SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Emadine. This scientific discussion has been updated until 1 October 2003. For information on changes after this date please refer to module 8B.

1. Introduction

This application has been submitted and evaluated under the Centralised procedure on the basis that it contains a new active substance, emedastine INN, a selective and topical histamine H_1 antagonist developed for ophthalmic use in the symptomatic treatment of seasonal allergic conjunctivitis. The indication applies to adult patients as well as children older than 3 years, and the recommended posology is two instillations of a 0.05% w/v solution per day. Emedastine was initially developed for systemic use by the Japanese company Nippon Organon, and is currently marketed in Japan for allergic rhinitis and urticaria with a posology of 2 mg orally twice daily.

Ocular allergy is a chronic disease that represents one of the most frequent allergic reactions and one of the most frequent clinical problems encountered by ophthalmologists or allergists. The disease affects people of all ages, with no difference in sex distribution. The largest group of allergic conjunctivitis is associated with environmental allergens. The importance of ocular allergy is due more to repeated occurrence than to seriousness.

Serious *sequelae* (e.g. eye involvement) are extremely rare in patients with seasonal or perennial conjunctivitis although the quality of life of patients may be highly affected due to the frequency and duration of the disease. Some patient may experience seasonal allergic conditions or year-round symptoms.

The most prevalent forms of ocular allergies are Seasonal Allergic Conjunctivitis (SAC) and Perennial Allergic Conjunctivitis (PAC), respectively defined by the duration of irritation of the offending allergens. It is considered that this is not a disease, which requires chronic use of ophthalmic drugs – i.e. the patients use the drug for some days or weeks, once or a few times during the year. The best management of SAC and PAC would consist of identifying the antigen responsible for the allergic response and avoiding exposure to the antigen. However, it is generally recognised that it is difficult to adequately control the environmental variables in allergic conjunctivitis. Therefore, besides a traditional clinical development plan, the applicant has used an alternative approach: - studies based on the Conjunctival Allergen Challenge (CAC), also known as the Conjunctival Provocation Test (CPT). In the CAC model, asymptomatic allergic patients are given a predetermined topical dose of allergen to induce an allergic reaction under standardised conditions. On this particular point of development, Alcon sought the advice of the CPMP who replied that they could accept CAC studies as evidence of efficacy provided that the CAC model was fully validated by clinical data.

Alternative topical ocular antiallergic treatments include cromolyn sodium, steroids (although major side effects do not allow chronic use as requested for this disease), NSAIDs (however not recognised in this indication in all EU countries at present) and antihistamines, which act by blocking histamine H_1 receptors. Very few antihistamine compounds have been developed for topical ocular use, however topical levocabastine 0.05 % is one of these compounds currently authorised in the EU, and it has been used as a comparator product in some of the clinical studies.

2. Part II: Chemical, pharmaceutical and biological aspects

EMADINE is authorised as EMADINE 0.05% w/v, eye drops, solution in multidose presentations (EMADINE MD) and EMADINE 0.05% eye drops, solution, single-dose container (EMADINE SD).

EMADINE 0.05% w/v, eye drops, solution (EMADINE MD)

Composition

Emadine Eye drops are presented as a buffered, preserved, sterile, multi dose solution of 0.0884% w/v emedastine difumarate equivalent to 0.05% w/v emedastine.

Other ingredients include the preservative benzalkonium chloride 0.01% w/v, the buffer trometamol, sodium chloride, hypromellose 2900, hydrochloric acid and/or sodium hydroxide for the adjustment of pH, and purified water. All ingredients with the exception of the active substance comply with relevant PhEur monographs. Clinical trial formulations containing the equivalent of 0.005%, 0.01%, 0.05%, 0.1% and 0.5% emedastine were developed for clinical dose response studies.

No overage is introduced.

Container

The 5 or 10 ml bottle is an opaque, low-density polyethylene (LDPE) bottle, with a LDPE dispensing plug, a white polypropylene closure and an extended 'skirt' that locks to the bottle.

Development pharmaceutics

Emedastine difumarate is very soluble in water. Preformulation studies supported by toxicology studies were carried out to optimise the formulation so that the resulting product is stable, isotonic, well-preserved and non-irritant solution with a pH of ca. 7.4.

The choice of the concentration of benzalkonium chloride (BAC) as a preservative was based on standard preservative efficacy studies; at release, the product complies with PhEur criteria A (also complies with 80% of the stated amount of BAC), although after 1 year storage B criteria are met. The manufacture of the eye drops is based on a sterile filtration process since terminal sterilisation by a thermal method may result in distortion and differential shrinkage of the composite container, resulting in increased probability of subsequent leaking and sterility failure.

Manufacturing process

The equipment is steam sterilised, and sterilisation of packaging components is by ethylene oxide, EO. (EO-related residues are limited to < 1ppm)

Hypromellose and benzalkonium chloride are dissolved in purified water and steam sterilised.

Trometamol, sodium chloride and emedastine difumarate are dissolved in purified water, with pH adjustment if necessary, bioburden tested, and subjected to double sterile filtration (0.2 µ) After final volume adjustment, the solution is aseptically filled into sterile bottles, and fitted with sterile plugs and closures.

Relevant microbiological in-process control includes raw materials < 100 CFU/ml or /g, water < 1 CFU/100 ml, hypromellose/BAC solution < 100 CFU/ml, bulk emedastine solution < 10 CFU/100 ml, and filter integrity. Maximum holding times are defined and validated.

Process validation

The critical stages in the manufacturing process have been validated by means of chemical and (micro) biological tests

Active substance

Information on the active substance has been supplied in the form of a DMF from the manufacturer, Nippon Organon KK, Japan. Confidential information in the 'closed' part of the DMF has been evaluated without disclosure to the marketing authorisation applicant.

Emedastine INN is: 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-benzimidazole, MWt 302.2, presented in this formulation as the difumarate salt, MWt 534.57. It has no chiral centres or geometric/structural isomers. Two polymorphs are known, although this has no consequences for the product as the active substance is in solution. Emedastine is manufactured by a 4-stage synthesis with relevant control of intermediates.

Active substance specification

The main purity specifications have been set at 98.5-101% on an anhydrous basis, with no known impurity greater than 0.2% and no unknown impurity greater than 0.1%. The specified limits for impurities in the active substance have been justified by reference to toxicology studies and the low systemic exposures expected during normal use of the product, and are in agreement with CPMP/ICH

guidance on this subject. Residual solvents are also specified at a suitably low level in agreement with CPMP/ICH guidance.

Appropriate microbiological control is performed with a suitable limit for bioburden.

Other ingredients

Satisfactory information has been provided on the excipients present in the formulation which are all of PhEur quality. Specifications for container materials are satisfactory.

Product specification

The specification for content of active substance at release is 95 – 105% of label, and a slightly broader specification which does not compromise the efficacy and safety of the product has been established for the end of shelflife. Degradation products are controlled as related substances at release, although as usual, a higher limit for these substances is allowed at end of shelflife, justified by reference to stability studies, toxicology studies and the low exposures expected during normal use of the product.

The preservative, BAC is controlled at release within the limits 90 – 110% of the stated amount, and these limits also apply at the end of shelflife. (Satisfactory preservative efficacy has been demonstrated for product containing BAC at a level of 80% of the stated amount).

Other tests include pH, osmolality, colour, visual clarity, viscosity, particulate matter, and sterility.

All control methods have been validated in a satisfactory way.

Stability of the product

Stability of the Active Substance

On the basis of the data submitted, the active substance appears to be very stable.

It is stable to high temperature (up to 50°C) and high humidity (75%) for six months.

It is unaffected by light stress (1000 lux) for six months. Long term studies have been carried out over 3 years. Overall, the data support the proposed retest period of 3 years.

Stability of the finished product

Stability data for six stability lots filled in the proposed marketing containers have been generated under ICH conditions. Batch results support shelf life and storage conditions as stated in the SPC.

EMADINE 0.05% eye drops, solution, single-dose container (EMADINE SD)

Composition

EMADINE SD eye drops solution (single-dose) is a buffered, unpreserved, sterile ophthalmic solution of 0.0884% emedastine difumarate equivalent to 0.05% w/v emedastine, 0.5 mg/ml. Other ingredients include the buffer trometamol, sodium chloride, hypromellose 2900, hydrochloric acid and/or sodium hydroxide for the adjustment of pH, and purified water. All ingredients with the exception of the active substance comply with relevant PhEur monographs. No overage is introduced. (The quantitative composition of this single-dose form is the same as the multidose form of EMADINE, except that it contains no preservative).

The product is packaged in single units of a low-density polyethylene BFS dispenser ("Blow-Fill-Seal"). The package system is comprised of five 0.35ml single-dose dispensers presented in a single strip. The primary package is overwrapped in an aluminium laminate pouch which is used to protect from light, control water loss on storage and to provide evidence of use ('tampering').

Active substance

Information on the active substance has been supplied in the form of a DMF from the manufacturer, Nippon Organon KK, Japan. Confidential information in the 'closed' part of the DMF has been evaluated without disclosure to the marketing authorisation applicant.
Emedastine INN is: 1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-benzimidazole, MWt 302.2, presented in this formulation as the difumarate salt, MWt 534.57. It has no chiral centres or geometric/structural isomers. Two polymorphs are known, although this has no consequences for the product as the active substance is in solution. Emedastine is manufactured by a 4-stage synthesis with relevant control of intermediates.

Active Substance Specification

The main purity specifications have been set at 98.5-101% on an anhydrous basis, with no known impurity greater than 0.1% and no unknown impurity greater than 0.1%. The specified limits for impurities in the active substance have been justified by reference to toxicology studies and the low systemic exposures expected during normal use of the product, and are in agreement with CPMP/ICH guidance on this subject. Residual solvents are also specified at a suitably low level in agreement with CPMP/ICH guidance.

Appropriate microbiological control is performed with a suitable limit for bioburden.

Stability

On the basis of the data submitted, the active substance appears to be very stable.
It is stable to high temperature (up to 50°C) for three months and high humidity (75%) for six months. It is unaffected by light stress (1000 lux) for six months. Long term studies have been carried out over 3 years. Overall, the data support the proposed retest period of 3 years.

Other ingredients

Satisfactory information has been provided on the excipients present in the formulation which are all of PhEur quality. The container material of the primary package complies with the Ph.Eur specifications for LDPE.

Product development and finished product

Concerning the pharmaceutical development of the single-dose form of EMADINE, there is a qualitative and quantitative justification of all the excipients based on stability data and safety considerations already established for the multidose form. The omission of the preservative benzalkonium chloride precludes a multidose presentation, and necessitates presentation in a single-dose form. During the stability studies, a degradation product: emedastine N-oxide is identified; it has already been justified for the multidose form. Emedastine N-Oxide is a potential degradation product in the multidose form but also a metabolite.

The manufacturing process is similar to that for the multidose form. Equipment is steam sterilized. Hypromellose is dissolved in purified water and the solution is steam sterilised.
Trometamol, sodium chloride and emedastine difumarate are dissolved in purified water, with pH adjustment if necessary, bioburden tested, and subjected to double sterile filtration (0.2 µ) After final volume adjustment, with addition of purified water via the sterilisation filters, the solution is filled into single-dose LDPE dispensers by BFS technology, and overwrapped.
Relevant microbiological inprocess control includes raw materials < 100 CFU/ml or /g, water < 1 CFU/100 ml, hypromellose solution < 100 CFU/ml, bulk emedastine solution < 10 CFU/100 ml, and filter integrity. Maximum holding times are defined and validated.

Product Specification

The specification for content of active substance at release is 95 – 105% of label, and a slightly broader specification, which does not compromise the efficacy and safety of the product, has been established for the end of shelflife. Degradation products are controlled as related substances at release, although as usual, a higher limit for these substances is allowed at end of shelflife, justified by

reference to stability studies, toxicology studies and the low exposures expected during normal use of the product.

Other tests include pH, osmolality, colour, visual clarity, viscosity, particulate matter, and sterility. All control methods have been validated in a satisfactory way.
Batch analysis data indicate a uniform product complying with the agreed specification.

Stability of the Product

Results have been generated by validated, stability-indicating methods and indicate satisfactory stability in solution. Six batches, up to 200 kg, have been tested in studies under ICH conditions up to 12 months at the time of submission. Storage conditions included 25°C and 30°C at 60%RH. Accelerated studies were carried out at 40 °C low RH (40%).
Degradation products have been justified with reference to toxicology studies, and the results in general justify the unopened shelflife as proposed in the SPC.

Unlike the multidose form of EMADINE, each single-dose unit has no preservative, and should therefore be used immediately and discarded. Results of stability studies on samples outside the pouch showed that the first degradation products were detected at low levels at five days and the product remained within shelf-life specifications for up to 10 days. Therefore, as an additional precaution, the SPC recommends that each single-dose unit should be used within 7 days after opening the pouch.

Discussion on chemical, pharmaceutical and biological aspects

Benzalkonium chloride, whilst being the most commonly used preservative in ophthalmic products such as EMADINE multidose, does have its own side effects (e.g. irritation) in certain patients. Therefore, this single-dose form of EMADINE has been developed to meet a need for a more tolerable preservative-free formulation.
The quality characteristics of this product are almost identical to those for the multidose form of EMADINE, e.g. same active substance, similar manufacturing process apart from the final filling, sealing and overwrapping stages, similar specifications, etc.
One difference is in the appearance of the N-oxide degradant in the single-dose form. This was detected in the original EMADINE multidose studies but not present to a significant extent in the product. However, it seems that the selected type of primary packaging material chosen for the single-dose form (LDPE) is more permeable to oxygen than the selected one for EMADINE multidose. This may explain why the N-oxide degradant appears in this new dosage form and justifies the use of an overpouch.

In summary, the manufacture and control of the active substance and finished product have been validated, and indicate satisfactory product uniformity at release. Quality characteristics relevant to clinical use have been investigated during the shelflife studies, and are satisfactory for an ophthalmic product of this type.

3. Part III: Toxico-pharmacological aspects

EMADINE 0.05% w/v, eye drops, solution (EMADINE MD)

Pharmacodynamics

Pharmacodynamic preclinical studies have been well conducted. A complete battery of *in vitro* and *in vivo* assays demonstrates that emedastine difumarate is a topically active, selective and potent H1 histamine receptor antagonist. A clear separation exists between doses of emedastine with antihistaminic/antiallergic effects and those exhibiting effects on the central nervous, cardiovascular, respiratory, and gastrointestinal systems.

- no significant interaction was noted between emedastine and alpha adrenergic, dopamine D2, serotonin S2, and numerous other receptors; emedastine is devoid of muscarinic or adrenergic effects.
- at effective antihistamine concentrations, emedastine does not affect general behaviour, motor activity, nor has any neuropharmacologic activity (the psychotropic product profile is near that

of ketotifen without local anaesthetic activity) or effects on the cardiovascular, respiratory, and gastrointestinal systems, indicating minimal side effect potential.

- its antihistamine profile is close to that of ketotifen

No electrophysiological studies have been described in the dossier.

Pharmacokinetics

Ocular Route

After topical ocular administration emedastine penetrates the anterior chamber and distributes to various ocular tissues. Emedastine is generally cleared rapidly from eye structures except with pigmented tissues (iris-ciliary body) where a greater uptake and a prolonged retention were observed ($t_{½}$ 23 days). This observation is not unexpected and logically explained by binding of emedastine to melanin.

Oral Route

Numerous toxicology studies of the preclinical program were conducted using the oral route:

- repeated dose studies (rat and dog), reproduction toxicity studies (rat and rabbit) and carcinogenicity studies (rat and mouse). The results allow the following conclusions –

- emedastine is almost totally absorbed after oral administration to rat, dog and guinea pig.

- the absolute bioavailability is about 50% in this latter species and extremely low in rat and dog (4 to 5 %) due to an extensive first pass effect.

- Tissue distribution in rat showed a slight uptake by brain (less than 0.5%) of the total radio-activity, a low foetal exposure (about 1% of the total dose) in pregnant rats and moderate milk secretion in this species.

- Binding to plasma proteins was assessed to be about 40% in rat and dog and 80% in guinea pig.

- Metabolism was investigated in rat, guinea pig and dog. In all these species emedastine was extensively metabolised in the liver with important qualitative interspecies differences. A slight induction of hepatic enzymes was observed in rat.

- emedastine was shown to be almost completely eliminated within 96 hours in rats. The elimination is balanced between urinary (40%) and fecal routes (60%).

Toxicokinetics of emedastine by oral route in species included in the main toxicity studies is poorly documented. The lack of toxicokinetic data was regarded as a deficiency of the dossier, but the applicant has provided evidence of sufficient exposure of the animals in terms of plasma concentrations. Moreover, there is some evidence that emedastine does not accumulate significantly over time.

Toxicology

General comments concerning the toxicological evaluation of emedastine:

Toxicological studies have been conducted in mice, rats, dogs, rabbits and monkeys.

Pharmacological activity has been mainly evaluated in guinea pigs.

Evaluation of toxicity following systemic administration used emedastine in distilled water. For topical application the clinical formulation was not always utilised. However, the six-month topical ocular evaluation in monkeys did use the final formulation of emedastine (except for a minor modification, ie hypromellose 2910 instead of hypromellose 2900).

Five impurities have been identified in emedastine raw material. Due to the low amount of these impurities in batches of emedastine, it is unlikely that these products are of toxicological significance.

Toxicology studies were conducted in compliance with GLP.

Single dose toxicity

Acute toxicity studies have been correctly performed.

Acute toxic signs in mice and rats included a decrease in spontaneous movements, ataxic gait and convulsions.

Repeated dose toxicity

Oral administration

In rats, liver toxicity effects were observed: increase in liver weight, increase in ALT and AST and transient increases in bilirubin. These signs were associated with centrilobular hepatocytes swelling and degeneration of liver cells and were generally observed at 50 and 250 mg/kg.

Kidney toxicity was present in the 3-month study at 250 mg/kg with increases of BUN, calcium and inorganic phosphates. However, these effects were not accompanied by any histologic alterations. The NOEL in rats after oral administration is 10 mg/kg.

In dogs, the 75 mg/kg dose caused overt toxicity (salivation, tachypnea, convulsions, ataxia, gasping) associated with death (3/6 males and 4/6 females). Liver signs were present at 15 mg/kg in the 3-month study and at 45 mg/kg but not at 15 mg/kg in the one-year study. These signs were mainly increased in liver weight and ALP, centrilobular hepatocytes swelling and endoplasmic reticulum hyperplasia. These signs were not detected after a 1-month recovery. Male testicular toxicity was observed at 45 mg/kg after one year in one study with decreased testicular weight, atrophy of the prostatic epithelium and local deciduation of the seminiferous tubule epithelium. However, when this one-year study was repeated with a 3-month recovery period this effect was not observed.

The NOEL in dogs after oral administration is 3 mg/kg.

Ocular administration

Toxicological evaluation following topical ocular administration of emedastine (1-, 3-, 6-months) in rabbits at dosages up to 1% (2.8 mg/kg, 4 times daily) did not result in systemic or ocular toxicity. Slit-lamp biomicroscopic examination of the study animals did not reveal any treatment-related findings. Conjunctival congestion (hyperemia) of minimal severity was noted in all treatment and control groups. Corneal pachymetry data were unremarkable.

The NOEL was 1% in these studies.

Topical ocular application of emedastine in monkeys for 6 months at dosages up to 0.1% (4 times daily) did not induce systemic toxicity. Corneal limbal mononuclear cell infiltrates were noted in ¼ males treated with 0.05% and in 4/4 males and ¼ females treated with 0.1%. Sclera mononuclear cell infiltrates were present in ¼ males and ¼ females treated with 0.05% and in 2/4 males and ¼ females treated with 0.1%.

Measurements of emedastine in ocular tissues showed the following order of distribution: periocular palpebral conjunctiva > ICB > choroid >cornea > retina > aqueous humor.

Reproduction studies

A complete battery of assays evaluating the effects of emedastine on reproductive functions was performed. Results showed slight non-significant modifications of the following fertility parameters at 140 mg/kg: reduction of the number of implantations and the number of live fetuses, increase in the number of dead fetuses. The NOEL was 40 mg/kg

Embryotoxicity and teratogenic effects.

In rats, half the animals studied received a caesarean section on day 21, and half delivered naturally. Effects on the F0 dams were limited to decreased body weight gain since 40 mg/kg. At 140 mg/kg, reduced number of implantations and live fetuses and increase in number of dead fetuses were recorded at caesarean section. At the same dosage, reduced number of survivors at day 4 post-partum and at weaning and in number of live births were observed at spontaneous delivery section.

Reproductive function of F1 generation was normal and F2 fetuses were not affected by emedastine treatment of F0 animals.

The NOEL for fetal effects was 40 mg/kg, and 10 mg/kg for maternal toxicity.

In rabbits, maternal toxicity was observed at 75 mg/kg but no fetal effects were recorded.

The NOEL was 75 mg/kg for fetal effects and 15 mg/kg for maternal toxicity.

In summary, emedastine is not considered to be teratogenic.

Perinatal and postnatal effects.

Results showed decreased body weights in F0 animals at 40 mg/kg and in F1 animals at 140 mg/kg. NOELs were 10 mg/kg for F0 animals and 40 mg/kg for F1 animals.

In general, the results of reproduction studies showed that emedastine was embryotoxic but not teratogenic, and affected reproductive parameters only at high doses. Effects of emedastine on F1 animals in the peri- post-natal study in rats may be the consequence of additional exposure during the lactation period since pharmacokinetic studies demonstrated the presence of emedastine in milk. Pharmacokinetic studies performed in rats have shown that emedastine can cross the placental barrier.

Genotoxic potential

A complete battery of mutagenicity tests has been performed with emedastine difumarate. The mutagenic potential of emedastine has been correctly assessed using standard tests under

GLP conditions. Emedastine is not considered to be genotoxic.

Oncogenic/carcinogenic potential

An increase in hepatocellular carcinomas in mice was observed, but considered to be not statistically significant, not dose dependent, and occurred mostly in males. With respect to the non-significant increase in hepatocellular carcinomas and the intended non-chronic use of this compound, this finding is not a major concern.

Local tolerance/special toxicity studies

Whilst the sensitising potential protocol was considered to be less than optimal to address the question of allergenicity, it was concluded that if the results obtained in clinical use are negative, then it is not necessary to perform further tests in animals.

Ecotoxicity/environmental risk assessment

It was concluded that the manufacture and clinical use of Emadine will not cause toxic effects to the environment.

GLP status

It was concluded that all studies had been carried out in agreement with the requirements of GLP.

Conclusions on the preclinical dossier

Toxicity results found following systemic exposure showed that emedastine induced liver toxicity as a probable consequence of its enzyme-inducer potential. Safety ratios for systemic toxicity have only been calculated on a dose basis and are considered not fully reliable. However, the doses used probably resulted in systemic exposure of the animals much higher than that obtained in man with topical use.

Topical ocular administration resulted in the absence of any significant local or systemic toxicity. In monkeys a higher incidence of mononuclear cell infiltrates in the corneal limbus and sclera have been found in males in the high dose group. Since corneal infiltration has also been observed in patients, it should be mentioned in the SPC as a warning in section 4.4, and preclinical information in 5.3. In addition it should be followed in the PSURs.

Emedastine was not teratogenic. Reproductive functions were only affected following exposure to emedastine at high doses, administered orally.

Emedastine is neither genotoxic nor carcinogenic. However, exposure levels were not measured in treated animals. In mice a slight but not statistically significant increase in hepatocellular carcinomas

was reported. The applicant provided historical data for the strain in question in the same facilities and the results were judged to be unremarkable in this context. Since this was found in only one species and emedastine is not genotoxic, it is considered that this is not a major concern with regard to the clinical use of the product.

In addition it should be mentioned that animal results indicate that emedastine has the potential to increase QTc intervals and to induce arrhythmias like other antihistamine compounds. These effects were observed in dogs but the NOEL corresponds to levels 23-fold higher than those found in clinical trials (7 ng/ml as compared with 0.3 ng/ml, i.e., the limit of detection for emedastine). This finding is mentioned in the SPC section 5.3.

EMADINE 0.05% eye drops, solution, single-dose container (EMADINE SD)

Pharmacodynamics

The mode of action of emedastine and its activity as a H_1 antagonist has previously been established. No additional information has therefore been submitted or considered necessary by the CPMP for EMADINE SD.

Pharmacokinetics

The pharmacokinetic profile of emedastine has already been established and therefore no additional data have been submitted or considered necessary by the CPMP for EMADINE SD.

Toxicology

No data were submitted for pharmacodynamics, pharmacokinetics, single and repeated dose toxicity, on reproduction toxicology, on mutagenicity or carcinogenecity as the applicant refers to data submitted in the initial marketing authorisation application for EMADINE MD.

Presence of a degradation product: emedastine N-oxide

During stability studies one degradation product (emedastine N-oxide) that was not present in the initial EMADINE MD was detected and specified at a level of 0.6 %.

However, this product is known as a minor metabolite in rat and human, and a major one in dog and guinea pig. Therefore, the Applicant argued that the systemic toxicity of emedastine N-oxide has been previously evaluated as part of the study of the toxicology of its parent drug emedastine, which was provided in the initial marketing authorisation application for EMADINE MD.

The MAH presented two arguments:

1. The first argument is that emedastine difumarate has been authorised and marketed in Japan for oral use. The maximum daily dose administered is 4 mg/d or 0.08 mg/kg/d.

   Since Emedastine N-oxide is formed at a level of 0.4 %, patients are exposed to 0.016 mg/d or 0.32 µg/kg/day.

   When topically applied by ocular route the exposure to emedastine is very low (0.095 mg/d) which corresponds to 0.95 µg/d of N-oxide provided by the metabolism route plus degradated impurity. Therefore, the maximum daily exposure comparatively to the oral route is approximately 16 times lower.

Comparison of exposure to emedastine N-oxide in human following oral or ophthalmic dosing

Route in Human	**Emedastine Dose**	**Emedastine N-oxide Exposure**	**Oral/Ophthalmic Safety Margin**
Oral	4 mg/day (0.08 mg/kg/day)	0.016 mg/day (0.32 µg/kg/day [1])	>16
Topical ocular	0.095 mg/day (1.9 µg/kg/day)	0.95 µg/day (0.019 µg/kg/day [2])	

1 Calculated based on urinary excretion (0.4%)
2 Calculated assuming emedastine N-oxide at specification limits (0.6% referred to the parent drug) and 0.4% conversion rate of emedastine into emedastine N-oxide

2. The second argument is based on the systemic toxicity of emedastine in animals. Since N-oxide is a known metabolite, minor in rat (0.07 %), but major in dog (10.4 %), it can be accepted that adequate exposure to the metabolite has been achieved in the main toxicology studies : chronic administration in dog (1 year), and rat (6 months and 2 years).

   Reproduction toxicity studies were performed in rat and rabbit by the oral route. Emedastine was administered in the diet. The stability of the product in the fed conditions is not known, and its bioavailability was not studied. However, the NOEL for development and maternal effects was 40 mg/kg/d and 10 mg/kg/d respectively. It can be judged that a sufficient safety margin for N-oxide by the ocular route is established.

   Considering mutagenicity studies, one reference (Wada 1990, MAH internal report) on in vitro metabolism of emedastine difumarate has demonstrated that in rat liver microsomal S9 fraction, N-oxide is formed. Thus it was assumed that in mutagenicity in vitro tests with activation, the metabolite N-oxide was present and assessed.

Results of a topical ocular study performed in rabbits

The applicant submitted a new one month ocular irritation study in rabbits to assess the topical irritation of the emedastine and its impurity N-oxide. Three groups were included:

- one receiving the highly degraded EMADINE SD (stored in stressful conditions at high temperature), containing 1,7 % of Emedastine N-oxide;
- one receiving EMADINE SD recently prepared (without emedastine N-oxide),
- the last one untreated and considered as control group.

The treatment consisted of one drop in each eye, four times daily. No clinical signs related to adverse treatment effects were observed. Mean body weights of the two treated animal groups and of the control group were comparable.
The only ocular change was a minimal conjunctival congestion (hyperaemia) observed among animals treated or untreated.
At necropsy no gross lesions were observed. Microscopic evaluation demonstrated the lack of a local irritant effect.

Discussion on toxico-pharmacological aspects

From a toxicological viewpoint, the absence of benzalkonium chloride (a preservative well known for its side effects) is greatly appreciated, particularly in case of repeated dosage.
Considering the level of this new impurity (< 0.6 %) and the well-known profile of the N-oxide metabolite (in human by both the oral and the ocular routes as well as in animal by the systemic route) it is improbable that the presence of emedastine N-oxide could be a safety concern.

The applicant was requested in the List of Questions to clarify the origin of the N-oxide. The applicant responded that emedastine N-oxide, is a known degradation product of emedastine difumerate and exclusively identified as impurity in the preservative free formulation (<0.6%), is considered to be

possibly connected with the BFS container (low-density polyethylene blow-fill-seal dispenser) used to package the single units. The response was considered satisfactory.

The applicant was also requested by the CPMP in their List of Questions to justify the lack of mutagenicity performed on emedastine N-oxide. The Applicant provided satisfactory clarifications regarding the genotoxic potential of emedastine N-oxide. From these data it can be concluded that the level of exposure to emedastine N-oxide metabolite in mutagenicity tests was sufficient [conversion rates of emedastine into emedastine N-oxide are respectively in the rat liver microsomal S9 fraction : 7.5% and in Human : 0.4%]. Moreover, comparison of preclinical toxicity studies in rats to clinical usage shows a large safety margin for N-oxide exposure reaching at least 1000 up to 5000.

Regarding the topical ocular study the applicant was asked in the List of Questions to explain the choice of using an untreated group control instead of a vehicle control group and to further discuss the findings as the same ocular changes are observed among all animals (treated and untreated). In the response the Applicant responded that regarding the topical ocular study, its purpose was to determine the ocular irritation potential of emedastine N-oxide when present in the formulation of EMADINE SD. Ocular changes observed among all animals (treated and untreated) were identified in the historical data base. These changes appear in agreement with the spontaneous ocular findings in animal and are considered to be not treatment related.
Moreover, the absence of vehicle control group in the topical ocular study is justified by the reference to the main Six-Month Topical Ocular Irritation Study in Rabbits carried out with EMADINE MD (multidose container) in which no relevant findings were observed in the group of animals treated with EMADINE MD vehicle.

4. Part IV: Clinical aspects

EMADINE 0.05% w/v, eye drops, solution (EMADINE MD)

Over 500 subjects/patients were randomised to be included in efficacy studies involving various concentrations of emedastine, and over 320 of these (ITT) were exposed to emedastine 0.05%. The safety database consisted of over 950 subjects/patients exposed to various concentrations of emedastine and over 670 of these were exposed to emedastine 0.05%.

The majority of subjects were caucasian and no particular significance was given to eye colour during enrolment.

97 children aged 3 – 16 years were included in efficacy and safety studies described in the dossier.

A particular feature of the clinical dossier has been the development of standardised Conjunctival Allergen Challenge studies (CAC) as a 'model' of clinical efficacy, described later in this report.

Clinical studies have been performed according to current GCP standards and agreed international ethical principles.

Pharmacodynamics

In vivo topical administration of emedastine produces a concentration-dependent inhibition of histamine-induced conjunctival vascular permeability. Studies with emedastine have not shown effects on adrenergic, dopaminergic, and serotonin receptors.

CAC model studies can be considered as pharmacodynamic studies in man.

Since they were used as dose ranging and efficacy studies, they will be discussed in the section of this report dealing with clinical efficacy.

Investigations into the effect of topical emedastine on the ECG were not performed; the applicant did not provide PK or interaction data with respect to the potential of emedastine via the ophthalmic route to prolong the QT interval. However, due to the very low level of plasma emedastine at the recommended dose, and extensive experience of the oral product, the risk is considered negligible when used according to the directions in the SPC.

Pharmacokinetics

Systemic levels in plasma have been measured by a GC/MS technique following once daily ocular administration of various strengths of emedastine in solution (0.01, 0.05, 0.1 and 0.5 %). Results arising from a small healthy volunteer group (n=10) were not quantifiable in most cases, i.e. below the limit of quantitation of the analytical method used, 0.3 ng/ml. Quantifiable results were obtained only after administration of the 0.5% product where plasma concentrations of 0.3 – ca. 0.5 ng/ml were recorded.

These studies were supplemented by investigations into the pharmacokinetic properties of emedastine after oral administration of various doses ranging from 0.5 up to 8 mg/day. Direct comparison between 'ocular' and 'oral' results was not possible due to the use of different analytical techniques. However the limited data available allows the conclusion that systemic plasma levels of emedastine following ocular use are indeed very small when compared to oral use, as expected.

Clinical efficacy

Dose – response studies and main clinical studies

Concerning efficacy, a total of 5 studies were carried out, in two categories:

1. Four CAC studies :
   - two dose-response studies, C-93-19 & C-94-90
   - two studies assessing the efficacy of emedastine with reference product and placebo: C-95-71 versus levocabastine 0.05% & C-96-14 versus ketorolac 0.5%.
2. One clinical 'environmental' trial to confirm the results of the above pharmacological approach, C-95-54.

The Conjuctival Allergen Challenge (CAC)

It is generally recognised that it is difficult to adequately control the environmental variables in allergic conjunctivitis. Therefore, besides the traditional clinical development plan, the Applicant used a new approach: the Conjunctival Allergen Challenge (CAC) also known as Conjunctival Provocation Test (CPT) studies.

The CAC model is supposed to work by means of the same immunopathological mechanism that is operative in the disease of allergic conjunctivitis. In the CAC model, asymptomatic allergic patients are given a predetermined topical dose of allergen to induce an allergic reaction in standardised conditions. The efficacy of a compound is tested by drug single administration before the Conjunctival Allergen Challenge. The relevance of this model is supported by the emergence of the signs and symptoms characteristic of allergic conjunctivitis upon initial challenge with an offending allergen.

On this particular point of development, Alcon requested Scientific Advice from the CPMP before submission of the dossier – '*Will the CPMP accept conjunctival allergen challenge studies as pivotal clinical trials to prove the effectiveness of an anti allergy molecule in allergic conjunctivitis?* 'The CPMP replied that it could accept this proposal provided that the CAC model was fully validated by clinical data.

CAC methodology is of interest for the evaluation of allergic conjunctivitis because the study conditions are standardised and reproducible with regard to:

- creation of disease conditions,
- evaluation of well defined situation (onset and duration of action of treatment focused on selected efficacy parameters),
- possible selection of a homogeneous population of patients
- response to a definite dose and category of allergen.

1. CAC Studies

CAC dose-response trials, C-93-19 & C-94-90:

Overview:

Study Objectives	Design	Treatment regimen (topical ocular instillation)	Treatment comparison
C-94-90 -efficacy of 2 concentrations (0.005-0.05%) versus 'placebo' (emedastine vehicle)	Triple-masked randomised parallel-group design placebo-controlled with additional contralateral placebo	One drop on two separate occasions ; - visit 3 (10 min before CAC) - visit 4 (4 hrs before CAC)	- in one eye: emedastine 0.005%, or emedastine 0.05% - in the contralateral eye: vehicle
C-93-19 - efficacy of 3 concentrations (0.05-0.1-0.5%) versus placebo (emedastine vehicle)	Triple-masked randomised parallel-group design placebo-controlled with additional contralateral placebo	One drop on two separate occasions ; - visit 3 (10 min before CAC) and - visit 4 (4 hrs before CAC)	- in one eye: emedastine 0.05%, or emedastine 0.1%, or emedastine 0.5%,or vehicle* - in the contralateral eye : vehicle

* The parallel placebo group design was included in study C-93-19 since it was suspected that emedastine could have a carryover effect, i.e., from one eye to the contralateral eye, which might bias the results of the contralateral placebo (in reducing apparent differences between placebo and active drug).

Number of subjects

Study	No.of subjects randomised	Product (%)	No. of subjects intent-to treat (ITT)	Number of discontinued subjects at visit 4
C-94-90	120	emedastine 0.005	60	0
		emedastine 0.05	60	0
C-93-19	240	emedastine 0.05	60	1 lost to follow up
		emedastine 0.1	60	1 Redness > 1
		emedastine 0.5	60	2 lost to follow up 1 *Redness > 1
		vehicle	60	1 lost to follow up
Total	360		360	6

* Patients with redness > 1 at visit 4 before challenge could not be assessed for duration of action

The triple masked design means that the patient is blinded, as well as the prescribing physician and the physician assessing the treatment effect; it may provide a less biased assessment.

Efficacy criteria

Concerning primary efficacy criteria, itching and redness are representative of the most frequent and incapacitating symptoms of acute allergic conjunctivitis with a predominance of itching that leads the patient to seek treatment. Therefore, itching and redness were selected as key efficacy parameters and quantified on a nine point scale including half points, from 0 – 4 (redness was assessed as the sum of scores for regional redness in three vessel beds observed by slit lamp examination, i.e. ciliary redness+ conjunctival redness+ episcleral redness).

In both studies the objectives were to evaluate the efficacy of emedastine with regard to

- Onset of Action when instilled 10 min before CAC, and
- Duration of Action when instilled 4 hrs before challenge.

In both cases itching and redness scores were compared at 3 min, 10 min and 20 min. A paired t-test

was used to compare itching and redness following emedastine and those following contralateral placebo at each challenge and post challenge times. Differences were recorded as 'Δ from contralateral placebo (ΔCP)', a negative value being in favour of emedastine. Statistical methods used for comparisons were considered to be appropriate.

For comparisons between two concentrations of emedastine, the score data were analysed using an analysis of covariance model. All hypothesis tests were performed with a 0.05 probability of a Type 1 error. In study C- 93-19 an analysis of variance was used to compare itching and redness in subjects dosed with placebo in both eyes.

Results:

C-94-90:

- Onset of action. The results of the study indicate that both 0.005% and 0.05% concentrations of emedastine were statistically superior to placebo, at all time points. 0.05 % concentration of emedastine was statistically superior to placebo for the duration of action at all time points but emedastine 0.005 % was not statistically superior to placebo on redness at 10 and 20 minutes post challenge observation.
  The magnitude of the effects due to emedastine 0.05% can be seen from the mean ΔCP scores at 3, 10 & 20 min. post-challenge, i.e.,
  Itching –1.47, -1.46 & -1.15
  Redness –1.68, -1.24 & -0.72

- Duration of action. Better results were observed for 0.05% as compared to 0.005%. Mean ΔCP scores for emedastine 0.05% at 3, 10 & 20 min. post-challenge were :
  Itching: -1.53, -1.55 & -1.15
  Redness: -2.06, -1.08 & -0.78

C-93-19:

- Onset of action. The results of the study indicate that two tested concentrations of emedastine (0.05%, 0.1%) were statistically superior to placebo at all time points. Conversely, emedastine 0.5% was not superior on redness at 20 minutes post challenge observation, possibly related to the poor local tolerance of this high dosing. Relevant mean ΔCP scores for the 0.05% concentration at 3, 10 & 20 min. post-challenge as compared to placebo were:

	3 min	*10 min*	*20 min*
Itching:			
Emedastine 0.05%	-1.41	-1.46	-1.08
Placebo	-0.16	-0.10	-0.21
Redness:			
Emedastine 0.05%	-1.17	-0.93	-0.94
Placebo	-0.08	-0.13	+0.14

- Duration of action. The three tested concentrations of emedastine (0.05%, 0.1%, 0.5%) were statistically superior to placebo, at all time points. Emedastine 0.05% and 0.1% are equally effective in inhibiting itching and redness. Emedastine 0.1% was significantly better than 0.5% in inhibiting itching and redness. As above, relevant mean ΔCP scores were as follows, 4 hour challenge:

	3 min	*10 min*	*20 min*
Itching:			
Emedastine 0.05%	-1.29	-1.46	-0.92
Placebo	+0.06	+0.08	+0.06
Redness:			
Emedastine 0.05%	-1.03	-1.02	-0.98
Placebo	+0.01	+0.25	+0.36

In general the following conclusions can be drawn from these CAC model results:

- the 0.005% concentration is not considered to be effective
- the 0.05% and 0.1 % concentrations are non-different and equally well tolerated,
- the 0.5% concentration is poorly tolerated

Thus, based on these CAC dose response studies, the 0.05% concentration is the lowest effective concentration investigated, and thus the best choice with regard to the available data.

CAC Comparative efficacy studies

In addition to CAC dose response studies above, the dossier also contained two studies assessing the efficacy of emedastine in comparison with reference products and placebo, C-95-71 and C-96-14:

C-95-71 is a comparative study versus levocabastine 0.05%, a product of the same class, i.e. histamine H1 antagonist and considered to be the most relevant of the two comparative studies. An additional placebo control group was included in the design. The C-95-71 protocol is similar to the above CAC dose-response studies except for:

- allergen challenge test conducted 2 hours (instead of 4) post dosing and results observed at 3, 5 and 10 minutes after CAC instead of 3, 10 and 20 minutes;
- primary efficacy parameters, itching as before but 'conjunctival redness' measured instead of the sum of redness in three vessel beds;
- dose per instillation, 2 drops instead of 1 drop.

C-95-71 Overview

Study Objectives	Design	Treatment regimen (topical ocular instillation)	Treatment comparison
C- 95-71 Efficacy and safety of emedastine 0.05%	triple-masked active-controlled randomised parallel-group design	Two drops on two separate occasions: - visit 3 (10 min before CAC) and	**1st group** n=64 - one eye: emedastine 0.05% - contralateral eye: levocabastine 0.05%
versus levocabastine 0.05%	with additional placebo control group	- visit 4 (2 hrs before CAC)	**2nd group** n=33 - one eye: emedastine 0.05% or levocabastine 0.05% - contralateral eye: emedastine vehicle

Number of subjects

Study	Tested product (%)	Nb of subjects in intent-to treat (ITT)	Nb of evaluated subjects for efficacy
C-95-71	emedastine 0.05 Levocabastine 0.05	64	60
	emedastine 0.05 Placebo	16	16
	levocabastine 0.05 placebo	17	15
	Total	97	91

Results

Observed differences in Onset of Action and Duration of Action were generally in favour of emedastine. Results indicate equivalence between treatments with regard to redness and itching, ie, the 95% CI for the mean difference is included in the ± 0.8 equivalence zone. This equivalence zone was defined *a priori* but it was not clearly justified by clinical data. It is not possible to conclude to any superiority of emedastine over levocabastine in alleviating itching for the following reasons:

- demonstration of superiority was not the purpose of the study;
- there was no initial hypothesis to determine the tested difference;
- the resulting clinical difference between treatments is modest and does not seem to be clinically relevant (i.e 0.2 unit scale for emedastine).

C-96-14 is a comparative study versus ketorolac 0.5%, a NSAID product, regarded as a supportive study, as ketorolac does not belong to the same therapeutical class as emedastine. The objective was to demonstrate the superiority of emedastine over ketorolac 0.5%.

36 subjects were enrolled in a triple masked, active controlled, crossover design study and were randomised to receive two drops of emedastine 0.05% (n=18) or ketorolac 0.5% (n=18) in one eye with placebo control in the contralateral eye.

The results show that emedastine 0.05% is statistically superior to placebo and ketorolac 0.5% in inhibiting ocular itching and redness at all time points post 10 minutes challenge.

2. Clinical trial (C-95-54)

Overview

Study Objectives C –95-54	Design	Treatment regimen and duration (topical ocular instillation)	Treatment comparison
Efficacy and safety in treatment of allergic conjunctivitis	randomised multicenter triple-masked parallel group	one or two drops twice daily for six weeks	emedastine 0.05% levocabastine 0.05%

Number of subjects

Study	Randomised to treatment	Tested product (%)	ITT*	PP**
C-95-54	222	emedastine 0.05	109	97
		levocabastine 0.05	112	105
		total	221	202

* intent-to –treat ** per protocol

This study was performed to confirm CAC studies results on efficacy. Since the onset of allergic seasonal conjunctivitis is typically related to the presence of specific airborne allergens such as pollens (notably ragweed, grass and tree pollens) spores and moulds, the treatment has been tested in different world areas. The choice of the comparator is acceptable, but a placebo is lacking.

Primary efficacy parameters were similar to the above studies, i.e.

- Ocular symptoms: itching
- Ocular signs: redness (slit lamp examination), both in terms of a 9 point scale

In addition, secondary efficacy parameters related to itching and redness as appropriate were recorded by the physician and taken from patients' diaries.

The effects of the two treatments in the short term (0, 5, 10, 30 and 120 minutes), and in the long term (0, 14, 30 and 42 days) were compared.

The statistical objective of the clinical study was to demonstrate equivalence between emedastine and levocabastine. The acceptance criterion for equivalence was that the 95% CI for the mean difference in primary parameters should be contained within a pre-defined equivalence zone of ±0.5 unit. Per protocol and Intention to treat analyses were performed. Usually the per-protocol analysis is the most conservative approach in an equivalence trial.

Results

A) short term effects

	itching, mean scores				
	0	*5 min*	*10 min*	*30 min*	*120 min*
PP analysis					
Emedastine 0.05%	5.11	3.82	3.49	2.88	2.70
Levocabastine	5.14	3.81	3.09	2.83	2.63
ITT analysis					
Emedastine 0.05%	5.07	3.74	3.42	2.85	2.63
Levocabastine	5.02	3.66	2.96	2.72	2.52

	redness, mean scores				
	0	*5 min*	*10 min*	*30 min*	*120 min*
PP analysis					
Emedastine 0.05%	4.47	3.64	3.24	2.84	2.70
Levocabastine	4.5	3.73	3.28	2.95	2.74
ITT analysis					
Emedastine 0.05%	4.36	3.54	3.15	2.74	2.54
Levocabastine	4.39	3.59	3.16	2.84	2.64

B) long term effects

	itching, mean scores			
	0	*14 d*	*30 d*	*42 d*
PP analysis				
Emedastine 0.05%	4	1.49	1.13	0.88
Levocabastine	4	2.20	1.94	1.98
ITT analysis				
Emedastine 0.05%	3.93	1.56	1.33	1.13
Levocabastine	3.93	2.21	2.04	2.04
	redness, mean scores			
	0	*14 d*	*30 d*	*42 d*
PP analysis				
Emedastine 0.05%	2.71	0.89	0.70	0.49
Levocabastine	2.64	1.35	1.2	1.12
ITT analysis				
Emedastine 0.05%	2.65	0.92	0.83	0.66
Levocabastine	2.61	1.35	1.24	1.16

Six weeks is an acceptable duration of treatment for seasonal but not perennial allergic conjunctivitis which is a recurrent seasonal disease. As originally presented, it was difficult to draw any firm conclusions from the results of this trial. There was no evidence that the study was designed as an equivalence study in the dossier, except in the protocol. There was no clinical justification for the equivalence interval chosen which is again different from that chosen with levocabastine in study

C-95-71 (or with ketorolac). The number of drops by instillation was not clearly defined (1 or 2 in protocol), and there was no justification for the twice daily dosage.

The scales used were different, depending on whether assessment was performed by a physician or by the patient in a diary and furthermore it was not known whether the nine point scale used for the patient's self evaluation is clinically validated.

The lack of placebo arm control is the major drawback of this study.

The company provided a re-analysis and re-presentation of the results in their responses to the list of questions and in the oral explanation. (See Benefit / Risk discussion in section 6 of this report).

Clinical studies in special populations

At risk populations (in study C-95-54)

Treatment	Mean age (years) [range]	No. of paediatric patients	No. of patients ≥65 to 76 yrs.
Emedastine	9.1 [4 – 16]	20	2
Levocabastine	9.0 [5 – 14]	22	7
Total		44	9

Paediatric patients

Although only a limited population of paediatric patients has been studied, this is considered to be useful information in the clinical trial, and is reflected in the SPC. Allergic conjunctivitis can affect children and the type of allergic conjunctivitis met in children is close to that of adults. Results indicate that the efficacy profile of emedastine is similar for adult and paediatric patients.

Elderly patients

Very few elderly patients were enrolled, insufficient to support an indication in the elderly.

Renal & hepatic impairment

No data were provided in relation to populations with renal or hepatic impairment. Liver metabolism is evident from studies with oral emedastine and animal toxicology studies, therefore the use of the product is not recommended in these patients in the SPC.

EMADINE 0.05% eye drops, solution, single-dose container (EMADINE SD)

The efficacy of EMADINE 0.05% eye drops, solution in the symptomatic treatment of seasonal allergic conjunctivitis was established for EMADINE 0.05% eye drops, solution, multi dose and no new clinical data have been submitted for EMADINE 0.05% eye drops, solution, single-dose.

The preservative free formulation of the EMADINE 0.05% eye drops, solution, single-dose offers theoretical advantages for patients suffering from allergic and cytotoxic reactions to treatment with preservative containing formulations. This is particularly of interest for inflamed allergic eyes more sensitive than healthy eyes to the application of any kind of eye drop and requiring recurrent local anti-allergic treatments. Moreover, the discomfort (stinging and burning) caused by the instillation of eye drops may be further increased by the presence of a preservative in the formulation.

The removal of benzalkonium chloride from the formulation is not expected to modify the clinical effectiveness of emedastine difumarate, since its action is limited to the external surface of the eye. Indeed, emedastine eye drops act only at a topical level to block the binding of histamine to the H_1 receptors on conjunctival nerve cells to reduce itching and on smooth muscle cells of conjunctival vessels to reduce redness.

In view of the similarity in formulation of the single-dose and multidose eye drops of emedastine, and since neither systemic absorption nor ocular penetration into the eye are required for effectiveness, the lack of additional clinical data in the single-dose file is acceptable.

Safety

EMADINE 0.05% w/v, eye drops, solution (EMADINE MD)

Patient exposure

In all studies reported in the dossier over 950 subjects/patients have been exposed to various concentrations of emedastine and over 670 have been exposed to emedastine 0.05% w/v.

6-week safety	C-94-93 (362 subjects enrolled, 242 received emedastine)
6-week safety	C-94-86 (67 subjects enrolled, 35 treated with emedastine)
clinical trial	C-95-54 (221 evaluated for safety)

Adverse events and serious adverse events/deaths

C-94-93

This randomised "triple-masked" parallel group safety study was conducted in asymptomatic allergic patients. Emedastine eye solution 0.05 % was compared to placebo (=vehicle of emedastine) with a 2:1 randomisation. The dosage regimen was 1-2 drops q.i.d. for 6 weeks.

Office visits took place at Days 0, 7, 14, (28: telephone call), 42, and after 2-3 days off-therapy.

Criteria of evaluation were intraocular pressure (IOP), visual acuity, pulse, systolic and diastolic blood pressure.

Results: A number of 362 patients were enrolled and 31 discontinued the study prematurely.

Minor deviations in protocol adherence were observed for 17 patients, and 14 were discontinued due to protocol violations as their baseline slit lamp examination revealed conjunctival injection. The average number of doses per day were 3.72 and 3.70 for the emedastine, respectively placebo group.

Of the 242 subjects who received emedastine 17 (7 %) experienced 25 ocular events related to the therapy. Ocular discomfort, hyperaemia, dryness, corneal staining, pruritus and one ocular infiltrate were most important adverse events reported.

Of the 120 subjects who received placebo 7 subjects (6 %) experienced 11 events of similar kind as with the active drug.

The pattern of adverse events was similar for the cohort of children receiving emadine, but no adverse experiences in children who received placebo were reported. A few non-ocular events related to emadine treatment were recorded, the most notable being dermatitis. Apart from one case of moderate asthenia no treatment related nonocular events were recorded in children receiving emedastine eye drops.

Conclusion: No serious adverse events were reported during the study. Overall, the emadine eyedrops were well tolerated with a q.i.d. regimen for 6 weeks, both in children of 3-16 years and subjects wearing contact lenses (which were removed prior to and reinserted 10 min after drug instillation). No specific or clinically relevant findings were noted in relation to the following safety parameters:

IOP, visual acuity, dilated fundus examination, and cardiovascular data

C-94-86

This study was originally designed to compare the efficacy and safety of emedastine 0.05 % eye drops to cromolyn 2 % eye drops, both applied 4 times daily for 6 weeks in patients with moderate to severe allergic conjunctivitis. A randomised "triple-masked" parallel group multi-centre design was applied. Because of strategic plan changes the patient recruitment was however stopped after the inclusion of 67 patients instead of the intended number of ~200. A safety evaluation only therefore could be performed. The criteria of inclusion comprised a history of seasonal allergic conjunctivitis, confirmed by a positive skin test and present signs and symptoms characteristic of the disease: at least 4 on an itch score (0 - 4) and at least 2 on a redness score (0 - 4). Evaluation criteria included adverse events obtained as solicited complaints from study patients; the frequency, incidence and causality to study drug also was assessed.

Results: A number of 67 patients with a mean age of 32 years (6-69) for the emadine group patients and 31 years (6-70) for the cromolyn group were enrolled. The majority of the patients belonged to the caucasian race and half of the patients had brown eyes.

No serious adverse events were reported, related or unrelated to therapy. No clinically significant differences in the safety parameters visual acuity, increase in intraocular pressure, change in pupil diameter, no difference apart from one whole in the retina (unrelated to therapy) in the cromolyn group in fundus examination. In the emedastine group 2 patients discontinued due to adverse events: one developed ocular hyperaemia, one had ocular hyperaemia, pruritus and discharge. No patients discontinued in the cromolyn group.

The reported adverse events show an incidence of 17 % in the emedastine group and 13 % in the cromolyn group. In the emedastine group 3 patients experienced discomfort, hyperaemia or pruritus while in the cromolyn group 2 patients experienced discomfort.

Conclusion: A q.i.d. application of 0.05 % emedastine eye solution for (up to) 6 weeks in patients with seasonal allergic conjunctivitis is safe and generally well tolerated. The reported adverse events were moderate or mild, with ocular discomfort and hyperaemia occurring most frequently. Two out of 35 patients were withdrawn because of ocular adverse events.

C-95-54 clinical trial

The safety population consisted of 221 patients. Three patients in the emedastine group discontinued due to adverse events: one because of ocular discomfort, one developed bacterial conjunctivitis and one patient had rhinitis. The first adverse event was considered related to the trial drug. No patients were withdrawn in the levocabastine group. No serious adverse events were reported during the study.

Generally, the adverse events were mild to moderate and resolved spontaneously.

Adverse reactions in this study were between 14 – 18%, with a predominance of ocular discomfort, blurred vision, ocular pruritus, dry eye, tearing, ocular fatigue and corneal infiltrate, all related to the treatment. In the levocabastine group 12.5 % had adverse experiences related to the treatment. The majority consisted of ocular discomfort ocular pruritus, blurred vision and tearing. For both preparations ocular discomfort was the most frequently reported treatment related ocular event: 7 % for emedastine and 11 % for levocabastine.

In approx. 10 % of the patients who received emedastine and 1 % who received levocabastine ocular events were observed which were not considered to be related to the treatment.

The ocular events reported in the adult and paediatric population were similar in nature and intensity.

No clinically significant changes with either of the trial medications were recorded in the following safety parameters: IOP, visual acuity, corneal pachymetry (central, temporal, nasal, upper, lower corneal thickness), specular microscopy (endothelial cell density, polymorphism and polymegatism), pupil diameter, and fundus examination (vitreous, retina, macula, choroidea, optic nerve, disc pallor).

Conclusion: No serious adverse events were reported. The recorded events were generally mild to moderate. In both the emedastine group and the levocabastine group the frequency of ocular events was approximately 13 %. For both drugs ocular discomfort was most frequently reported (in 7%, respectively 11 %). Three patients in the emedastine group discontinued treatment due to ocular adverse events. No clinically significant changes in the secondary safety parameters were recorded.

Assessment of specific safety issues

13 subjects were wearing contact lenses, which were removed prior to administration and reinserted 10 minutes later. No subject wearing contact lenses was discontinued from the studies due to an adverse event. The SPC advises a suitable strategy for patients wearing soft contact lenses.

Concerning concomitant drug administration, numerous topical and systemic medications were also used during the studies. No adverse event was reported which could be attributed to concomitant use of other medications.

It is known that benzalkonium chloride can cause punctate keratopathy and /or toxic ulcerative keratopathy and whilst this was not specifically evaluated in the safety assessment, it was concluded this should be reflected in the SPC.

Oral emedastine has been shown to prolong the QT interval; however, no cases of torsades de pointe were reported with oral emedastine in Japan over 5 years. It is noted that the studies on emedastine by the oral route were performed during 1985 – 1990 at a time when the cardiac effects of antihistamines were not fully described, and there are no specific investigations of arrhythmias in this dossier. The applicant did not provide PK or interaction data with respect to the potential of emedastine via the ophthalmic route to prolong the QT interval. However due to the very low plasma level of emedastine obtained via the ophthalmic route, and extensive experience of the oral product, the risk is considered negligible in this case. However, a statement is included in the SPC section 5.3 relating to the prolongation of QT interval in dogs, and in the overdose section 4.9.

EMADINE 0.05% eye drops, solution, single-dose container (EMADINE SD)

The safety of EMADINE 0.05% eye drops, solution in the symptomatic treatment of seasonal allergic conjunctivitis was established for EMADINE 0.05% eye drops, solution, multidose and no new safety data have been submitted for EMADINE 0.05% eye drops, solution, single-dose.

The new presentation free of benzalkonium chloride, is expected to be without the well-known cytotoxicity of that preservative, even if theoretical and not demonstrated in the application.

In the clinical trials for EMADINE MD over 950 subjects/patients received various concentrations of emedastine and over 670 of these were exposed to emedastine 0.05%.
Reported adverse events were mild to moderate and usually resolved without treatment. The most frequent ocular events associated with EMADINE MD included ocular discomfort, ocular pruritus, ocular hyperaemia, ocular dryness, blurred vision and corneal staining. No serious adverse events were reported in

the studies; no subject aged 3-16 years of age was discontinued due to an adverse event; and no deaths were recorded in the studies. Corneal infiltration was observed in two patients and is kept under specific review in the PSURs.

The safety assessment for EMADINE SD is based on the PSURs for EMADINE MD. The multi-dose presentation was launched in the EU in 1999 and thus, four PSURs (covering the period 01 January 1999 to 21st December 2000) have been analysed by the CPMP.

During the reported period, the total number of units of EMADINE MD sold worldwide was 1. 043.298. No change in the SPC has been requested based on the assessments of the PSURs.

The safety profile of EMADINE MD demonstrated in clinical studies is confirmed by post marketing experience. Only non serious adverse events were reported to the MAH. Review of spontaneous post-marketing reports during the 2 year period confirms that the adverse events possibly associated with the use of EMADINE MD occur infrequently, are generally non-serious and resolve without any sequelae.

5. Overall conclusions and benefit/risk assessment

EMADINE 0.05% w/v, eye drops, solution (EMADINE MD)

Quality

The company has developed a product of satisfactory quality in relation to the clinical use, i.e. a buffered, sterile, isotonic solution which is preserved against microbial contamination during storage and use. The manufacturing process has been validated and provides a satisfactory assurance that the product will be sterile when opened for the first time. Methods used for batch control and stability studies have been validated and should ensure a product of reproducible quality.

Efficacy

In the conjunctival allergen challenge studies a statistically superior efficacy to placebo was demonstrated with emedastine 0.05 % solution in controlling redness and itching in subjects with a history of allergic conjunctivitis. Emedastine was equivalent to levocabastine 0.05 % in preventing and relieving itching and in reducing redness. The onset of action was rapid, i. e. less than 10 minutes. The minimally-effective concentration was found to be 0.05 %.

For conclusions relating to the clinical trial, see Benefit / Risk Assessment.

Safety

Adverse events reported were mild to moderate and usually resolved without treatment. The most frequent ocular events associated with emedastine eye drops 0.05% included ocular discomfort, ocular pruritus, ocular hyperaemia, ocular dryness, blurred vision and corneal staining. No serious adverse events were reported in the studies; no subject aged 3-16 years of age was discontinued due to an adverse event; no deaths were recorded in the studies.

Overall, no clinically relevant changes in intraocular pressure, pupil diameter, visual acuity, fundus parameters or ocular signs were demonstrated. In general, the overall incidence of ocular adverse events was 14-18% in two trials in symptomatic patients.

As mononuclear cell infiltration has been observed in monkeys in the pigmented ocular tissue and corneal infiltration was reported in two patients (although this is known to occur independently of treatment in patients with allergic conjunctivitis), it was concluded that this should be mentioned in the SPC as a warning in section 4.4, and preclinical information in 5.3. The company has been requested to keep this under review and it should be specifically followed in the PSURs.

Benefit/risk assessment

In order for the CPMP to come to a decision regarding satisfactory proof of efficacy, the company was asked to give an oral presentation which addressed the following two residual issues:-

i) The CAC studies which compared the product to placebo were not validated, e.g., they did not reflect the proposed clinical use of the product.

ii) The clinical trial did not include a placebo arm and thus lacked internal validation.

The CPMP took into account that it is not always possible to show a difference with placebo with products of this type, and thus internal validation is deemed necessary.

Therefore, the applicant was asked to present information which justifies that the efficacy of the product is indeed superior to placebo.

Following the company's oral explanation the issues were discussed:

i) The CPMP considered that the CAC studies may be considered as supportive evidence of efficacy, and noted the generally positive results in favour of emedastine.

ii) As the clinical trial did not include a placebo arm, the appropriateness of the comparator product becomes crucial. It should be kept in mind that levocabastine is authorised and used in the EU and is considered to show acceptable evidence of clinical efficacy. The results of the trial showed a statistically significant difference of emedastine over levocabastine. In addition, and as the trial was designed as an equivalence trial, it would be inappropriate to conclude that emedastine is clinically superior to levocabastine. However, the results led the CPMP to conclude that there is enough proof that emedastine is not inferior to levocabastine which can be considered to be a suitable comparator.

This, together with the rest of the evidence presented,

- preclinical data showing superior histamine H1 receptor affinity / potency of emedastine in comparison with levocabastine
- supporting evidence from the CAC studies which add to the evidence of efficacy from the clinical trial prompted the CPMP to conclude that the efficacy of emedastine has been acceptably shown.

The company originally applied for an indication relating to the prevention of allergic conjunctivitis, however this was rejected. In addition, the company's request for an indication relating to the treatment of conjunctivitis, was modified. Therefore, on the basis of all information presented to date, it is reasonable that the indication should relate to short-term symptomatic treatment of seasonal allergic conjunctivitis, rather than prevention. There is satisfactory evidence that the minimally-effective concentration to balance efficacy and safety aspects in this indication is 0.05% w/v.

The CPMP on the basis of the quality, efficacy and safety data available, recommended that a Marketing Authorisation should be granted for this product, when used according to the conditions defined in the SPC.

EMADINE 0.05% eye drops, solution, single-dose container (EMADINE SD)

Quality

The important quality characteristics of EMADINE single-dose are well-defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic of a solution for ophthalmic use. The specifications and batch analytical results indicate a consistent product with uniform clinical performance from batch to batch. There are no outstanding quality issues, which have a negative impact on the benefit/risk balance.

Preclinical pharmacology and toxicology

The lack of additional preclinical and toxicology studies is acceptable in view of the similarity in formulation of the single-dose and multidose presentations of emedastine, and the presence of emedastine N-oxide raises no safety concern considering the level of this impurity (< 0.6 %) and the

well-known profile of the N-oxide metabolite (in human by both the oral and the ocular routes as well as in animal by the systemic route).

Efficacy

The removal of benzalkonium chloride from the formulation is not expected to modify the clinical effectiveness of emedastine difumarate, since its action is limited to the external surface of the eye. In view of the similarity in formulation of the single-dose and multidose presentations of emedastine, and since neither systemic absorption nor ocular penetration into the eye are required for effectiveness, the lack of additional clinical data in the single-dose file is acceptable.

Safety

The new presentation free of benzalkonium chloride, is expected to be without the well-known cytotoxicity of that preservative, even if theoretical and not demonstrated in the application.

The safety of EMADINE SD is acceptable because of the similarity in formulation of the single and multidose presentations and because the adverse events possibly associated with the use of EMADINE MD occur infrequently, are generally non-serious and resolve without any sequelae.

Benefit/risk assessment

The overall benefit/risk assessment is considered to be positive considering that

- The removal of benzalkonium chloride from the formulation is not expected to modify the clinical effectiveness of emedastine difumarate in the treatment of seasonal allergic conjunctivitis as demonstrated for EMADINE MD
- The new presentation, free of benzalkonium chloride, is expected to be without the well-known cytotoxicity of that preservative
- The presence of emedastine N-oxide raises no safety concern considering the level of this impurity (< 0.6 %) and the well-known profile of the N-oxide metabolite (in human by both the oral and the ocular routes as well as in animals by the systemic route)
- The safety of EMADINE SD is acceptable because of the similarity in formulation of the single and multidose presentations and because the adverse events possibly associated with the use of EMADINE MD occur infrequently, are generally non-serious and resolve without any sequelae.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of EMADINE 0.05% eye drops, single-dose container in the symptomatic treatment of seasonal allergic conjunctivitis was favourable and therefore recommended the granting of the marketing authorisation.