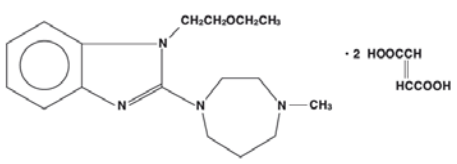
1. NAME OF THE MEDICINAL PRODUCT

EMADINE ® 0.05% ophthalmic solution **(emedastine)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 0.5 mg emedastine (equivalent to 0.884 mg emedastine difumarate).
Preservative: 1 ml of solution contains 0.1 mg benzalkonium chloride.
Emedastine difumarate is a white, crystalline, water-soluble fine powder with a molecular weight of 534.57. The chemical structure is presented below:



Chemical Name: 1H-Benzimidazole,1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl), (E)-2-butenedioate (1:2)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile ophthalmic solution.
Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMADINE® ophthalmic solution contains emedastine, a relatively selective H1-receptor antagonist.
EMADINE ophthalmic solution is indicated for the temporary relief of the signs and symptoms of allergic conjunctivitis.

4.2 Posology and method of administration

Posology

The recommended dose is one drop in the affected eye twice per day.

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

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

Use in patients with hepatic or renal impairment
EMADINE ophthalmic solution has not been studied in patients with hepatic disease or renal impairment and therefore, its use is not recommended in this population.

Method of administration

For ocular use.
After cap is removed, if tamper evident snap collar is loose, remove before using product.
To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use. Do not use if the solution has become discolored.
Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.
If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use:

- EMADINE ophthalmic solution is for topical use only and not for injection or oral use.
- Contact lenses:
  - EMADINE ophthalmic solution should not be used to treat contact lens related irritation.
  - Patients should be advised not to wear a contact lens if their eye is red.
  - EMADINE ophthalmic solution contains benzalkonium chloride which may be absorbed by soft contact lenses, cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of EMADINE ophthalmic solution and wait at least 15 minutes before reinsertion. Patients should only reinsert their lenses if their eyes are not red.

Ocular Corneal Infiltrates: Ocular corneal infiltrates were reported in conjunction with the use of EMADINE. In the case of corneal infiltrate, the product should be discontinued and appropriate management should be implemented.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Fertility
Studies in animals have shown no evidence of impaired fertility following administration of dosages up to 30 mg/kg/day. No human fertility data are available.

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. However, at 70,000 times the maximum recommended ocular human use level, emedastine difumarate was shown to increase the incidence of external, visceral and skeletal anomalies in rats. There are, however, no adequate and well controlled studies in pregnant women.
EMADINE ophthalmic solution should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or foetus.

Breast-feeding Emedastine has been identified in the milk of rats following oral administration. It is not known whether topical administration to humans could result in sufficient systemic absorption to produce detectable quantities in breast milk. Caution should be exercised if EMADINE ophthalmic solutionis administered during breast-feeding

4.7 Effects on ability to drive and use machines
EMADINE ophthalmic solution has no or negligible influence on the ability to drive and use machines.
Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects
Summary of the safety profile
In clinical trials lasting for 42 days, the most common adverse drug reactions were eye pain and eye pruritus, occurring in 1% to 2% of patients.

Tabulated list of adverse reactions
The following adverse reactions are classified according to the following convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials.
Some of these events were similar to the underlying disease being studied.

System organ class	**Adverse reactions**
Psychiatric disorders	*Uncommon*: abnormal dreams
Nervous system disorders	*Uncommon*: headache, dysgeusia
Eye disorders	*Common*: eye pain, eye pruritus *Uncommon*: corneal infiltrates, vital dye staining cornea present, vision blurred, eye irritation, dry eye, foreign body sensation in eyes, lacrimation increased, asthenopia, ocular hyperaemia
Skin and subcutaneous tissue disorders	*Uncommon*: rash

Additional adverse experiences reported in less than 5% of patients include the following: asthenia, bad taste, burning or stinging, dermatitis, discomfort, keratitis, rhinitis, sinusitis, and tearing.

4.9 Overdose
No specific reactions are to be expected with an ocular overdose of the product. An ocular overdose of EMADINE ophthalmic solution may be flushed from the eye(s) with lukewarm water.
Somnolence and malaise have been reported following daily oral administration. Oral ingestion of the contents of a 15 ml DROPTAINER* dispenser would be equivalent to 7.5 mg.
In case of overdosage, treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: decongestants and antiallergics, other antiallergics.
ATC code: S01GX06.

Emedastine is a potent selective and topically effective histamine H1 antagonist (Ki = 1.3 nM). *In vitro* examinations of emedastine's affinity for histamine receptors (H1, H2 and H3) demonstrate 10,000 fold selectivity for the H1 receptor, Ki's = 1.3 nM, 49,067 nM and 12,430 nM, respectively. In vivo topical ocular administration of emedastine produces a concentration-dependent inhibition of histamine-stimulated conjunctival vascular permeability. Studies with emedastine have not shown effects on adrenergic, dopaminergic and serotonin receptors.

In an environmental study, patients with allergic conjunctivitis were treated with EMADINE ophthalmic solution for six weeks. The results demonstrated that EMADINE ophthalmic solution provides relief of the signs and symptoms of allergic

conjunctivitis. In conjunctival antigen challenge studies, in which subjects were challenged with antigen both initially and up to four hours after dosing, EMADINE ophthalmic solution was demonstrated to be significantly more effective than placebo in preventing ocular itching associated with allergic conjunctivitis.

5.2 Pharmacokinetic properties

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'- oxoanalogs of 5- and 6-hydroxyemedastine and the N-oxide are also formed as minor metabolites.

5.3 Preclinical safety data
Non-clinical data reveal no hazard for humans from emedastine, based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenicity, or toxicity in reproduction. Repeated ocular administration in animal studies showed no untoward effects.
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzalkonium chloride, trometamol, sodium chloride, hypromellose, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

6.2 Incompatibilities
Not applicable.

6.3 Special precautions for storage
Do not store above 30°C. Do not freeze.
Do not use this medicine after the expiry date which is stated on the packaging.
Discard 4 weeks after first opening.
Keep this medicine out of the sight and reach of children.

6.4 Nature and contents of container
Opaque, plastic DROPTAINER® dispenser containing 3ml or 5 ml.
Not all presentations may be available locally.

6.5 Special precautions for disposal
No special requirements.

6.6 Manufacturer
See folding box

(Information issued: May2014.SINv1)

Novartis Pharma AG, Basel, Switzerland