ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EMADINE 0.5 mg/ml, Eye Drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains emedastine 0.5 mg (as difumarate)

Excipients: Benzalkonium chloride 0.1 mg/ml

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops, (solution).
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of seasonal allergic conjunctivitis.

4.2 Posology and method of administration

EMADINE has not been studied in clinical trials beyond six weeks.

Posology
The dose is one drop of EMADINE to be applied to the affected eye(s) twice daily.

When used with other ophthalmic medicines, an interval of ten minutes should be allowed between applications of each medicinal product.

Elderly population
EMADINE has not been studied in elderly patients older than 65 years, and therefore its use is not recommended in this population.

Paediatric population
EMADINE may be used in paediatric patients (3 years of age and older) at the same posology as in adults.

Hepatic and Renal impairment Use
EMADINE has not been studied in these patients and therefore, its use is not recommended in this population.

Method of administration

For ocular use.

To prevent contamination of the dropper tip and solution, care should be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

4.3 Contra-indications

Hypersensitivity to emedastine or to any of the excipients.

4.4 Special warnings and special precautions for use

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

Excipients
Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since EMADINE contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

In addition benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of EMADINE and wait 15 minutes after instillation of the dose before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed .

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of emedastine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Nevertheless, considering the absence of effects of emedastine on adrenergic, dopaminergic and serotonin receptors, EMADINE can be used during pregnancy if the dosage recommendation in section 4.2 is respected.

Lactation
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 is administered during breast-feeding.

4.7 Effects on ability to drive and use machines

As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

In 13 clinical studies involving 696 patients, Emadine was administered one to four times daily in both eyes for up to 42 days. In clinical trials, approximately 7% of patients experienced an adverse drug reaction associated with the use of Emadine; however, less than 1% of these patients discontinued therapy due to these adverse drug reactions. No serious ophthalmic or systemic adverse drug reactions were reported in the clinical trials. The most frequent adverse drug reaction was eye pain, reported at an overall incidence of 2.0%.

The following adverse reactions listed below were observed in clinical studies or with post marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

Cardiac disorders
Not known: tachycardia

Nervous system disorders
Common: headache
Uncommon: sinus headache, dysgeusia

Eye disorders
Common: eye pain, eye irritation, blurred vision, eye pruritus, dry eye, corneal staining, conjunctival hyperaemia
Uncommon: corneal infiltrates, foreign body sensation in eyes, lacrimation increased, asthenopia, ocular hyperaemia

Skin and subcutaneous tissue disorders
Uncommon: rash

Psychiatric disorders
Uncommon: abnormal dreams

4.9 Overdose

No data are available in humans regarding overdose by accidental or deliberate ingestion. In case of accidental ingestion of the content of a bottle of EMADINE, the potential of emedastine to increase the QT interval should be borne in mind and appropriate monitoring and management should be implemented.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: decongestants and antiallergics; other antiallergics,

ATC code: **S01G X 06**

Emedastine is a potent selective and topically effective histamine H_1 antagonist (K_i = 1.3 nM). *In vitro* examinations of emedastine's affinity for histamine receptors (H_1, H_2, and H_3) demonstrate 10,000-fold selectivity for the H_1 receptor, K_i's = 1.3 nM, 49,064 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.

5.2 Pharmacokinetic properties

Absorption
Emedastine is absorbed systemically, as are other topically administered drug substances. In a study involving ten normal volunteers dosed bilaterally twice daily for 15 days with EMADINE 0.5 mg/ml eye drops solution, 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 human oral bioavailability of emedastine is approximately 50% and maximum plasma concentrations were achieved within one-two hours after dosing.

Metabolism
Emedastine is principally metabolised by the liver**.** The elimination half-life of topical emedastine is ten hours. Approximately 44% of an oral dose is recovered in the urine over 24 hours, with only 3.6% of the dose excreted as parent drug substance. Two primary metabolites, 5-and 6-hydroxyemedastine, are excreted in the urine as both free and conjugated forms. The 5′-oxo analogues of 5-and 6-hydroxyemedastine and the N-oxide are also formed as minor metabolites.

5.3 Preclinical Safety Data

Emedastine difumarate demonstrated low acute toxicity in a number of species by various routes of administration. No clinically significant local or systemic effects were observed in long-term topical ocular studies in rabbits.

Corneal limbal mononuclear cell infiltrates were noted in 1/4 male monkeys treated with 0.5 mg/ml and in 4/4 males and 1/4 females treated with1.0 mg/ml. Scleral mononuclear cell infiltrates were present in 1/4 males and 1/4 females treated with 0.5 mg/ml and in 2/4 males and 1/4 females treated with1.0 mg/ml. Mean peak plasma levels were approximately 1 ng/ml and 2 ng/ml for the 0.5 and 1.0 mg/ml treatments respectively.

Emedastine was found to increase the QT interval in dogs; the NOEL corresponds to levels 23-fold higher than those found in patients (7 ng/ml as compared with 0.3 ng/ml, i.e., the limit of detection for emedastine).

Emedastine difumarate was not found to be carcinogenic in studies in mice and rats. Emedastine difumarate was not genotoxic in a standard battery of *in vitro* and *in vivo* genotoxicity assays.

In a teratology study in rats, foetotoxic but not teratogenic effects were observed at the highest dose evaluated (140 mg/kg/day); no effects were observed at a lower level (40 mg/kg/day) which corresponds to an exposure well in excess of that produced by the therapeutic recommended dose. No reproductive toxicity was observed in a study in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride 0.1 mg/ml
Trometamol,
Sodium chloride,
Hypromellose,
Hydrochloric acid/sodium hydroxide (to adjust pH)
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

EMADINE should not be used for longer than 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and content of container

EMADINE is supplied in 5 ml and 10 ml opaque plastic DROP-TAINER bottles.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Alcon Laboratories (UK) Ltd.
Pentagon Park
Boundary Way
Hemel Hempstead
Herts HP2 7UD
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/095/001-2.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th January 1999.
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10. DATE OF REVISION OF THE TEXT