11 September 2009
EMEA/602052/2009
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emadine

emedastine
Procedure No.: EMEA/H/C/000223/A45/0013

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2012. Reproduction is authorised provided the source is acknowledged.

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	EMADINE 0.05%, Eye Drops, Solution
INN (or common name) of the active substance(s):	Emedastine difumarate
MAH:	ALCON
Currently approved Indication(s)	Symptomatic treatment of seasonal allergic conjunctivitis.
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: decongestants and antiallergics; other antiallergics, ATC code: **S01G X 06**
Pharmaceutical form(s) and strength(s):	Eye Drops, Solution in multidose container Eye Drops, Solution in single dose container 0.05%

I. INTRODUCTION

EMADINE application has been registered in 1999 under the centralised procedure on the basis that contained a new active substance, emedastine difumarate, a selective and topically effective histamine H1 antagonist developed for ophthalmic use in the symptomatic treatment of seasonal allergic conjunctivitis.
Currently, the indication applies to adult patients as well as children older than 3 years with a recommended posolgy of two instillations per day.
A unpreserved formulation (without benzalkonium chloride 0.01%) has been authorised at a later date as a line extension.

A paediatric file was first submitted on October 2008 and then completed to meet EMEA request regarding additional paediatric data since the original EU registration of this product. Finally, the MAH (Alcon) has submitted on 6 May 2009 a short critical expert overview based on a literature review of 17 references discussing either the overall benefit/risk balance or/and the paediatric use of EMADINE 0.05%, eye drops solution, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

Even if no critical view of the MAH was expressed in the first submission of 3 published studies making reference to a paediatric use with EMADINE (October 2008), the MAH clearly stated in the completed file submitted on 6 May 2009 that the additional paediatric data do not influence the benefit/risk for EMADINE 0.05%, eye drops solution and that there is no a consequential regulatory action.
Alcon does not consider that the prescribing information for this product needs to be amended in respect of paediatric use.
According to the MAH, it is considered that the available data support the continued use of emedastine difumarate 0.5 mg/ml eye drops in paediatric patients.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

The preparation used in the published studies was the current preserved formulation of Emadine (Alcon) eye drops, solution. Its effective ingredient is emedastine difumarate 0.05%. The eye drops solution is preserved with 0.01% benzalkonium chloride.
According to the present file no paediatric data are available for the unpreserved formulation.

II.2 Non-clinical aspects

Not applicable

II.3 Clinical aspects

The clinical overview has been written by Dr Jose Armentia Pérez de Mendiola, who is an ophthalmologist at the Ophthalmology Ward at the Hospital del Mar y de la Esperanza (Barcelona).

1. Introduction

Background

In the original file, besides a traditional clinical development plan (environmental study), the Applicant has used an alternative approach: a standardised Conjunctival Allergen Challenge studies (CAC) as a "model" of clinical efficacy 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 standardized conditions.

Itching and redness were selected as primary efficacy criteria as they were representative of the most frequent and incapacitating symptom and sign of acute allergic conjunctivitis; these were assessed on 9 points scales [0-4].

The environmental trial addressed the question of Emadine's efficacy and safety in a representative population using a treatment duration of six weeks which was considered as an acceptable duration for seasonal allergic conjunctivitis.

Background on paediatric data submitted in the original file:

According to the European Authorisation Emadine eye drops solution can be currently used in children older than 3 years of age. Indeed, although only a limited population of paediatric patients has been studied, this was considered to be useful information and was reflected in the SPC (section 4.2). Based on the following paediatric data, results indicated that the efficacy and safety profile of emedastine was similar for adult and paediatric patients.

→Over 500 subjects/patients were randomised to efficacy studies involving various concentrations of emedastine, and over 320 of these were exposed to emedastine 0.05%.

→The safety database consisted of 950 subjects/patients exposed to various concentrations of emedastine, and over 670 of these were exposed to emedastine 0.05%.

→There were 97 children aged 3-16 years participating in the efficacy and safety studies.

Distribution of paediatric subjects in the original Emadine file

protocol type	protocol	Treatment group	number of paediatric subjects/patients	mean age (years) [range]
Safety (over 6 weeks)	C 94-93	emedastine 0.05% placebo	67 33	8.6 [3-16] 8.7 [3-16]
Safety (over 6 weeks)	C 94-86	emedastine 0.05% cromolyn sodium	10 7	12.2 [6-16] 10.8 [6-16]
efficacy &safety (pivotal environmental)	C 95-54	emedastine 0.05% levocabastine 0.05%	20 22	9.1 [4-16] 9 [5-14]
totals		emedastine comparators	97 62	

No subject aged 3-16 years of age was discontinued due to an adverse event; no deaths were recorded in the studies. Overall, the pattern of adverse events was similar for the cohort of children and adults receiving Emadine (discomfort, hyperaemia, dryness, corneal staining, pruritus were most important ADRS reported). In patients aged 3-6 years, *ocular discomfort* was slightly higher and the most frequent (6.5%) related ocular adverse event as reported in the table below.

Frequency of adverse events by age groups

coded adverse events	Emedastine eye drops 0.05% n = 677			placebo (emedastine ophtalmic vehicle) n = 230		
	ages 3-6 years n = 31	ages 7-16 years n = 66	ages > 16 years n = 580	ages 3-6 years n = 9	ages 7-16 years n = 24	ages > 16 years n = 197
discomfort	6.5%	3%	2.4%	0%	0%	1.5%
pruritus	0%	1.5%	1.2%	0%	0%	0%
infiltrate	0%	1.5%	0.2%	0%	0%	0.5%
hyperemia	0%	0%	1.0%	0%	0%	0.5%
drye eye	0%	0%	1.0%	0%	0%	0%
blurred vision	0%	0%	0.7%	0%	0%	1%
corneal staining	0%	0%	0.5%	0%	0%	1%
tearing	0%	0%	0.3%	0%	0%	1%
eye fatigue	0%	0%	0.3%	0%	0%	0%
forein body sensation	0%	0%	0.2%	0%	0%	0.5%
irritation	0%	0%	0.2%	0%	0%	0%
Body as a whole Headache	0%	0%	0.3%	0%	0%	0%
Asthenia	0%	1.5%	0%	0%	0%	0%
Nervous abnormal dreams	0%	0%	0.2%	0%	0%	0%
skin & appendages dermatitis	0%	0%	0.2%	0%	0%	0%
Special senses taste perversion	0%	0%	0.2%	0%	0%	0%

In accordance with Article 45 of the Regulation, the MAH submits an overview based on 17 literature references.

17 published reviews are provided among them 9 are not specifically related to Emadine (in two Emadine is never cited) but all are reviews on allergic diseases and usual cares recommended by practitioners and one presents a monography of Emadine.
Most of these articles refer to either a global view of ocular allergic diseases or/ and to the wide range of medications available to control their symptoms (presented as ocular allergy guidelines). Classification of the different categories of ocular allergic diseases and their target population are reminded. Classification, advantages or disadvantages of each category of medications are discussed with regard to target populations.

It is reminded that seasonal and perennial allergic conjunctivitis are the most common types of ocular allergies while atopic and vernal keratoconjunctivitis are less common but more severe forms of ocular allergy that may affect children.

Based on these references Emadine (emedastine difumarate) is clearly classified as a potent second generation histamine H1 antagonist (non sedating).

According to this literature review,
- Topical treatments are preferred over systemic for isolated allergic eye disease because of their faster relief of ocular symptoms and limited systemic side effects.
- The efficacy of emedastine has been consistently demonstrated in clinical trials comparing different available antihistamines (levocabastine, ketotifene) nor other antiallergic treatments as mast cells stabilising (nedocromil) or non steroidal anti-inflammatory agent (ketorolac) and placebo using in most cases the CAC model or a similar technique.

These data add little to the knowledge regarding emedastine.

Nevertheless, three studies are describing a paediatric use of Emadine, in addition to the data provided in the original file.

The three references are listed below:

-Comparaison of emedastine 0.05% or nedocromil sodium 2% eye drops and placebo in controlling local reactions in subjects with allergic conjunctivitis; V.Orfeo, European journal of ophthalmology, vol 12, N°4.2002/pp 262-265.
-Endre L: The Effect of Emedastine Eyedrops and the Safety of Its Use in Children Suffering from Acute Seasonal Allergic Conjunctivitis Orvosi Hetilap 148(6):251-254, 2007. Clinical studies And Endre L: Effects of Emedastine Eyedrops on Acute Seasonal Allergic Conjunctivitis in Children. 144(14):665-667, 2003. Original article).

Original copies and certified translations (when needed) of these 3 published articles making reference to an additional paediatric experience of emedastine were provided by the MAH.
These studies were not sponsored by the MAH.

Among these references, the 3 studies described below provide paediatric experience in addition to that previously provided in the original file.

Additionally, references 13&18 (Verin Ph, Easty DL; 2001), 10 (Secchi A, Leonardi A; 2000) and 11 (Secchi A, Ciprandi G; 2000) refer to the environmental study previously provided and assessed in the original registration file. According to the Author A. Secchi which publication (11) had for purpose to discuss more in depth the paediatric use of Emadine based on the cohort of 42 children from 4 to 16 years as included in the environmental study, emedastine is both safe and efficacious in treating SAC in a six week environmental study of paediatric subjects and is considered by the author in 2000 as an important new agent in the treatment of paediatric ocular allergy.

Clinical studies

Preparation studied in clinical studies:
Emadine (Alcon) eye drops.
Its effective ingredient is emedastine difumarate 0.05%. The eye drops solution is preserved with 0.01% benzalkonium chloride.

Literature reference 17 (Endre L, 2007):

Endre László; The Effect of Emedastine Eyedrops and the Safety of Its Use in Children Suffering from Acute Seasonal Allergic Conjunctivitis. Orvosi Hetilap 148(6):251-254, 2007. Certified English translation of the original Hungarian article (September 30, 2008).

In this article, the author reports on experience obtained with Emadine eye drops (H_1-receptor antagonist) that can be used in paediatric patients.

Two studies are described in this publication;

-The first study is also discussed in *Endre László* 2003 publication, publication which was not referenced in the completed submission (*Effects of Emedastine Eyedrops on Acute Seasonal Allergic Conjunctivitis in Children. Orvosi Hetilap 144(14):665-667, 2003-*
Certified English translation of the original Hungarian article (October 1, 2008).

-The second study is only described in *Endre László* 2007 publication.

First Dr Endre L. study (n=20)

- **Description and Methods**

This paediatric Study was carried out between August 27 and October 26, 2001. The study took place during ragweed and Artemisia pollen season.

- According to the Author, the study had a very limited goal that focused on the immediate effect of **a single instillation (one drop)** of emedastine on acute seasonal allergic conjunctivitis.

- Study design

Designed as a single dose study, one drop of Emadine 0.05% was instilled in the tested eye and the effect compared with the untreated controlateral eye used as control.

- Study population /Sample size

The patients' population participating in the study consisted of 20 patients (12 boys and 8 girls) from 6 to 21 years (average 12.3 years) suffering from acute seasonal allergic conjunctivitis. All were at least hypersensitive to ragweed and Artemisia pollen. All had an allergic cold, and had received eye drops containing an antihistamine, because they all had eye symptoms.

- Treatments

Each patient received one drop of emedastine in one eye, and no treatment in the other eye.

- Outcomes/endpoints

The severity of ocular itching and the grade of ocular redness/hyperemia were scored on scales ranging from 0 to 4, most severe symptoms:
Itching sensation was assessed by the patient: 0 (absence) to 4 (extremely serious itching).

Palpebral and bulbar conjunctival hyperemia (redness) was assessed by the physician: 0 (normal) to 4 (dark red with petechiae).

Assessment of the immediate effect of Emadine was objectified by examination done every 2 minutes after instillation of the drop. The time for a significant improvement was recorded for each criterion.

Regarding safety, patients were asked to report any uncomfortable sensation.

- Statistical Methods

Not described

➢ **Results**

- Recruitment/ Number analysed; Baseline data; Efficacy results

Itching was statistically significantly reduced from 2.85 ± 0.75 points (baseline score for treated eye) to 0.45 ± 0.51 points on average in less than 3 min (corresponding to a difference of -2.40), with 50% of the children reporting that the itching sensation completely stopped in 2-3 min.
Redness was statistically significantly improved, from 2.35 ± 0.59 (baseline score for treated eye) to 0.55 ± 0.51 points in 7.7min on average (corresponding to a difference of -1.80).
The author reported that no change was observed over 20 min in the untreated control eye. Nevertheless, baseline and final values corresponding to untreated eyes are not reported in the publication.

- Safety results

One boy, 11 years old, reported an undesired side effect (burning sensation).

Assessor's conclusion
Results of this single dose study suggested that Emadine eye drops might rapidly and effectively reduce itching and conjunctival hyperemia in paediatrics.
These non randomised 20 children do not bring any additional relevant information regarding paediatric efficacy or safety. Burning sensation is currently listed in the SPC.

Second Dr Endre L. study (n=232)

➢ **Description and Methods**

- Objective(s)

The objective was to investigate the long term effectiveness and side effects of a treatment with Emadine in paediatric patients.

- Study design

The study was carried out according to an uncontrolled open label design.

- Study population /Sample size

232 children suffering from allergy to grass and/or ragweed pollen received Emadine eye drops as treatment for their eye symptoms during two pollen seasons between 2004 and 2005.

- Treatments

According to the Author since Emadine was also suitable for continual treatment lasting several months, all patients paediatric patients received Emadine eye drops (n*evertheless, the centralised EU agreement is currently restricted to seasonal allergic conjunctivitis (SAC), as the pivotal study was limited to six weeks duration and CAC studies were of very limited duration).*
Anyway, during this study, none of the 232 patients used Emadine eye drops continually but only in case of symptoms and for at least 3-5 days.

- Outcomes/endpoints

Assessment of long term efficacy was searched throughout the study treatment period by asking patients on their end of treatment ocular condition.

➢ **Results**

- Recruitment/ Number analysed

The average age of the 138 boys was 11.1 years (3 to 16), and the average age of the 94 girls was 11.3 years (3 to 16).
Among the selected patients, only two had allergic conjunctivitis alone; all of the rest of children also suffered from rhinitis and/or asthma. Consequently, they received appropriate treatment for this (those with rhinitis took 2nd-generation antihistamines, some also took a steroid nose spray; the asthmatics took a steroid or a steroid combined with inhaling a long-lasting bronchodilator).

- Baseline data

Not provided

- Efficacy results

The efficacy assessment is totally biased as there is no control and as patients had additional treatments for asthma or rhinitis (namely corticoids and/or antihistamines which may influence the evolution of ocular allergic conjunctivitis). According to patients' responses, Emadine eye drops did not lose their effectiveness during the course of the two pollen seasons.

- Safety results

In this study, of the 232 children participating in the "continued" treatment, none had to discontinue Emadine treatment because of some uncomfortable side effect. According to the author, no side effect was reported that could be connected with administration of the eye drops.

<u>Assessor's Conclusion</u>
The objectives of this study appear unclear. Nevertheless, this study did not raise any additional safety concern in paediatric patients.

Of the 252 (232+20) children treated by Endre László, only one patient reported a side effect (burning sensation) which is currently listed in the SPC.

Literature reference 19 (Orfeo V ; 2002):

- **Description**

Comparison of emedastine 0.05% or nedocromil sodium 2% eye drops (in one eye) and placebo (in the other eye) in controlling local reactions in subjects with allergic conjunctivitis.
V. Orfeo, Clinica Mediterranea, ophthalmology unit, Napoli – Italy- European journal of ophthalmology/vol.12n°4.2002 / pp 262-266.

- **Methods**

- The primary objective of the study was to assess the efficacy of nedocromil sodium 2% eye drops (mast cell stabilizer) as compared to emedastine 0.05% eye drops (Histamine H1 antagonist) in producing immediate relief of ocular allergic reaction previously induced by a predetermined and standardized topical ocular dose of allergen (conjunctival allergen challenge CAC / conjunctival provocation test CPT)

- Designed as double-blind, randomised, cross-over and placebo-controlled, this study was conducted according to the CAC model. *This pharmacodynamic model was discussed and accepted (Scientific advice for Emadine) as a relevant model to evaluate allergic conjunctivitis in standardised and reproducible conditions (i.e. creation of well defined disease condition (onset and duration of treatment on selected efficacy parameters), homogeneous population, definite dose and category of allergen) provided that it was fully validated by clinical data.*

- Study population /Sample size

30 subjects with a personal history of allergic conjunctivitis were selected, enrolled and tested according to CAC conditions.
No information regarding inclusion criteria are provided for number or age of patients.

- Treatments

At the second visit, subjects were randomly treated with 2 drops of emedastine or nedocromil in one eye and 2 drops of placebo in the controlateral eye. After 5 mn the offending allergen was instilled in both eyes according to current CAC procedure.
After one week the whole procedure was repeated (visit 3) using again the placebo in the control eye and the trial medication that was not administered at visit 2, in the other eye.

- Outcomes/endpoints

The intensity of the allergic reaction was evaluated 3, 10 and 20 mn after allergen instillation, by rating scores on a 9 points scale: (sign and symptom)
  - Itching (0 none, 4 incapacitating itch)
  - Redness (0 none, 4 very severe)

- Statistical Methods

Statistical analysis was done using Student's t-test with a conservative alpha value 0.01 (multiple comparisons).

- **Results**

N/A for paediatrics on the basis of the data described and discussed in this paper.

- Recruitment/ Number analysed

This remains unknown for paediatric subjects.
The overall population of the study included 30 subjects; 19 subjects were males and 11 were females. The mean age of the selected population was 22 years (range 7-38). Except for lower border age (7 years) no information is available regarding the number of paediatrics and the pattern of age. Since no analysis of efficacy or safety results is provided in this literature reference for paediatrics, *no relevant conclusion in connection with the subject of this paediatric assessment can be drawn from the presented data.*

- Baseline data

This remains unknown for paediatric subjects.

- Efficacy results

This remains unknown for paediatric subjects.
In the whole population tested, *emedastine 0.05% and nedocromil sodium 2% eye drops are both more effective than placebo in relieving ocular itching and in reducing ocular redness, 3, 10 and 20 minutes after instillation of allergen (p<0.01).*
Emedastine 0.05% was statistically significantly (p<0.01) more effective than nedocromil 2% for redness (3, 10 and 20 minutes after instillation of allergen); similar results are observed for itching at 3 and 10 minutes but just as effective as nedocromil at 20 minutes.

- Safety results

These remain unknown for paediatric subjects.
Nevertheless, no adverse reactions were reported in this study for either emedastine or nedocromil.

Assessor's Conclusion
Indeed, this study do not raise any additional safety concern in tested patients but the cohort of paediatric patients is not identified and therefore not analysed separately. Finally it impossible to conclude about a paediatric efficacy as the number and age of children included is unknown in this double-blind, randomised, cross-over and placebo-controlled, study conducted according to the CAC model.

2. Discussion on clinical aspects

Additional paediatric data submitted by the Applicant are scarce and do not add any relevant efficacy information to the previous original file regarding paediatric use. Nevertheless, no additional paediatric safety concern is highlighted from these data.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

Due to poor design, the additional single dose non randomised study (20 children) or open label uncontrolled study (232 children including 230 children who had concomitant interfering treatments for asthma or rhinitis) cannot bring any relevant efficacy data regarding use in children suffering from seasonal allergic conjunctivitis. In the other hand, even if the third study

provides a comparison of emedastine vs nedocromil vs placebo that includes 30 subjects from 7 to 38 years of ages, no conclusion can be raised from these data as the number and the range of age regarding the children cohort is lacking.
No unexpected additional paediatric safety concern is reported in these studies.

- **Recommendation**

According to the current SPC, EMADINE may be used in paediatric patients (3 years of age and older) at the same posology as in adults.
According to Article 45, the Applicant has submitted 3 additional studies including paediatrics that are of limited interest for a paediatric use as highlighted above. Nevertheless no safety concern was raised by these experiences. Only one adverse event was recorded. This is listed in the SPC. In the other hand the efficacy in paediatric patients is not challenged by these additional data.
No changes in the current SPC are required regarding paediatric use on the basis of these additional paediatric data submitted by the MAH.

☒ **Fulfilled**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

1- The Applicant, if available, should provide all details available regarding the efficacy and safety of the paediatric cohort included in the study carried out by V. Orfeo and provided as a literature reference by Alcon according to article 45 procedure.