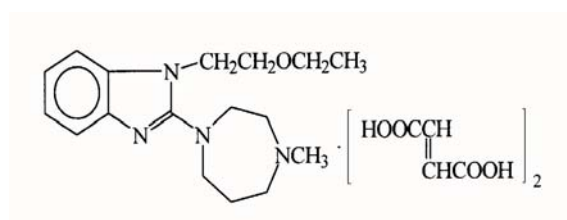
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EMADINE[®]
(emedastine difumarate ophthalmic solution) 0.05%

DESCRIPTION

EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% is a sterile ophthalmic solution containing emedastine, a relatively selective, H₁-receptor antagonist for topical administration to the eyes. Emedastine difumarate is a white, crystalline, water-soluble fine powder with a molecular weight of 534.57. The chemical structure is presented below:

Structural Formula:



Chemical Name:

1H-Benzimidazole, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl),
(E)-2-butenedioate (1:2)

Each mL of EMADINE 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/sodium hydroxide (adjust pH); and purified water. It has a pH of approximately 7.4 and an osmolality of approximately 300 mOsm/kg.

CLINICAL PHARMACOLOGY

Emedastine is a relatively selective, histamine H₁ antagonist. *In vitro* examinations of emedastine's affinity for histamine receptors (H₁: K_i=1.3 nM, H₂: K_i=49,067 nM, and H₃: K_i=12,430 nM) demonstrate relative selectivity for the H₁ histamine receptor. *In vivo* studies have shown concentration-dependent inhibition of histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. Emedastine appears to be devoid of effects on adrenergic, dopaminergic and serotonin receptors.

Following topical administration in man, emedastine was shown to have low systemic exposure. 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. 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.

In an environmental study, patients with allergic conjunctivitis were treated with EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% for six weeks. The results demonstrated that EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% provides relief of the signs and symptoms of allergic conjunctivitis.

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In conjunctival antigen challenge studies in which subjects were challenged with antigen both initially and up to four hours after dosing, EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% was demonstrated to be significantly more effective than placebo in preventing ocular itching associated with allergic conjunctivitis

INDICATIONS AND USAGE

EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% is indicated for the temporary relief of the signs and symptoms of allergic conjunctivitis.

CONTRAINDICATIONS

EMADINE[®] is contraindicated in persons with a known hypersensitivity to emedastine difumarate or any of EMADINE's components.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY-NOT FOR INJECTION OR ORAL USE.

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. Do not use if the solution has become discolored.

Patients should be advised not to wear a contact lens if their eye is red. EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% should not be used to treat contact lens related irritation. The preservative in EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05%, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red**, should be instructed to wait at least ten minutes after instilling EMADINE[®] (emedastine difumarate ophthalmic solution) 0.05% before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Emedastine difumarate demonstrated no carcinogenicity effects in lifetime studies in mice and rats at dietary doses more than 80,000 times and more than 26,000 times the maximum recommended ocular human use level of 0.002 mg/kg/day for a 50 kg adult, 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 15,000 times the maximum recommended ocular human use level.

Pregnancy: Pregnancy Category B.

Teratology and peri- and post-natal studies have been conducted with emedastine difumarate in rats and rabbits. At 15,000 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/post-natal 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 response, this drug should be used during pregnancy only if clearly needed.

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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 is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

In controlled clinical studies of EMADINE lasting for 42 days, the most frequent adverse reaction was headache (11%). The following adverse experiences were reported in less than 5% of patients: Abnormal dreams, asthenia, bad taste, blurred vision, burning or stinging, corneal infiltrates, corneal staining, dermatitis, discomfort, dry eye, foreign body sensation, hyperemia, keratitis, pruritus, rhinitis, sinusitis, and tearing. Some of these events were similar to the underlying disease being studied.

OVERDOSAGE

Somnolence and malaise have been reported following daily oral administration. Oral ingestion of the contents of a 15 mL DROP-TAINER would be equivalent to 7.5 mg. In case of overdose, treatment is symptomatic and supportive.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in the effected eye up to four times daily.

HOW SUPPLIED

EMADINE (emedastine difumarate ophthalmic solution) 0.05% is supplied as follows: 5 mL in opaque, plastic DROP-TAINER[®] dispensers.

5 mL: NDC 0065-2000-05

Storage

Store at 4°C - 30°C (39° - 86°F)

Rx Only

U.S. Patents Nos. 4,430,343 and 5,441,958

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