

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

Levocabastine

LEVOPHTA 0.05% / Livostin 0,5 mg/ml

DE/W/062/pdWS/001

Rapporteur:	Germany
Finalisation procedure (Day 120):	17.09.2014
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section IX
INN (or common name) of the active substance(s):	Levocabastine
MAH (s):	See section IX
Pharmaco-therapeutic group (ATC Code):	R01AC02 S01GX02
Pharmaceutical form(s) and strength(s):	See section IX

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.3 and possibly 4.8 SPC and the corresponding sections of the PL

Summary of outcome

- No change
- Change
 - New study data: <section(s) xxxx, xxxx>
 - New safety information: <section(s) xxxx, xxxx>
 - Paediatric information clarified: sections 4.1, 4.2, 4.8, 5.2 SPC
 - New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

III. INTRODUCTION

Two MAHs (Bausch & Lomb (levocabastine eye drops), Janssen (levocabastine eye drops and nasal spray)) submitted 52 completed paediatric study(ies) and publications for levocabastine, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

Critical expert overviews have also been provided.

Janssen proposed to remove the lower age limit for the eye drops as well as the nasal spray. This proposal is discussed below.

In addition, the following documentation has been included as per the procedural guidance:

- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product, and related PL wording

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Levocabastine is marketed as eye drops and nasal spray. No special paediatric pharmaceutical form is deemed necessary.

IV.2 Non-clinical aspects

Based on toxicology studies performed in the year 1992 where either juvenile rats were included (acute toxicity studies) or Segment II and Segment III studies were performed in rats, it can be stated, that levocabastine administration to young animals or in utero to neonatal animals showed no clinically relevant primary or reproductive toxicities.



IV.3 Clinical aspects

1. Introduction

Levocabastine is a selective histamine H1 antagonist. It is licensed as eye drops and nasal spray for the symptomatic treatment allergic conjunctivitis/rhinitis. Recommended lower age limits vary across the EU (e.g. > 12 years in Portugal, ≥1 year in Germany). The international birth date is January 1990 for levocabastine eye drops and February 1990 for levocabastine nasal spray. Levocabastine is licensed in 54 countries worldwide. In the EU, the eye drops are marketed in Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Iceland, Italy, Lichtenstein, Luxembourg, Malta, the Netherlands, Norway, Portugal, Slovakia, Spain, and Sweden.

The nasal spray is available in: Austria, Czech Republic, Denmark, Finland, Germany, Greece, Iceland, Italy, Lichtenstein, Luxembourg, Norway, Portugal, Slovakia, Spain, and Sweden.

Bausch & Lomb submitted reports for:

Study number	Study title	Number of patients enrolled	Number of pediatric patients enrolled
LEVO 93-01	Non comparative study of the safety of levocabastine 0.05% eye drops (Levophta®) in allergic conjunctivitis (Etude non comparative de la tolérance de LEVOPHTA®, collyre à la lévocabastine 0,05%, dans les conjonctivites allergiques)	148	16 (including 1 discontinued on Day 0)
LEVO 94-01 Richard C, Trinquand C and Bloch-Michel E, Comparison of topical 0.05% levocabastine and 0.1% lodoxamide in patients with allergic conjunctivitis. Study Group. <i>Eur J Ophthalmol</i> 1998, 8:207-216	Randomized double-masked study comparing efficacy and safety of 2 antiallergic eye drops, Levophta® versus Almide® in allergic conjunctivitis (Etude randomisée en double insu comparant l'efficacité et la tolérance de deux collyres anti-allergiques LEVOPHTA® versus ALMIDE® dans les conjonctivites allergiques)	93	16

The following publications were also submitted:

Author	Title	Type	Content Summary
Wüthrich and Gerber (1995)	Levocabastine eye drops are effective and well tolerated for the treatment of allergic conjunctivitis in children	Clinical efficacy and safety	
Secchi, et. al. (2000)	An efficacy and tolerance comparison of emedastine difumarate 0.05% and levocabastine hydrochloride 0.05%:	Clinical Safety	Demonstrated long term safety and efficacy of 0.05% levocabastine ophthalmic suspension in pediatric subjects.

	reducing chemosis and eyelid swelling in subjects with seasonal allergic conjunctivitis. Emadine Study Group.		
Bauer and Unkauf (2001)	Efficacy and safety of intranasally applied dimetindene maleate solution. Multicenter study in children under 14 years suffering from seasonal allergic rhinitis	Clinical Safety	Demonstrated safety of 0.05% levocabastine solution given intranasally twice daily to pediatric subjects for 2 weeks.
Wang et. al, (2001) (article in Chinese)	The curative effect of livostin spray on treating allergic rhinitis of children].	Clinical Safety	Demonstrated safety of levocabastine after intranasal administration to pediatric subjects
Kurzawa et. al. (1998) (article in Polish)	Clinical efficacy and safety of levocabastine++ in the therapy in children suffering from seasonal allergic rhinitis and conjunctivitis who are less than 12 year of age	Clinical Safety	Demonstrated safety of levocabastine after intranasal administration to pediatric subjects
Arreguin et. al. (1998) (article in Spanish)	Levocabastine versus cetirizine for perennial allergic rhinitis in children	Clinical Safety	Demonstrated safety of levocabastine after intranasal administration to pediatric subjects
Mazzotta et. al. (1998)	Treating allergic rhinitis in pregnancy. Safety considerations	Clinical Safety review	Summary of data showed no increase in congenital malformations in pregnant women exposed to chemicals of the same class of levocabastine (i.e., piperidines)
Simons and Simons (1999)	Clinical pharmacology of new histamine H1 receptor antagonists	Clinical Pharmacology & Pharmacokinetics	Overview of levocabastine pharmacokinetic and pharmacodynamic properties
Pesko-Koplowitz et. al. (1999)	Lack of effect of erythromycin and ketoconazole on the pharmacokinetics and pharmacodynamics of steady-state intranasal levocabastine	Clinical Pharmacokinetics	Demonstrated levocabastine is metabolically stable, not a substrate for cytochrome P-450 enzymes, and unlikely to have any significant drug-drug interactions
Heykants et. al. (1995)	The pharmacokinetic properties of topical levocabastine. A review	Clinical Pharmacokinetics review	Review of levocabastine pharmacokinetic properties
Baroody and Naclerio (2000)	Antiallergic effects of H1-receptor antagonists	Pharmacology review	Review of known pharmacology and pharmacodynamics of H1 receptor antagonists
Assanasen and Naclerio (2002)	Antiallergic anti-inflammatory effects of H1-antihistamines in humans	Pharmacology review	Review of known pharmacology and pharmacodynamics of H1 receptor antagonists

Janssen submitted the following study reports and publications:

**Amended Table 1. from the applicant's Levocabastine Pediatric Workshare Tables – HA Request document
Clinical Studies Included in the Levocabastine Pediatric Workshare**

First Author or Study Number	Study Title	Total Number of Patients Enrolled	Number of Pediatric Patients Enrolled
Pharmacokinetic Studies			
CRR LEV-INT-2 1993 ^{Fout!} Verwijzingsbron niet gevonden.	Levocabastine vs cromoglycate in children with seasonal allergic rhinoconjunctivitis.	196	196
CRR R50547/48 1988 ^{Fout!} Verwijzingsbron niet gevonden.	Levocabastine nasal spray in the treatment of rhinitis in asthmatic children: a double blind comparison with placebo	38	38

First Author or Study Number	Study Title	Total Number of Patients Enrolled	Number of Pediatric Patients Enrolled
CRR R50547/62 1988 ^{Fout!} Verwijzingsbron niet gevonden.	Double-blind comparison of levocabastine nasal spray with sodium cromoglycate in the topical treatment of seasonal allergic rhinitis.	39	15 (≤15 years old), 6 (16-20 years old)
Safety and Efficacy Studies			
CRR JC LEV-D/9005 1994 ^{Fout!} Verwijzingsbron niet gevonden.	Objective and clinical evaluation of the efficacy and safety of levocabastine-D nasal spray in the management of paediatric patients with seasonal allergic rhinitis: A double blind comparison with levocabastine, oxymetazoline, and placebo.	243	243
CRR LEV-RSA-2 1998 ^{Fout!} Verwijzingsbron niet gevonden.	A single-blind trial to compare the efficacy, tolerability and safety of levocabastine nasal spray as compared to sodium cromoglycate nasal spray in children aged 6 months to 5 years with perennial allergic rhinitis./Part I.	215	215
CRR R50547/30 1986	Levocabastine versus placebo and cromoglycate in atopic conjunctivitis. A double-blind placebo controlled study.	17	4
CRR R50547/31 1986 ^{Fout!} Verwijzingsbron niet gevonden.	A double-blind study in allergic conjunctivitis, comparing the levocabastine eye-drops with placebo and cromoglycate.	12	2
LEV-INT-10 1997 ^{Fout!} Verwijzingsbron niet gevonden.	Levocabastine in perennial allergic rhinoconjunctivitis. An open, long-term trial in children.	115	115
CRR R50547/21 ^{Fout!} Verwijzingsbron niet gevonden.	Tolerance of levocabastine eye drops; an open study in volunteers and patients.	20	8
CRR R50547/CH 1987	Levocabastine nasal spray in patients with pollinosis. Double-blind, placebo controlled evaluation [translation].	16	3
Bauer C	Efficacy and safety of intranasally applied dimetindene maleate solution [translation].	100	100
Bonini S	Levocabastine eye drops in vernal keratoconjunctivitis	22	22
Ciprandi G	Double-masked, randomized, parallel-group study comparing olopatadine 0.1% ophthalmic solution with cromolyn sodium 2% and levocabastine 0.05% ophthalmic preparations in children with seasonal allergic conjunctivitis [translation].	52	52
Emeryk A	Combined intranasal therapy of seasonal allergic rhinitis (SAR) in children: topical levocabastine plus disodium cromoglycate provides better clinical improvement of nasal symptoms than disodium cromoglycate alone.	25	25
Falconieri P	Effectiveness of levocabastine eyedrops in children with allergic conjunctivitis: a double-blind study [translation].	23	23
Gallegos M	Levocabastine eye drops solution versus a sulphacetamide-prednisolone-phenylephrine eye drops suspension for the treatment of vernal allergic conjunctivitis [translation].	35	35

First Author or Study Number	Study Title	Total Number of Patients Enrolled	Number of Pediatric Patients Enrolled
Graue-Wiechers E	Double blind study of topical levocabastine versus topical placebo in the management of vernal conjunctivitis [translation].	40	40
Hrubiško M	Is concomitant local and oral antihistamine treatment of allergic rhinoconjunctivitis well-founded? A clinical study of levocabastine + astemizole [translation].	40	20
Kurzawa R	Evaluation of the clinical efficacy and safety of levocabastine in the treatment of seasonal allergic rhinitis and conjunctivitis in children under the age of 12 years [translation].	32	32
Lanna M	Effects of levocabastine versus antazoline in younger patients affect by vernal conjunctivitis [translation].	20	20
Lemagne JM	Levocabastine in the treatment of allergic conjunctivitis	213	20 (<14 years old), 89 (14-30 years old) ¹
Möller C	The efficacy of levocabastine eye drops in birch pollinosis: a double-blind comparison with sodium cromoglycate in the area surrounding Umea.	65	47 (6-15 years old), 17 (16-20 years old) ²
Njaa F	Levocabastine compared with sodium cromoglycate eyedrops in children with both birch and grass pollen allergy.	55	55
Odelram H	Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis.	37	37 (6-19 years old) ³
Okuda M ^{Fout!} Verwijzingsbron niet gevonden.	Clinical investigation of R 50547 (levocabastine hydrochloride) nasal spray in pediatric perennial allergic rhinitis [translation].	60	60
Osuna L	Levocabastine versus cetirizine for the treatment of perennial allergic rhinitis in children [translation].	30	30
Rimas M	Topical levocabastine protects better than sodium cromoglycate and placebo in conjunctival provocation tests	25	25
Sabbah A	Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children.	113	113
Sawa M	Clinical evaluation of R50547 ophthalmic suspension in allergic conjunctivitis and vernal conjunctivitis - open study in children [translation].	44	44
Secchi A	Safety and efficacy comparison of emedastine 0.05% ophthalmic solution compared to levocabastine 0.05% ophthalmic suspension in pediatric subjects with allergic conjunctivitis.	42	42
Tizler Cieslik E	A comparison of levocabastine and sodium cromoglycate in children with allergic conjunctivitis due to house dust mite.	48	48
Vassileva H	Results of the treatment of the seasonal pollinosis allergic rhinitis with the topical preparations livostin, bicromat and vibrosil.	78	78
Verin P	Clinical evaluation of twice-daily emedastine 0.05% eye drops (emadine eye drops) versus levocabastine 0.05% eye drops in patients with allergic conjunctivitis.	222	42

¹ Number of patients aged > 18 years not specified.

² Number of patients aged 18-20 years not specified.

³ Number of patients aged 18-19 years not specified.

First Author or Study Number	Study Title	Total Number of Patients Enrolled	Number of Pediatric Patients Enrolled
Wuethrich B	Levocabastine eye drops are effective and well tolerated for the treatment of allergic conjunctivitis in children [translation].	233	233
Zebede M	Comparison of the efficacy and safety of intranasal therapy with levocabastine vs oxymetazoline in children with perennial allergic rhinitis [translation].	60	60
Bernardini R	Eosinophil cationic protein (ECP) and tryptase in the nasal lavage fluid (NLF) of children with grass pollen rhinitis: levocabastine effect.	24	24

2. Clinical study(ies)

Studies submitted by Bausch & Lomb

Eye drops:

Levo-93-01: Non comparative study of safety of levocabastine 0.05% eye drops (Levophta) in allergic conjunctivitis (1993-1994) (The applicant provided the study report in French. Only the synopsis was provided in English.)

➤ Description

This was a Phase IV, open, uncontrolled, multi-centre, 2 week safety study conducted in 24 centres in France.

➤ Methods

- **Objective(s):** to evaluate the local and systemic safety of Levophta, 0.05% levocabastine eye drops, in patients suffering from allergic conjunctivitis
- **Study design:** open, uncontrolled trial
- **Study population /Sample size:** the study enrolled 148 patients (16 paediatric patients, one discontinued on Day 0) > 6 years of age suffering from allergic conjunctivitis for at least 24 hours with history of previous attacks.
- **Treatments:** Levophta 1 drop BID, possibly 1 drop TID or QID
- **Outcomes/endpoints:** main criteria were subjective tolerance by VARS (visual analog scale), local and systemic tolerance assessed by occurrence of AEs.
- **Statistical Methods:** non comparative statistics (further information not provided)

Results

- **Recruitment/ Number analysed:** 148 patients including 16 paediatric patients were enrolled. 23 patients discontinued prematurely (10 lost to follow-up, 6 worsening of disease, 5 due to AEs, 1 consent withdrawn, 1 signs disappeared at D10 (??))
- **Baseline data:** The study enrolled 43 males and 105 females. Mean age was 40 years.

- **Efficacy results:** Clinical subjective and objective signs (prickling, burning, photophobia, itching, hyperthermia, conjunctival edema, eyelid edema, tearing) decreased during the study (50% resolved at Day 7).
- **Safety results:** Local tolerance to drug installation was satisfactory ($\leq 25\%$ of VARS at Day 7) and improved after the first days. 33 patients (22%) reported 46 AEs. Most common AEs, each reported in 6 patients were allergy worsening, burning sensation and headache. No summary on SAEs is given. However, one macular haemorrhage, one tetany and one wrist fracture were reported.

Assessor's comment: This is an uncontrolled safety study which enrolled a low number of paediatric patients. The lack of a comparator hampers interpretability. No separate analysis of the paediatric patients has been provided in the study synopsis. However additional information combining paediatric data from studies LEVO 93-01 and LEVO-94-01 has been found in the clinical expert report. One child discontinued at D0 due to vernal keratoconjunctivitis which was an exclusion criterion. 31 children (5-17 years, 15 male, 16 female) received 2-4 installations of study treatment per day for 2 weeks. 24 were treated with 2-4 installations of levocabastine and 7 children were treated with 4 installations of lodoxamide per day. 17 subjects suffered from seasonal and 14 subjects suffered from perennial allergic conjunctivitis. Treatment compliance was good or very good in all but 2 subjects. Efficacy as judged by the investigator was good or very good in most cases. In 5/24 children in the levocabastine group it was not considered to be satisfactory. Tolerance was good or very good in most cases but bad or medium in 5/24 children in the levocabastine group and 1/7 children treated with lodoxamide. There were no SAEs. Four AEs were recorded. 3/24 children in the levocabastine group (headache, blepharoconjunctivitis which led to discontinuation, paralimbic keratitis of immuno-allergic type) and 1/7 children (viral conjunctivitis) reported an AE. The number of children is still low and it is not clear if comparable efficacy to lodoxamide can be claimed, however no changes to the SPC are warranted.

Levo-94-01: Randomized double masked study comparing efficacy and safety of 2 antiallergic eye drops, Levophta versus Almide in allergic conjunctivitis (1995-1996) (The applicant provided the study report in French. Only the synopsis was provided in English.)

➤ **Description**

This was a Phase IV, double masked, randomised, controlled, parallel group, 2 week safety and efficacy study conducted in 6 centres in France.

➤ **Methods**

- **Objective(s):** to evaluate the efficacy and tolerance of two anti-allergic drugs, in patients suffering from allergic conjunctivitis
- **Study design:** double masked, randomised, active-controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled 93 patients (16 paediatric patients) >6 years of age suffering from chronic or acute allergic conjunctivitis.
- **Treatments:**

Levophta (0.05% levocabastine eye drops): 1 drop BID
versus
Almide (0.1% Lodoxamide eye drops): 1 drop QID

- **Outcomes/endpoints:**
Efficacy: Score of subjective and objective signs at D 0, 7, 4
Safety: Tolerance on instillation, AEs
- **Statistical Methods:**
Initial comparison of the 2 groups: quantitative parameters: t-test/Kruskal-Wallis, qualitative parameters: chi-2/Fischer, scoring: Wilcoxon test
Efficacy: objective-subjective scores: non parametric repeated measure analysis of variance (CATMOD), sum of objective signs, sum of subjective signs: Student test/Kruskal-Wallis for each visit. Investigator evaluation: chi-2/Fisher
Safety: Tolerance on instillation: non parametric Kruskal-Wallis test each day, AEs: Mantel Haenszel test.

Results

- **Recruitment/ Number analysed:** 93 patients including 16 paediatric patients were enrolled. 13 patients discontinued prematurely (9 (5 from the levocabastine and 4 from the lodoxamine group) due to AEs, 4 (3 from the levocabastine group) due to other reasons).
- **Baseline data:** The study enrolled 54 males and 39 females. Mean age was 30 years.
- **Efficacy results:** Significant decrease of clinical signs with time, without any difference between the treatment groups. Satisfactory global efficacy evaluation (no details are given in the English synopsis).
- **Safety results:** Good local and systemic tolerance in both groups. (No details are given in the English synopsis).

Assessor's comment: The information given in the English synopsis is rather sparse. The French study report gave the following information: sum of the subjective scores (right eye changed from a mean of 6.01 at Day 0 to 2.13 at D14(change from baseline:-3.88) in the levocabastine group. In the lodoxamide group it changed from 6.40 to 1.71 (change from baseline: -4.69). The sum of the objective score (right eye) changed from a mean of 4.29 at day 0 in the levocabastine group to 1.58 (change from baseline : - 2,71). In the lodoxamide group it changed from 4.57 to 1.30 (change from baseline:- 3.27). No formal non-inferiority testing seems to have taken place. . 39 patients (levocabastine: 16, lodoxamide: 2) reported AEs. 54 AEs were reported in total. For combined paediatric data please see comment above. No changes to the SPC can be deduced.

Studies submitted by Janssen:

PK studies:

Nasal spray and eyedrops:

CRR LEV-INT-2 (1993): Levocabastine versus cromoglycate in children with seasonal allergic rhinoconjunctivitis

➤ Description

This was a double blind (single blind in UK), controlled, parallel group, 4 week safety and efficacy multicentre study conducted in Austria, Great Britain, The Netherlands and South Africa.

➤ Methods

- **Objective(s):** to evaluate the efficacy, safety and tolerance of levocabastine in comparison to cromoglycate in children 6-15 years of age.
- **Study design:** double blind (UK single blind), active-controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled patients 6-15 years of age suffering from moderate to severe nasal symptoms of allergic rhinoconjunctivitis.
- **Treatments:**

Levocabastine 0.05% nasal spray and eye drops BID
versus
Cromoglycate 2% nasal spray and eye drops QID

Nasal spray had to be administered throughout the study, eye drops when needed.

- **Outcomes/endpoints:**
Efficacy: Score of signs of allergic rhinoconjunctivitis at D0,14,28, overall severity on visual analogue scale, global evaluation of treatment
Safety: AEs, haematology and blood biochemistry
Pk data (South Africa only)
- **Statistical Methods:**
ITT analysis was performed. Individual symptoms were analysed and the highest score for histamine induced nasal symptoms was calculated, as well as the sum of nasal symptoms and the sum of all symptoms. For the evaluation of the patient's diaries the AUC was calculated for each symptom.
For intergroup comparisons the Mann-Whitney U.Test or the Fisher's exact test were used (two-tailed). For intra-group comparisons, the Wilcoxon-test was applied.

Results

- **Recruitment/ Number analysed:** 95 patients (5-20 years) were enrolled in the levocabastine group. 101 patients were enrolled in the cromoglycate group. 24 patients discontinued prematurely (6 (4 from the levocabastine and 2 from the cromoglycate group) due to AEs).
- **Baseline data:** Treatment groups were comparable at baseline for most characteristics. The investigator's score for sneezing was significantly higher in the levocabastine group. Patients in the cromoglycate group used more antiasthmatic medication including inhaled corticosteroids.
- **Efficacy results:** Few differences were seen between both groups when the whole population was analysed. Tearing was significantly lower in the cromoglycate group for the entire trial period.
- **Safety results:** 35 % reported an AE (reported in CRF, if reports in diaries are added 67% of the patients in the levocabastine group and 62% of the patients in the cromoglycate group reported an AE). No SAE was reported. Headache was the most

frequently reported AE. The pattern of AEs was comparable between groups. No consistent effects on haematological and biochemical parameters were seen.

- **PK data:** Levels were available from 52 patients. Time of blood sampling was not standardized. Mean level was 3.92 ng/ml.

Assessor's comment: The applicant submitted this report under the heading PK studies, although it mainly was an efficacy and safety study focusing on the nasal spray. The additional use of the eye drops was done as needed which hampers the interpretability of the study. Part of the study was conducted in a single blind manner. Analysis for the single and the double blind part are also given separately in the report. The decision to conduct the study with two different designs is not considered beneficial as regards quality of the data. Although results were mostly comparable between groups, the study was not designed to establish non-inferiority/ equivalence between treatments. The design lacks assay sensitivity. The PK data is very hard to assess with timing of sampling not standardized. No change to the SPC is warranted.

Nasal spray:

CRR R50547/48 (1986): Levocabastine nasal spray in the treatment of rhinitis in asthmatic children: a double blind comparison with placebo

➤ **Description**

This was a double blind, randomised, placebo-controlled, parallel group 4 week study conducted in one centre in South Africa.

➤ **Methods**

- **Objective(s):** not given in protocol (seems to be efficacy and safety compared to placebo)
- **Study design:** double blind, randomised, placebo-controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled asthmatic children with a typical history of rhinitis.
- **Treatments:**

Levocabastine 0.5 mg/ml nasal spray 2 sprays in each nostril up to 4 times daily versus placebo

- **Outcomes/endpoints:**
Efficacy: symptom evaluation by investigator, global evaluation by investigator and patient/caregiver
Safety: AEs, haematology and blood biochemistry
PK data after 2 and 4 weeks
- **Statistical Methods:**
Wilcoxon matched pairs signed-ranks test for intragroup comparisons. Mann-Whitney U test for intergroup comparisons.

Results

- **Recruitment/ Number analysed:** 19 patients (6-15 years of age) were enrolled in each group and analysed for efficacy and safety.
- **Baseline data:** More patients with severe symptoms were enrolled in the levocabastine group.
- **Efficacy results:** Significantly greater improvements in severity of itchy nose at week 2 and sneezing at week 4 were seen in the levocabastine group.
- **Safety results:** 3 patients in the levocabastine group and 4 patients in the placebo group reported an AE. No consistent effects on haematological and biochemical parameters were seen.
- **PK data:** Mean plasma levels were 3.2 ng/ml after 2 weeks and 2.1 ng/ml after 4 weeks.

Assessor's comment: this study compared levocabastine nasal spray to placebo in a rather low number of patients. This comparison resulted in significant differences for a limited number of comparisons only. Comparison to an active comparator is missing. No change to the SPC is warranted.

CRR R50547/62 (1986): Double blind comparison of levocabastine nasal spray with sodium cromoglycate in the topical treatment of seasonal allergic rhinitis

➤ **Description**

This was a double blind, randomised, active-controlled, parallel group 2 or 4 week study conducted in one centre in Spain.

➤ **Methods**

- **Objective(s):** not given in protocol (seems to be efficacy and safety compared to placebo)
- **Study design:** double blind, randomised, active-controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled outpatients with clinical symptoms of seasonal allergic rhinitis verified by skin or RAS test.
- **Treatments:**
Levocabastine 0.5 mg/ml nasal spray 2 sprays in each nostril 4 times daily
versus
sodium cromoglycate (20 mg/ml) nasal spray 2 sprays in each nostril 4 times daily
- **Outcomes/endpoints:**
Efficacy: symptom evaluation by investigator, global evaluation by investigator and patient/caregiver, patient self rating of nasal symptoms by means of visual analogue scales (VAS)
Safety: AEs, haematology and blood biochemistry
PK data after 2 and 4 weeks
- **Statistical Methods:**

Wilcoxon matched pairs signed-ranks test for intragroup comparisons. Mann-Whitney U test for intergroup comparisons.

Results

- **Recruitment/ Number analysed:** 19 patients (9-36 years of age) were enrolled in the levocabastine group. 13 patients were between 9 and 20 years of age. 20 patients (8-42 years of age) were enrolled in the cromoglycate group. 8 patients were 8 to 20 years old. One patient in the levocabastine group and 5 patients in the cromoglycate group were excluded from the analysis (Score of nasal symptoms too low, lost to follow up, drop-out for inefficacy) .One patient in the cromoglycate group dropped out due to an AE. All patients were analysed after 2 weeks. Data from 6 patients were also reported at week 4.
- **Baseline data:** Groups were balanced for most baseline criteria. Sneezing was significantly more severe in the cromoglycate group.
- **Efficacy results:** No significant differences were found in the investigator's symptom severity scores and the global evaluations by investigator and patients. Taken from the patients' diaries, the median overall VAS score for nasal symptoms was significantly better in the levocabastine group. The percentage of symptom-free days was higher, the percentage of days with moderate or severe symptoms lower and the AUC of daily symptom severity score was smaller in the levocabastine compared to the cromoglycate group for almost all symptoms, except for blocked nose. Levocabastine significantly alleviated sneezing and itchy nose compared to cromoglycate.
- **Safety results:** 4/19 patients in the levocabastine group and 6/19 patients in the cromoglycate group reported an AE. One patient dropped- out for severe nasal irritation and nausea in the cromoglycate group. No differences in haematological and biochemical assessments were found after 2 and 4 weeks.
- **PK data:** Plasma levels were between 0.28 and 18.2 ng/ml.

Assessor's comment: The choice of the comparator is debatable comparison to a licensed antihistamine would have better. The results of this study do not warrant changes to the SPC.

Assessor's overall comment on PK data: In the clinical overview the applicant gives a comparison of adult and paediatric data for the nasal spray. Plasma levels were overall comparable although firm conclusions are not possible due to the very limited and low-quality information available. No change to the SPC is proposed. No data on PK of eye drops (as mono-therapy) has been submitted.

Safety and efficacy studies:

Nasal spray:

CRR JC LEV-D/9005 (1991-2): Objective and clinical evaluation of the efficacy and safety of levocabastine-D nasal spray in the management of paediatric patients with

seasonal allergic rhinitis: A double blind comparison with levocabastine, oxymetazoline, and placebo

➤ **Description**

This was a prospective, double blind, randomised, placebo and active-controlled, parallel group 7 day study.

➤ **Methods**

- **Objective(s):**
to compare the subjective and objective of topical nasal levocabastine-D with placebo
- **Study design:** prospective, double blind, randomised, active-controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled outpatients aged 6-13 years with clinical symptoms of seasonal allergic rhinitis severe enough to warrant antiallergic therapy and verified by skin tests.
The sample size estimates were based on a comparison of levocabastine D to placebo, using the area under the curve of the daily diary symptom score for nasal congestion. The unpaired t-test was employed, resulting in an estimate of 66 patients per treatment group in order to have 80 % power when comparing each mono-component to levocabastine D.
- **Treatments:**
Levocabastine 0.5 mg/ml nasal spray 2 sprays in each nostril BID
versus
Oxymetazoline 0.5 mg/ml nasal spray 2 sprays in each nostril BID
Versus
Levocabastine D spray (0.5mg/ml levoacabastine + 0.5 mg/ml oxymetazoline) nasal spray
2 sprays in each nostril BID
Versus
Placebo
- **Outcomes/endpoints:**
Primary efficacy parameters included:
summed symptom severity scores for all nasal symptoms excluding congestion, both including and excluding itchy throat
symptom severity score for nasal congestion
VAS for nasal symptom relief
Response rate
Objective parameters: nasal air resistance, number of eosinophils in nasal secretion, tympanic membrane compliance, saccharin transit time
- **Statistical Methods:**
Primary and secondary efficacy variables were analysed using two tailed test with α set at 0.05 for significance. The primary analysis of subjective and objective efficacy parameters was done on the comparison of levocabastine D and placebo.
In order to analyse the different primary parameters difference scores from baseline to the last available visit were analysed using the ANOVA to test for the effects of treatment group and study centre by treatment group interaction, or the Cochran-Mantel-Haenszel

procedure was applied to test for centre effect, where this was not found the Pearson's chi-square test was used to assess the difference among treatment groups. The objective parameters were used to compare the response of all treatment groups by means of the ANOVA test.

Results

- **Recruitment/ Number analysed:** 251 patients were enrolled. Mean age was 9.1 years. 2 patients, one in the levocabastine group and one in the oxymetazoline group discontinued prematurely. 8 patients were considered to be unevaluable due to protocol violations.
- **Baseline data:** mean duration of the disease was the lowest in the levocabastine group. Age, sex and height were not significantly different between groups.
- **Efficacy results:** the results are summed up in the CSR:

THERAPEUTIC RESULTS	
<p>Primary Parameters:</p> <ul style="list-style-type: none"> - Nasal symptoms excluding congestion - Nasal symptoms excluding congestion plus itchy throat - Nasal congestion - Global evaluations and response rate - VAS assessment of nasal congestion - VAS assessment of other nasal symptoms - Time to first relief of symptoms - Clinical improvement of SAR symptoms - Objective parameters (anterior rhinomanometry, eosinophils in nasal secretions, tympanometry, saccharin transit time) <p>Secondary Parameters:</p> <ul style="list-style-type: none"> - Ocular symptoms - Itchy throat - Total symptoms - Total nasal symptoms - Premature discontinuation due to lack of efficacy - Use of rescue medication - Duration of effect 	<p>No statistically significant differences</p> <p>Marginally significant difference ($p=0.0269$) between levo-D and oxymetazoline (in favour of levo-D) for mean AUC of difference from baseline ($\alpha=0.025$)</p> <p>Some treatment by centre interaction for difference from baseline, but small N makes results not reliable</p> <p>No statistically significant differences for any of these parameters</p> <p>For nasal airway resistance, statistically significant differences (in favour of levo-D) between levo-D and placebo ($p=0.0001$) and levo-D and levo ($p=0.0019$), as well as (in favour of oxy) between oxy and placebo ($p=0.0001$), for difference from baseline. No statistically significant differences for the other three parameters.</p> <p>Statistically significant difference ($p=0.014$) between levo-D and placebo (in favour of levo-D) for use of rescue medication. No statistically significant differences for the other six parameters.</p>

- **Safety results:** 39, 55, 42, 44 AEs were reported in the levocabastine, oxymetazoline, levocabastine-D and placebo group, respectively. Most common AEs were asthma and headache. Physical exams, vital signs, laboratory test and ECGs did not reveal clinically relevant safety results.

Assessor's comment: this study compares the combination of levocabastine and oxymetazoline to the mono-substances and to placebo. A number of primary EPs are used. The results are not consistent. No changes to the SPC of levocabastine mono-substance are warranted.

CRR LEV-RSA-2-1998 (1995): A single blind trial to compare the efficacy, tolerability and safety of levocabastine nasal spray as compared to sodium cromoglycate nasal spray in children aged 6 months to 5 years with perennial allergic rhinitis/ Part I

➤ **Description**

This was a phase IIIb, multicentre, single blind, randomised, stratified (0.5-2 years, >2 years- 6 years), active controlled, 4 week study conducted in 5 centres in South Africa.

➤ **Methods**

- **Objective(s):**
to determine the efficacy, tolerability and safety of levocabastine vs sodium cromoglycate in children with perennial allergic rhinitis.
- **Study design:** single blind, active-controlled, randomised, stratified (0.5-2 years, >2 years- 6 years) parallel-group trial
- **Study population /Sample size:** the study enrolled patients aged 0.5-6 years with perennial symptomatic allergic rhinitis verified by skin tests.
Target number of subjects was 82 per group (no justification given). At least 200 were to be recruited to allow for a 20% drop-out rate.
- **Treatments:**
Levocabastine 0.5 mg/ml nasal spray 1 spray in each nostril BID
versus
Sodium cromoglycate 20 mg/ml nasal spray 1 spray in each nostril QID
- **Outcomes/endpoints:**
Primary efficacy parameter: Response rate at endpoint, defined as “excellent or good by subject: No. of subjects (%)
- **Statistical Methods:**
For the primary efficacy parameter the treatment groups were compared using the Wilcoxon rank sum test. Additionally to detect age class differences, an analysis of variance models with treatment, age class and their interaction was carried out.

Results

- **Recruitment/ Number analysed:** 108 patients were enrolled in the levocabastine arm. 107 patients were enrolled in the sodium cromoglycate arm. Mean age was 2.0 years (range 0.0-5.0 years). 9 patients dropped out in the levocabastine arm (AEs). 13 patients dropped-out in the sodium cromoglycate arm (7 due to AEs). Rate of protocol deviations (mainly concomitant treatment) was high in both groups (levocabastine: n= 29, sodium cromoglycate: n= 37).
- **Baseline data:** groups were balanced at baseline.

- **Efficacy results:** At endpoint an overall response rate of 69% was observed in both treatment groups (primary EP). Response rates were similar in both age groups. Regarding the secondary EP runny nose at week 2, the levocabastine patients did significantly better. The remaining results were comparable between groups. Onset of action was faster in the levocabastine group.
- **Safety results:** 72% of the patients in the levocabastine group compared to 65% of the patients in the cromoglycate group reported AEs. The most frequently reported AEs were coughing (levocabastine: 16%, sodium cromoglycate: 12%), fever (levocabastine. 12%, sodium cromoglycate: 16%), viral infection (levocabastine: 14%, sodium cromoglycate: 17%), otitis media (levocabastine: 16%, sodium cromoglycate: 8%), upper respiratory tract infection(levocabastine: 16%, sodium cromoglycate: 13%), rhinitis (13% both groups), pharyngitis (levocabastine: 15%, sodium cromoglycate: 6%) and bronchospasm (considered not drug related) (levocabastine 10%, sodium cromoglycate 1%). 4 subjects in the levocabastine group (pneumonia, otitis media, gastroenteritis, upper respiratory tract infection) and 3 subjects in the sodium cromoglycate group experienced SAEs (asthma; convulsion, with fever and upper respiratory infection and dizziness with faintness, rash maculo-papular and sweating increased). 8 subjects in the levocabastine arm and 7 subjects in the sodium cromoglycate arm withdrew due to an AE. No consistent changes in lab chemistry were seen.

Assessor's comment: this study compares levocabastine at a low dose to sodium cromoglycate. Results were comparable. However no firm conclusions regarding equivalence of both treatments can be drawn as the study had an insensitive design. No safety signal was detected. No change to the SPC is warranted.

CRR R50547/CH (1984-6): Levocabastine nasal spray in patients with pollinosis. Double blind, placebo controlled evaluation

➤ **Description**

This was a double blind, placebo controlled, randomised study using two different formulations of levocabastine (alkaline and neutral solution).

➤ **Methods**

- **Objective(s):**
to assess the safety and efficacy of levocabastine nasal spray.
- **Study design:** double blind, placebo controlled, parallel-group, 2 week study
- **Study population /Sample size:** 10 patients suffering from symptomatic and verified allergic rhinitis to grass pollen. Exclusion criteria were among others: age less than 18 years. However, three paediatric patients (13-17 years of age) were enrolled. The patients initially enrolled in the study were treated with the alkaline solution. In 1986 6 additional patients were enrolled and received the neutral solution.
- **Treatments:**
Levocabastine nasal spray, two puffs per nostril BID (daily dose 0.2mg)
In series I alkaline nasal spray was used, while in series II the spray was neutral in ph.

Versus
placebo

- **Outcomes/endpoints:**
Symptom score evaluating typical allergic symptoms of the nose and the eye performed by the study physician and the patient plus overall perception of severity by the patient on VAS.
- **Statistical Methods:**
No details given.

Results

- **Recruitment/ Number analysed:** 10 healthy volunteers were evaluated after 1 week treatment. 10 patients were enrolled. All except for two were evaluated after one week. All but two were evaluated at the end of their treatment. A high percentage of patients used concomitant medication. These patients seem to have been excluded from at least a part of the analyses. It is not really clear how many patients were included in the analyses.
- **Baseline data:** The total symptom score was higher in the placebo group while the groups were balanced otherwise.
- **Efficacy results:** The percentage reduction in the total nasal symptom score rated by the investigator was on the border to significance ($p=0.5$). No significant difference in the overall evaluation of treatment success was found. The average improvement during the entire observation period was significantly better in the levocabastine group ($p=0.0005$).
- **Safety results:**

Only two patients (placebo group: nasal irritation, levocabastine series I: burning of eyes while on concomitant eye drops) reported AEs.

Assessor's comment: This is another rather small study. A lot of patients used concomitant medication. The study was inconclusive for some key end-points which might be due to the low number of participants. No changes to the SPC are warranted.

Eye drops:

CRR R50547/30 (1986): Levocabastine versus placebo and cromoglycate in atopic conjunctivitis. A double-blind placebo controlled study

- **Description**
This was double blind, placebo and active controlled 2 week study in patients aged 7 to 36 years.
- **Methods**
 - **Objective(s):**

to compare efficacy and safety of levocabastine vs cromoglycate and placebo all administered as eye drops.

- **Study design:** double blind, active-and placebo controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled 17 patients aged 7-36 years (4 paediatric patients). Patient selection was based upon typical symptomatology and /or anamnesis for atopic conjunctivitis.
No details on the sample size calculation are provided in the report.
- **Treatments:**
Levocabastine eye drops (concentration not given) one drop per eye QID
versus
Sodium cromoglycate eye drops (concentration not given) one drop per eye QID
Versus
Placebo eye drops one drop per eye QID
- **Outcomes/endpoints:**
Ocular symptoms were assessed at selection and after 2 weeks of treatment.
- **Statistical Methods:**
No details given

Results

- **Recruitment/ Number analysed:** Recruitment was low due to bad weather conditions. 17 patients (levocabastine: 6; cromoglycate: 6, placebo: 5) aged 7-36 years (4 paediatric patients: 1 levocabastine, 3 cromoglycate) were enrolled. 1 paediatric patient of the cromoglycate group was lost to follow-up.
- **Baseline data:** No details given.
- **Efficacy results:** Due to the low number of patients no conclusions were drawn.
- **Safety results:** One paediatric patient in the levocabastine group and one patient in the cromoglycate group reported irritation after instillation.

Assessor's comment: Data on this study is rather sparse. Due to the low number of patients the study was inconclusive. No changes to the SPC are warranted.

CRR R50547/31 (1986): A double blind study in allergic conjunctivitis comparing the levocabastine eye drops with placebo and cromoglycate

➤ **Description**

This was double blind, placebo and active controlled 6 week study.

➤ **Methods**

- **Objective(s):**

to compare efficacy and safety of levocabastine vs cromoglycate and placebo all administered as eye drops.

- **Study design:** double blind, active-and placebo controlled, parallel-group trial
- **Study population /Sample size:** the study enrolled 12 patients aged 15-64 years (2 paediatric patients) with atopic conjunctivitis.
No details on the sample size calculation are provided in the report.
- **Treatments:**
Levocabastine eye drops (concentration not given) one drop per eye QID
versus
Sodium cromoglycate eye drops (concentration not given) one drop per eye QID
Versus
Placebo eye drops one drop per eye QID
- **Outcomes/endpoints:**
Ocular symptoms were assessed by the patient and an ophthalmologist at selection and after 1, 2, and 6 weeks of treatment. Flourescein tests were done and ocular pressure measured.
- **Statistical Methods:**
No details given

Results

- **Recruitment/ Number analysed:** Recruitment was low due to bad weather conditions. 12 patients aged 15-64 years (2 paediatric patients: 1 levocabastine, 1 cromoglycate) were enrolled. Only four patients completed the study. The paediatric patient in the levocabastine group was reported lost to follow-up after 2 weeks. The patient in the cromoglycate group stopped after 1 week.
- **Baseline data:** No details given.
- **Efficacy results:** Due to the low number of patients no conclusions were drawn.
- **Safety results:** The paediatric patient in the levocabastine group reported irritation after instillation.

Assessor's comment: Data on this study is rather sparse. Due to the low number of patients the study was inconclusive. No changes to the SPC are warranted.

CRR R50547/21: Tolerance of levocabastine eye drops; an open study in volunteers and patients

➤ Description

This was an open, uncontrolled safety study.

➤ Methods

- **Objective(s):**

to study the safety of chronic use of levocabastine eye drops.

- **Study design:** open, uncontrolled safety study
- **Study population /Sample size:** in phase 1 the study enrolled 10 healthy volunteers (9 males, age range: 13 to 65 years), in phase 2 ten female patients (age range 6 to 45 years) presenting with symptoms of conjunctivitis (6 suffered from allergic and 4 from vernal conjunctivitis) were enrolled.
No information on sample size calculations is given.

- **Treatments:**

Levocabastine eye drops, 1 drop (0.025mg) per eye QID

Treatment duration:

Healthy volunteers: 1 week

Patients: as long as needed, minimum: 1 week (range: 1-4 weeks)

- **Outcomes/endpoints:**

Objective and subjective assessment of tolerance including an ophthalmological examination

- **Statistical Methods:**

No details given.

Results

- **Recruitment/ Number analysed:** 10 healthy volunteer were evaluated after 1 week treatment. 10 patients were enrolled. All except for two were evaluated after one week. All but two were evaluated at the end of their treatment.
- **Baseline data:** Please see study population.
- **Efficacy results:** in 89% of the evaluable cases efficacy was reported as excellent in 5 and good in 3 cases. Subjective symptoms improved fast with statistically significant improvement after one week. Objective results were statistically significant at the end of treatment.
- **Safety results:**

Part 1: No changes in objective measurements were observed. 6 volunteers rated tolerance excellent, 3 good and 1 moderate.

Part 2: No relevant changes in results of the ophthalmological tests could be found. Seven patients reported excellent tolerance, one patient rated tolerance good and two patients unsatisfactory.

Assessor's comment: This is another uncontrolled and rather small study. No changes to the SPC are warranted.

Lemagne JM et al.: Levocabastine in the treatment of allergic conjunctivitis (Saint Luc University Hospital, Brussel, 1990): Please note that only a short summary of the study has been provided:

109 patients < 20 years of age suffering from allergic conjunctivitis were treated with levocabastine 0.5mg/ml eye drops. Patients were to administer one drop of levocabastine per eye bid. Trial duration was 3 to 7 days. Patients had to rate ocular symptoms before and after each treatment. Global assessments were made by the investigators. 34 patients (number of paediatric patients not given) stopped treatment after 3 days for various reasons (cure, AEs, lack of efficacy). These patients were included in the analysis. 5 patients (number of paediatric patients not given) did not complete their dairies. Global evaluations by the investigator were available for all patients. Levocabastine was rated excellent or good in 69% of the patients, moderate in 16% and insufficient in 15% (paediatric data not given). 3% of the patients reported ocular irritation of significant importance (paediatric data not given). Regarding symptoms, a significant and fast relief was seen in most patients.

Assessor's comment: Only limited information is available on this study. Assessment of the results is hampered by the lack of a control group. No change to the SPC seems warranted.

Nasal spray and eye drops:

LEV-INT-10 (1994/5): Levocabastine in perennial allergic rhinoconjunctivitis. An open, long-term trial in children

➤ **Description**

This was an open, uncontrolled, 12 week, multicentre, Phase III study conducted in Austria, Belgium and South Africa.

➤ **Methods**

- **Objective(s):**

to study efficacy and safety of long-term treatment with levocabastine in children.

- **Study design:** open, uncontrolled, parallel-group, multicentre trial

- **Study population /Sample size:** the study enrolled patients aged 4 to 12 years suffering from symptomatic allergic rhinoconjunctivitis verified by skin test or RAST. Regarding the sample size at least 200 patients were to be recruited.

- **Treatments:**

Levocabastine nasal spray (0.5 mg/ml) 2 puffs per nostril BID
and (if needed)
Levocabastine eye drops (0.5mg/ml) 1 drop per eye BID

- **Outcomes/endpoints:**

The primary parameter was the response rate. The investigator gave a global evaluation. The response rate was defined as the scores "excellent" or "good".

- **Statistical Methods:**

For the primary efficacy parameter, the clinical response rate for the whole subject population as well as per country was tabulated.

Results

- **Recruitment/ Number analysed:** 115 subjects were recruited. One subject did not receive treatment. 11 subjects dropped out (4 due to AEs, 4 due to insufficient response). 32 subjects used concomitant treatments, which was recorded as protocol deviation.
- **Baseline data:** 61% of the patients were male. 98% were Caucasian. Age range was 3 to 13 years.
- **Efficacy results:** At endpoint a response rate of 89% was observed.
- **Safety results:** 66% of the patients reported AEs. The most frequently reported AE was viral infection. Two serious AEs occurred (alopecia, meningitis). 4 subjects withdrew due to AEs (epistaxis with rhinitis, alopecia, conjunctivitis with rhinitis, nausea and vomiting). No consistent change in blood chemistry or haematology was observed.

Assessor's comment: This study was conducted to study long term safety. With this regard study duration is rather short. Recruitment was below expectations. A high number of patients used concomitant treatments. This effect as well as the uncontrolled design of the study hampers the evaluation of efficacy. No safety signal was detected. No changes to the SPC are warranted.

PSUR data submitted by Bausch & Lomb on levocabastine eye drops:

Since 1993 8 cases of AEs were reported in children aged ≤15 years (Levophta: 3, Levofree: 3, Allergiflash: 2). One case was serious (asthmatic crisis with anaphylactic reaction). Levocabastine is contra-indicated in hypersensitivities and “hypersensitivity” was added to Section 4.8 during a variation procedure in June 2012. The non serious cases included headache (already labelled), and medication administration after expiration date or by oral route without adverse events. 4 cases reported administration in children less than 30 months of age without AEs.

Assessor's comment: No changes to the SPC are warranted.

Summary of the post-marketing data submitted by Janssen on levocabastine eye drops and nasal spray:

A search of SCEPTRE, the Global Medical Safety Database, was conducted for all medically confirmed and non-medically confirmed post-marketing cases involving the use of levocabastine in adult and paediatric populations. This cumulative search for review covered the period from January 1990 to 31 May 2012 for eye drops and February 1990 to 31 May 2012 for nasal spray.

Levocabastine Eye Drops

In the post-marketing data for the paediatric population ■ AEs were reported in ■ cases for levocabastine eye drops. Ages of individuals experiencing events ranged from 1 to 17 years (■ boys, ■ girls, and ■ of unknown gender).

Post-marketing AEs associated with levocabastine eye drops in the paediatric population were most frequently reported from the System Organ Classes (SOC) of Eye Disorders, followed by Skin and Subcutaneous Tissue Disorders, and General Disorders and Administration Site Conditions. Of the eye-related events, eye irritation (■), keratitis (■), eye pain (■), and eye swelling (3) were the most commonly reported AEs. The event of application site reaction tended to be reported more frequently in paediatric subjects aged 13 to 17; eye irritation was more frequently reported in ages 12 to 15. Among ■ paediatric patients <4 years of age the following AEs were reported: blepharitis, eyelid edema, hyperemia, pruritus, accidental drug intake by child,

eye swelling, ocular hyperemia, and drug ineffective. Among these events, █ were serious (accidental drug intake by child, eye swelling).

In general, the types of post-marketing AEs reported in the paediatric population were similar to those reported in adults. Keratitis is currently not listed in the CCDS.

Levocabastine Nasal Spray

In the post-marketing data for the paediatric population, █ AEs were reported in █ cases for levocabastine nasal spray. Ages of individuals experiencing events ranged from 0 to 17 years (█ boys, █ girls, and █ of unknown gender).

Post-marketing AEs associated with levocabastine nasal spray in the paediatric population were most frequently reported from the SOCs of Respiratory, Thoracic, and Mediastinal Disorders, followed by Psychiatric Disorders, and General Disorders and Administration Site Conditions. Of the respiratory-related AEs, epistaxis (█) and cough (█) were the most commonly reported AEs. None of the AEs were specific to any age groups within the paediatric population.

Among the youngest children (ie, for those <4 years of age), the following AEs were reported for patients receiving levocabastine spray (█ patients overall): eyelid edema, aggression (█ patients), irritability, exposure during breast feeding, and nasal discomfort. In addition, a neonatal death was reported in 1994 for 1 full-term infant whose mother was treated with levocabastine nasal spray 2 to 3 times per day for one month in the seventh month of pregnancy. Limited information was reported for the infant, who at birth had AEs of neonatal respiratory distress syndrome, cardiomegaly, hepatomegaly, neonatal anemia, and pulmonary hypertension. All AEs were considered by the Company to be possibly related; no causality was provided by the reporter. No follow-up information was provided (ie, laboratory/imaging results or autopsy). This case was not considered by the Company to change the benefit-risk balance of levocabastine.

No new patterns of AEs were identified for the paediatric population that would require a change to the SmPCs.

*Assessor's comment: In general the applicant's conclusion is supported. However, the applicant is asked to further evaluate the cases of keratitis. Inclusion of this AE in the SPC/PL should be discussed also taking into account adult data?
The case of infant death is tragic. Causality is not clear. As no further information seems to be available no firm conclusions can be drawn.*

Summaries of the publications submitted by Bausch & Lomb and /or Janssen:

Efficacy and safety:

Nasal formulation:

Bauer C. et al.: Efficacy and safety of intranasally applied dimetindene maleate solution (Drug Res 51, 232-237 (2001)): this was a single-blind, active controlled, randomised, multicentre, parallel group, 15 day study on 100 children < 14 years of age with seasonal allergic rhinitis to investigate the efficacy and tolerability of intranasally applied dimetindene. Levocabastine was used as reference product. Nasal and ocular symptoms were evaluated and a global assessment was done. It was concluded that both preparations were similar as regards efficacy and tolerability.

Emeryk A. et al. Combined intranasal therapy of seasonal allergic rhinitis in children: topical levocabastine plus disodium cromoglycate provides better clinical improvement of nasal symptoms than disodium cromoglycate alone (allergy 56(68), 77, 2001): 25 children aged 8-14 years suffering from seasonal allergic rhinitis were treated with disodium cromoglycate nasal spray, then levocabastine nasal spray two puffs bid was added for two weeks. Nasal

symptoms sneezing and rhinorrhoea were reduced during the combined treatment period. Rhinomanometry as well as saccharine transit time were not significantly different.

Okuda M. et al.: Clinical investigation of R 50547 nasal spray in paediatric perennial allergic rhinitis (Ibiki to Rinsho, 41(1), 417-31, 1995): this 4 week study enrolled 60 patients (5-16 years) with perennial allergic rhinitis. They were treated with levocabastine nasal spray (2x 0.025mg per nostril QID). The final global improvement rating showed that 50% of the patients were at least moderately improved. Specific nasal symptoms also showed improvements (sneezing 59%, rhinorrhea 57%, obstruction 66%). Two patients reported AEs (nasal irritation, headache and nausea).

Osuna L. et al.: Levocabastine versus cetirizine for the treatment of perennial allergic rhinitis in children (Rev Alerg Mex, 45(3), 7-11, 1998): 30 children with symptomatic perennial allergic rhinitis were randomized to be treated with open label cetirizine once daily or open label levocabastine nasal aerosol 0.5 mg/ml, two puffs per nostril BID) for 15 days. Symptoms improved significantly in both groups. No statistically significant differences were found. No safety signal was detected.

Vassileva H. et al.: Results of the treatment of the seasonal pollinosis allergic rhinitis with the topical preparations livostin, bicromat and vibrosil (Allergy, 52(37), 200-1, 1997) (Poster which only shortly summarizes the effects seen): 78 children (5-16 years) with allergic rhinitis were treated with either Livostin (levocabastine) nasal spray, Bicromat (cromoglicate) spray or Vibrosil (decongestant) for three months. The fastest effect was observed with Livostin. More patients in the Bicromat group had to use oral antihistamines and topical steroids compared to the Livostin group. The percentage of Eosinophils in nasal secretion was diminished in the Livostin and the Bicromat group. Except for slight nasal irritation in some patients in the Livostin group, no side effects were observed.

Wang S. et al.: The curative effect of livostin spray on treating allergic rhinitis of children (Lin Chuang Er Bi Yan Hou Ke Za Zhi 15(4), 171-2, 2001, article has been submitted in Chinese with English abstract): 113 patients were either treated with Livostin spray or saline spray. The author's conclusion was that Livostin was better than saline spray in relieving symptoms, keeping the curative effect and safety.

Zebede M. et al.: Comparison of the efficacy and safety of intranasal therapy with levocabastine versus oxymetazoline in children with perennial allergic rhinitis (Ann Allergy Asthma Immunol, 74(1), 100, 1995): this open, 2 week, parallel group study enrolled 60 paediatric patients (2-16 years) with allergic rhinitis. Patients were treated with levocabastine nasal spray (0.5mg/ml, two puffs daily) or oxymetazoline (0.25 mg/ml, two puffs daily). Global effectiveness at D14 was 94% in the levocabastine group compared to 47% in the oxymetazoline group. No AEs were reported.

Eye drops:

Abelson MB et al.: Differential diagnosis of ocular allergic disorders (Ann Allergy 70, 95-109, 1993): this publication gives a summary on allergic eye disease. Levocabastine is mentioned as a potential therapeutic option.

Abelson MB: Comparison of the conjunctival allergen challenge model with the environmental model of allergic conjunctivitis (Acta Ophthalmol Scand, Suppl, 228: 38-42, 1999): the author compares both models also using levocabastine as an example.

Bonini S. et al.: Levocabastine eye drops in vernal keratoconjunctivitis (Allergy 48 (16, Suppl.), p.41, 1993) this was a double blind, placebo controlled 4 week, parallel group study on 22 patients (age not given) with vernal keratoconjunctivitis. Evaluations included symptoms of the disease, compliance and tolerability. Results indicated that levocabastine eye drops were safe and effective in patients with vernal conjunctivitis.

Björkstén B et al.: Double-blind studies with levocabastine, sodium cromoglycate, and placebo in the topical treatment of children with allergic conjunctivitis, in Rhinoconjunctivitis; New perspectives in topical treatment, pp. 49, Hogrefes and Huber Publishers, Germany 1989: the authors report on two randomized, double-blind, active (and placebo)-controlled trials in children and adolescents (6-19 years of age) with allergic conjunctivitis. In the first study a conjunctival provocation test was performed in 25 patients (9-17 years of age) 15 minutes after one drop of levocabastine (0.5mg/ml), sodium cromoglycate (20 mg/ml) or placebo had been administered. Pre-treatment with levocabastine but not sodium cromoglycate or placebo significantly reduced sensitivity against a pollen extract. The difference between placebo and sodium cromoglycate was not significant. In the second study 37 patients (6-19 years of age) who received either Levocabastine 0.025 mg per eye bid or sodium cromoglycate 2 mg per eye qid for 5 week during the birch pollen season were compared. Symptom scores and AEs were similar in both active groups. Global evaluation favoured levocabastine.

Ciprandi G. et al: Drug treatment of allergic conjunctivitis. A review of the evidence. (Drugs; 43, 154-76, 1992): This publication summarizes therapeutic options also mentioning levocabastine.

Ciprandi G. et al. Double masked, randomized, parallel-group study comparing olopatadine 0.1% ophthalmic solution with cromolyn sodium 2% and levocabastine 0.05% ophthalmic preparations in children with seasonal allergic conjunctivitis (Curr Ther Res Clin Exp 65(2), 186-99, 2004): this publication describes two clinical studies which compared olopatadine 0.1% ophthalmic solution to active comparators. Study 1 compared the compound to cromolyn sodium. Study 2 enrolled 22 children from 5 to 11 years of age with grass pollen allergy and compared olopatadine to levocabastine 0.05% ophthalmic solution. Treatment duration was 6 weeks. Redness seen on slit lamp examination as well as self-rated ocular redness were significantly less intense in the olopatadine group. All treatments were well tolerated.

Davies BH et al., Topical levocabastine is more effective than sodium cromoglycate for the prophylaxis of seasonal allergic conjunctivitis (Allergy 48, 519-24, 1993): This was a double-blind, placebo and active controlled, 4 week trial in 95 patients (13 patients < 15 years of age, 5 patients treated with levocabastine, youngest patient 7 years of age) with allergic conjunctivitis comparing levocabastine eye drops (0.5 mg/ml, 1 drop per eye QID) to sodium cromoglycate eye drops (20mg/ml, 1 drop per eye QID) and placebo. Global therapeutic efficacy was rated significantly better in the levocabastine group compared to cromoglycate and the placebo group. A number of secondary end-points supported this finding. Incidence of AEs was comparable between the levocabastine and the placebo group.

Falconieri P. et al. : Effectiveness of levocabastine eyedrops in children with allergic conjunctivitis: a double blind study (Pediatric Asthma, Allergy&Immunol, 8(2), 111-5, 1994): This was a randomized, double-blind, placebo controlled cross-over study conducted in 23 children (4-14 years) with allergic conjunctivitis. All patients were treated with terfenadine p.o. and either levocabastine eye drops or placebo and subjected to a conjunctival provocation tests. Compared to placebo a significant shift of the threshold allergen concentration to the highest dose was noted during levocabastine treatment. The percentage of patients without ocular symptoms at

the highest dose was also significantly higher during levocabastine use. All treatments were well tolerated.

Gallegos M. et al: Levocabastine eye drop solution versus a sulphacetamide-prednisolone-phenylephrine eye drops suspension for the treatment of vernal allergic conjunctivitis (Investigacion Medical Internacional, 22, 67-72, 1995): This was an open label, prospective, randomized, 1 week study which enrolled 35 paediatric patients (4-15 years) suffering from vernal allergic conjunctivitis. Patients were treated with either levocabastine eye drops one drop bid or a suspension of sulphacetamide-prednisolone-phenylephrine one drop four times per day. No significant differences in symptom reduction were found when both groups were compared. No safety signal was detected.

Goes F et al.: Levocabastine eye drops in the treatment of vernal conjunctivitis (Documenta Ophthalmologica, 87: 271-81, 1994): The authors conducted a double-blind, placebo controlled, 4 week trial in 46 patients from 5 years of age (number of paediatric patients not given) who suffered from vernal conjunctivitis. Patients were administered with either levocabastine eye drops 0.5 mg/ml 1 drop per eye or placebo. For the primary end-point, the response to the individually most severe symptom, a significant difference compared to placebo was found after one week and at the end of treatment. Some secondary end-points support this result. No safety signal was detected.

Graue-Wiechers et al.: Double blind study of topical levocabastine versus topical placebo in the management of vernal conjunctivitis (Investigacion Medica Internacional, 21, 35-42, 1994): 40 patients (5-20 years) with vernal conjunctivitis were either treated with levocabastine 0.5 mg/ml (one drop per eye bid for seven days) ophthalmic suspension or placebo. The symptoms photophobia and tearing were significantly more improved in the levocabastine group. No significant differences were seen in other symptoms of vernal conjunctivitis. No safety signal was detected.

Lanna M. et al.: Effects of levocabastine versus antazoline in younger patients affected by vernal conjunctivitis (Annali di Ottalmologia e Clinica Oculistica, 122(12):629.34, 1996): This publication has only been provided in Italian.

Assessor's comment: The applicant is asked to provide the abstract of this publication in English.

Lazreg S et al: Traitement de la conjonctivite allergique perannuelle et saisonniere: comparaison de 2 protocoles therapeutiques (only abstract is provided in English), Ophthalmol, 31: 961-67, 2008): This is a randomized, prospective single centre survey on 102 patients with allergic conjunctivitis from 4 years of age. One group was treated with NAAG (N-acetyl-aspartyl-glutamate) over 4 weeks while the other group was treated with a combination of NAAG and levocabastine for one week followed by monotherapy with NAAG for the remaining three weeks. No significant differences in symptom scores were detected between groups. Tolerance to the treatment was better in the NAAG only treatment group.

Leonardi A. et al: Clinical and biological efficacy of preservative-free NAAGA eye-drops versus levocabastine eye-drops in vernal keratoconjunctivitis patients (Br J Ophthalmol 91: 1662-1666, 2007): this was an open-label, randomised, 4 week pilot study comparing preservative-free N-acetyl-aspartyl-glutamate eye drops (6 times per day, dose not given) to levocabastine eye drops (QID, dose not given). The primary end-point eosinophil cationic protein tear level was evaluated in a masked fashion. 23 patients with vernal keratoconjunctivitis with a median age of nine years were enrolled. ECP tear levels were significantly reduced in the NAAG

group compared to the levocabastine group. Burning sensation was significantly more frequently reported in the levocabastine group.

Möller C. et al.: The efficacy of levocabastine eye drops in birch pollinosis: a double-blind comparison with sodium cromoglycate in the area surrounding Umea (Pediatr Allergy Immunol, 1, 87-9, 1990): in this double blind active controlled, parallel group trial, 65 patients (7-19 years) with conjunctivitis due to birch pollinosis were treated with either levocabastine eye drops 0.5mg/ml one drop per eye bid or cromoglycate eye drops 20mg/ml one drop per eye qid for 5 weeks. No significant differences regarding symptoms of conjunctivitis were seen. Though children in the levocabastine group had a quicker reduction of symptoms after a pollen peak ($p < 0.05$) but were tired for significantly longer period ($p < 0.01$). Safety profile was comparable.

Njaa F. et al.: Levocabastine compared with sodium cromoglycate eye drops in children with both birch and grass pollen allergy (Pediatr Allergy Immunol, 3, 39-42, 1992): in this randomized, double-blind parallel group trial 55 children (6-16 years) with allergic rhinoconjunctivitis due to birch and grass pollinosis were treated either with levocabastine eye drops 0.5mg/ml one drop per eye bid or sodium cromoglycate eye drops 20 mg/ml one drop per eye qid for 3 months. All treatments were administered in addition to systemic therapy with terfenadine. The global evaluation as well as the evaluations of most symptoms did not show significant differences between groups. The sodium cromoglycate group experienced slightly less eye symptoms. No safety signal was detected.

Odelram H. et al: Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis (Allergy, 44(6), 432-6, 1989): This was randomized, double-blind, active – controlled, parallel group 5-week trial. 37(+2 drop-outs) children and adolescents (6-19 years) with birch pollen conjunctivitis were enrolled. A 7 day placebo run-in was followed by a 5 week treatment period comparing levocabastine eye drops (0.5mg/ml, 1 drop per eye bid, $n=21$) to sodium cromoglycate eye drops (20mg/ml, 1 drop per eye QID, $n=18$). No significant differences in eye symptom scores were detected. Patients' evaluations of efficacy was significantly in favour of levocabastine ($p < 0.01$). Safety parameters were comparable.

Rimas M. et al.: Topical levocabastine protects better than sodium cromoglycate and placebo in conjunctival provocation tests (Allergy, 45, 18-21, 1990): This randomized double-blind, active and placebo controlled three way cross over study enrolled 25 children (9-17 years) with pollen allergy. Three different treatments were applied: Levocabastine eye drops (0.5mg/ml, 1 drop per eye), sodium cromoglycate eye drops (20mg/ml, 1 drop per eye) or placebo. Conjunctival provocation tests were done before the treatment phase started to establish the allergen threshold dose. During the treatment phase, another conjunctival provocation test was performed 15 minutes after treatment. Pretreatment with levocabastine resulted in a median allergenic threshold of 32,000 BU compared to 10,000 BU in the cromoglycate group ($p < 0.01$) and placebo group ($p < 0.01$). No safety signal was detected.

Sabah A. et al.: Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children (Curr Med Res Opin, 14(3), 161-70, 1998): this randomized, active and placebo controlled parallel group trial compared the efficacy and safety of azelastine eye drops (0.05% one drop per eye BID) to levocabastine eye drops (0.05%, 1 drop per eye BID) and placebo. As regards the comparison to levocabastine the study had an open label design. 113 patients (4 -12 years) suffering from seasonal allergic conjunctivitis /rhinoconjunctivitis were enrolled. The primary variable, the response rate after three days was comparable in both active treatment groups. The overall assessment confirmed the superiority of both active treatments over placebo. AEs (mainly local irritant effects) were reported in 23% of the patients in the placebo group, 35% of the patients in the azelastine group and 38% of the patients in the levocabastine group.

Sawa M. et al.: Clinical evaluation of R50547 ophthalmic suspension in allergic conjunctivitis and vernal conjunctivitis-open study in children (Atarashii Ganka, 11(12), 1893-1902, 1994): 44 paediatric patients (40 eligible ones, 5-17 years) with allergic/vernal conjunctivitis were treated with levocabastine eye drops (0.25mg/ml, 1-2 drops per eye 2-4 times a day for 4 weeks). Main symptoms of allergic conjunctivitis (itchiness, redness) improved by 72.2% and 75.0% and improvements were 70% or better for all other symptoms. Clinical findings redness and swelling of palpebral conjunctiva and redness and swelling of the bulbar conjunctiva had improvement rates of $\geq 60\%$, while other symptoms showed lesser improvement with no substantial improvement for follicles and papillae on the palpebral conjunctiva. Final overall improvement was 82.5%. 2 patients reported AEs (stinging sensation after administration, allergic blepharitis).

Secchi et al.: Safety and efficacy comparison of emedastine 0.05% ophthalmic solution compared to levocabastine 0.05% ophthalmic suspension in pediatric subjects with allergic conjunctivitis (Acta Ophthalmol Scand, 78(1), 42-7, 2000) : This randomized, double-masked, parallel group active controlled trial compared emedastine 0.05% ophthalmic solution to levocabastine 0.05% ophthalmic suspension both administered BID in 42 paediatric patients (4-16 years) suffering from symptomatic allergic conjunctivitis. Treatment lasted for 42 days. Emedastine was shown to be significantly superior ($p < 0.05$) for the relief of itching, redness (both primary endpoints), chemosis, and physician impression score on D42. One patient in the emedastine group discontinued prematurely due to ocular discomfort. 3 of 20 patients in the emedastine group and 2 of 22 patients in the levocabastine group reported AEs (mostly local irritation).

Tiszler Cieslik E. et al.: A comparison of levocabastine and sodium cromoglycate in children with allergic conjunctivitis due to house dust mite (Allergy Clin Immunol News), suppl. 2, 16, 1994): This was a 4 week, double blind, placebo controlled trial in 48 children (6-14 years) with allergic conjunctivitis, which compared the efficacy and safety of levocabastine eye drops one drop per eye BID and sodium cromoglycate one drop per eye QID. Levocabastine was significantly better judged as being good or excellent by patients/ care givers. Ocular itching and swelling of the conjunctiva were significantly smaller and relief faster following treatment with LV. No AEs were reported.

Verin P. et al.: Clinical evaluation of twice- daily emedastine 0.05% eye drops versus levocabastine 0.05% eye drops in patients with allergic conjunctivitis (Am J Ophthalmol, 131(6), 691-8, 2001): this randomized, double masked, parallel group, 6 week study evaluated the efficacy and safety of emedastine eye drops (one drop per eye BID) in comparison to levocabastine eye drops (one drop per eye BID) in 222 patients (42 paediatric patients) with allergic conjunctivitis. Primary variables (ocular redness and itching) were significantly reduced in both groups ($p = 0.0001$). Emedastine was significantly superior compared to levocabastine for both primary endpoints for most time-points. No safety signal was detected.

Wuethrich B. et al.: Levocabastine eye drops are effective and well tolerated for the treatment of allergic conjunctivitis in children (Mediatros Inflamm, 4(suppl.), S16-S20, 1995): this uncontrolled, 4-week trial assessed the efficacy and safety of levocabastine eye drops (0.5 mg/ml, one drop per eye BID) in 233 children and adolescents (5-16 years) with seasonal allergic conjunctivitis. Total severity of ocular symptoms decreased by $84 \pm 34\%$ in patients < 12 years and $85 \pm 30\%$ in those ≥ 12 years indicating no correlation between efficacy and age. Application site reactions were the most common AEs (13% < 12 years, 9% ≥ 12 years).

Nasal formulation +Eye drops:

Hrubisko et al.: Is concomitant local and oral antihistamine treatment of allergic rhinoconjunctivitis well-founded? A clinical study of levocabastine + astemizole (Klinicka Immunologia a Alergologia, 7(2), 154-7, 1997): after a run-in of 5 days (longer for local steroids, ketotifen and astemizole) with no treatment, 20 paediatric patients (3-18 years) with pollinosis were treated for 5 days with levocabastine eye and nose drops (Livostin) followed by 5 days on the same treatment in combination with systemic astemizole (Hismanal). On days 15-28 of the study the patients received Livostin as before and Hismanal as required. A significant fall in daily symptom score (sneezing, itching of nose and eyes, running nose and eyes) was noted which decreased further after systemic therapy was added. However, the effect on swelling of the nasal mucosa and the eyelids was less pronounced. No safety signal was detected.

Janssens MML: Levocabastine: a new topical approach for the treatment of paediatric allergic rhinoconjunctivitis, Rhinology, Suppl.13, 39-49, 1992: This publication summarizes information on levocabastine available at the time of publication. It concludes that only limited data on the use in children is available.

Kurzawa R et al.: Evaluation of the clinical efficacy and safety of levocabastine in the treatment of seasonal allergic rhinitis and conjunctivitis in children under the age of 12 years (Pol Merkur Lekarski, 4(23), 269-72, 1998): 32 children (5-11 years) suffering from pollinosis were treated with levocabastine eye drops and nasal spray for 20 days (1 drop per eye bid, two sprays per nostril bid). Significant improvements in symptoms were seen in almost all cases. The authors conclude that levocabastine is a safe and efficacious therapy of pollinosis in children.

Publications on PD/PK

Nasal spray:

Bernardini R. et al.: Eosinophil cationic protein and tryptase in the nasal lavage fluid of children with grass pollen rhinitis: levocabastine effect (Allergy Asthma Proc, 19(2), 75-80, 1998): Concentrations of eosinophil cationic protein and tryptase were measured in the nasal lavage fluid of 24 children with grass pollen rhinitis. Nasal symptoms were recorded and nasal provocation tests were carried out with and without levocabastine nasal spray pretreatment. Levocabastine pre-treatment resulted in a significant increase in cumulative allergen dose. Tryptase concentrations did not significantly increase. No significant reductions in eosinophil cationic protein were found.

Heykants J et al.: The pharmacokinetic properties of topical levocabastine (Clin Pharmacokinet, 29(4), 221-30, 1995): the authors summarize the PK properties of levocabastine. No specific paediatric data is reported.

Pesco-Koplowitz L. et al.: Lack of Effect of Erythromycin and Ketoconazole on the Pharmacokinetics and Pharmacodynamics of Steady- State Intranasal Levocabastine (J Clin Pharmacol, 39, 76-85, 1999): this article reports a study in healthy male volunteers. No paediatric data reported.

Simons E et al.: Clinical Pharmacology of New Histamine H1 Receptor Antagonists (Clin Pharmacokinet, 36(5), 329-52, 1999): this article summarizes the PK and PD properties of levocabastine. No specific paediatric information on levocabastine is given.

Assanasen P et al.: Antiallergic anti-inflammatory effects of H1 antihistamines in humans (in Clinical allergy and immunology, 17: 1001-39, 2002): The authors summarize the properties of levocabastine. No specific paediatric data is given.

Assessor's comment on publications: the applicants submitted a number of publications on levocabastine used as nasal formulations or eye drops in paediatric patients. Most publications originate from the nineties. Levocabastine is compared to placebo and/or active controls, with varying success. No safety signals are detected and these publications do not change the benefit risk assessment of either preparation of levocabastine.

3. Discussion on clinical aspects and conclusion

The two applicants submitted altogether 52 clinical trials and publications.

Regarding PK data no firm conclusions can be drawn as available data is limited as well in quantity as in quality.

Regarding efficacy and safety, studies and publications which compare the effect of levocabastine to placebo and/or active controls have been submitted. Studies showed mixed results, but the overall benefit risk evaluation is not altered and no changes to the SPC are proposed based on these studies.

In addition post-marketing data has been submitted. According to the data provided by Janssen 5 children reported keratitis after the use of levocabastine eye drops. This AE has not been labelled and inclusion in the SPC/PIL should be discussed. Adult data should also be taken into account.

Regarding the frequency of application site reactions after use of levocabastine eye drops clarification is requested. SPCs state:

Bausch & Lomb: “ *General problems and administration site abnormalities*
Very rare: *administration site reaction including a burning sensation, red eyes, ocular irritation, ocular itching.*”

Janssen:

Table 2: Adverse Drug Reactions Identified During Postmarketing Experience with TRADENAME Eye Drops by Frequency Category Estimated from Spontaneous Reporting Rates

Eye Disorders	
Very rare	Eye pain, Conjunctivitis, Eyelid oedema, Eye swelling, Blepharitis, Ocular hyperaemia, Vision blurred
General Disorders and Administration Site Conditions	
Very rare	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred

Table 3: Adverse Drug Reactions Identified During Postmarketing Experience with TRADENAME by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

General Disorders and Administration Site Conditions	
Not known	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred

The frequency “very rare” means that the AE occurs in less than one of 10 000 patients. In the paediatric data submitted for this worksharing application site reactions were seen far more often. In the clinical overview submitted by Bausch&Lomb the applicant states that “.. *in an open study performed in 233 children between 5 and 16 years old ...ocular stinging or burning sensations upon instillation were the most common adverse events: it occurred at the frequency of 9.6% in children aged less than 12 years and 8.9% in those aged 12 or more.*” (clinical overview Bausch &Lomb, p 3/9). This is accordance with data from publications which also report higher frequencies for application site reactions (e. g. Sabah et al levocabastine ≈ 30%), Njaa et al levocabastine: 9/27). Regarding post-marketing information provided by Janssen, eye irritation was the most frequently reported eye-related AE. The applicants are asked to discuss.

Janssen suggested to remove the lower age limit in the SPC/PL which varies across the EU. It has to be kept in mind that this procedure only deals with data which has not been reviewed by the competent authorities before. Therefore the data which led to the paediatric license in some member states might not have been provided here. In order to obtain a license, adequate data to establish safety and efficacy in accordance with the Guideline on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis (CHMP/EWP/2455/02, further on referred to as “guideline”) is required. According to this guideline “... *as non-inferiority trials are not possible in SAR/PAR due to lack of assay sensitivity, pivotal studies should be double-blind randomised three arm parallel group studies including a placebo and active control arm. Alternatively, the therapeutic efficacy may be tested in a superiority trial against a well-established comparator. However, if the test product is not superior to the comparator non-inferiority cannot be claimed due to the lack a placebo arm for internal validation...Safety data are of paramount importance and 1- 3 months of paediatric safety data are required.*” Data available for this worksharing procedure gives the following picture:

Eye drops:

Studies CRR R50547/30 and CRR R50547/31 have an acceptable design. However both enrolled a very low number of children, used a higher dose than the one recommended for initial therapy in the SPC and in the end were inconclusive.

Davies BH et al. conducted a double-blind, placebo and active controlled, 4 week trial comparing levocabastine eye drops to sodium cromoglycate eye drops and placebo. Global therapeutic efficacy was rated significantly better in the levocabastine group compared to cromoglycate and the placebo group. A number of secondary end-points supported this finding. Incidence of AEs was comparable between the levocabastine and the placebo group. However the number of paediatric patients enrolled in this study is very low. Posology differs from the one recommended in the SPC as initial therapy. The active comparator is suboptimal which is also reflected in the fact that the results for cromoglycate group were not different from the ones in the placebo group for most end-points.

Rimas et al. reported on a randomized double-blind, active and placebo controlled three way cross over study which enrolled 25 children (9-17 years) with pollen allergy. The study tested the effect of levocabastine in comparison to cromoglycate and placebo on the allergenic threshold dose in a conjunctival provocation test. Levocabastine did significantly better than cromoglycate and placebo. According to the guideline this kind of study “...*may be used as supportive evidence.*” and is therefore not sufficient on its own. In addition the choice of comparator could be discussed. A rather similar study was reported by Björkstén et al which had the same shortfalls.

Tiszler et al. compared levocabastine to sodium cromoglycate and placebo in 48 children (6-14 years) with allergic conjunctivitis due to house dust mite allergy. Levocabastine was significantly better judged as being good or excellent by patients/ care givers. Ocular itching and swelling of the conjunctiva were significantly smaller and relief faster following treatment with LV. No AEs were reported. This study has only been provided as a very short summary. Therefore no final conclusion can be drawn. The number of participants is rather low and the choice of comparator could be debated. However, the applicants are welcome to provide additional information if available.

In summary the data provided for this worksharing is not sufficient to propose new lower age margins of levocabastine eye drops.

Nasal formulation:

No study fulfilling the requirements of the guideline has been submitted. No new age margin can be proposed.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Clinical: The applicants provided a number of clinical studies and publications. No new information that needs to be included in the SPC/PL can be deduced. Post-marketing reports of keratitis in children after the use of levocabastine eye drops might warrant the inclusion of this AE in the SPC/PL.

➤ Recommendation

Based on the data submitted, the MAH should provide additional information on the issues detailed in the List of Questions. In addition the SPC should be amended in accordance with the revised SPC Guideline. Request for amendments are also listed in the LoQ.

List of questions

Eye drops:

C1. The cases of keratitis from the post-marketing data should be further evaluated. Please discuss inclusion of "keratitis" in chapter 4.8 of the SPC and the corresponding section of the PIL also taking into account adult data.

C.2 Please provide the English version of the abstract of Lanna M. et al.: Effects of levocabastine versus antazoline in younger patients affected by vernal conjunctivitis (Annali di Ottalmologia e Clinica Oculistica, 122(12):629.34, 1996). This publication has only been provided in Italian.

C.3: Regarding the frequency of application site reactions the Chapters 4.8 of the SPCs (eye drops) state:

Bausch & Lomb: " *General problems and administration site abnormalities*
Very rare: administration site reaction including a burning sensation, red eyes, ocular irritation, ocular itching."

Janssen:

Eye Disorders	
Very rare	Eye pain, Conjunctivitis, Eyelid oedema, Eye swelling, Blepharitis, Ocular hyperaemia, Vision blurred
General Disorders and Administration Site Conditions	
Very rare	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred

Table 3: Adverse Drug Reactions Identified During Postmarketing Experience with TRADENAME by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

General Disorders and Administration Site Conditions	
Not known	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred

The frequency “very rare” means that the AE occurs in less than one of 10 000 patients. In the paediatric data submitted for this worksharing application site reactions were seen far more often. In the clinical overview submitted by Bausch&Lomb the applicant states that “.. *in an open study performed in 233 children between 5 and 16 years old ...ocular stinging or burning sensations upon instillation were the most common adverse events: it occurred at the frequency of 9.6% in children aged less than 12 years and 8.9% in those aged 12 or more.*” (clinical overview Bausch &Lomb, p 3/9). This is accordance with data from publications which also report higher frequencies for application site reactions (e. g. Sabah et al levocabastine ≈ 30%), Njaa et al levocabastine: 9/27). Regarding post-marketing information provided by Janssen, eye irritation was the most frequently reported eye-related AE. The applicants are asked to discuss.

Eye drops and nasal spray:

C.4 Section 4.1 of the SPC and the corresponding Chapter of the PL should specify the lower age limit for the paediatric population (SPC GL). Section 4.2 and the corresponding Chapter of the PL should also include age limits and in addition state that: “*The safety and efficacy of TM in children below x years of age have not been established.*” (SPC GL).

Nasal spray:

C.5 Section 5.2 of the SPC should include a paediatric section stating that paediatric data is sparse but PK most likely resembles the one in adults (SPC GL). The applicants are asked to give a proposal.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Eye drops:

C1.: The cases of keratitis from the post-marketing data should be further evaluated. Please discuss inclusion of “keratitis” in chapter 4.8 of the SPC and the corresponding section of the PIL also taking into account adult data.

Responses:

Bausch & Lomb: MAH: Cases of keratitis have been recorded by Janssen. Bausch + Lomb is not in a position to evaluate these cases. Until end of May, only one case of superficial punctate keratitis with Levophta® has been recorded by Bausch + Lomb in the adult population. In studies LEVO 93-01 and LEVO 94-01, one case of paralimbic keratitis of immuno-allergic type, in one eye in a child aged 8 years was reported. It was judged unlikely related to study treatment (levocabastine eye drops); the evolution was favorable. No other cases related to keratitis were reported. Based on the available data, the company suggests to not include the keratitis in the SmPC at that time and to monitor these cases in the next PBRER.

Janssen: An ad-hoc cumulative review of keratitis reported with use of Levocabastine during postmarketing experience in adults and children was prepared in October 2012 and with a data lock point of 31 July 2012. Please find this report attached in Appendix 1. This review found

that the evidence for an association between levocabastine eye drops and keratitis was insufficient for inclusion of keratitis as an ADR in the product labelling. Using the same search query as this report, a new query for the interval 01 Aug 2012 to 30 April 2014 was conducted. No cases of keratitis were found in adults or children for this review period. Therefore based on the available data, the company suggests that keratitis should not be included in the SPC at this time.

Assessor's comment: Janssen submitted a cumulative review of keratitis (Appendix 1 of the response document). The company conducted a cumulative search of SCEPTRE, the Global Medical Safety database for all valid, medically confirmed cases received through 31 July 2012 involving levocabastine eye drops as suspect or suspect interacting drug and at least 1 of the following AEs coded to the MedDRA PTs of Acanthamoeba keratitis, Allergic keratitis, Diffuse lamellar keratitis, Keratitis bacterial, Keratitis interstitial, Keratitis sclerosing, Keratitis-ichthyosis-deafness syndrome, Photokeratitis, Punctate keratitis, Ulcerative keratitis.) 9 cases were retrieved. The report includes the following narratives:

Pediatric Cases

JAMEX32351 (Ulcerative keratitis): This case involves a 9-year-old male with no medical history reported who was treated with Maxitrol® and levocabastine for papillary conjunctivitis and developed a corneal ulcer. The event onset was not reported; however, treatment medications for the corneal ulcer were prescribed approximately 3 weeks after levocabastine was initiated and included diclofenac, zincferin, tobramycin, levocabastine and therapeutic contact lens. The patient was referred to a corneal specialist and was subsequently lost to follow-up. No further information including outcome was reported.

MAH Comment: Concomitant medication of Maxitrol eye drops which lists keratitis as an adverse reaction in the product labeling.

JAGER24676 (Punctate keratitis): This case involves a 17-year-old female with no medical history or concomitant medications reported who developed punctate keratitis sometime after 3-4 applications of levocabastine eye drops prescribed for seasonal allergies. The reporter attributed the event as possibly allergy related. No further information including outcome was reported.

MAH Comment: Insufficient information reported to make an adequate medical assessment.

20060405323 (Corneal exfoliation, Punctate keratitis, Injury corneal, Pruritus): This case involves an 11-year-old female with a medical history of left eye pain, left eye hyperemia, and allergic conjunctivitis who was prescribed with 2 different kinds of eye drops (unspecified) for allergic conjunctivitis. Approximately 2 weeks later her symptoms had not improved and she was prescribed levocabastine eye drops for conjunctival hyperemia. Within the same month of levocabastine therapy initiation, she administered a dose and experienced eye pain, sensation of foreign body, and lacrimation approximately 5 minutes later. It was noted that she had not washed her hands prior to administering the dose. Levocabastine was discontinued and she was treated at an ophthalmology clinic with diclofenac sodium, gatifloxacin hydrate, and hyaluronate sodium eye drops. The event

improved after approximately 2 weeks time. The reporting physician suspected the patient had been administering the 2 additional kinds of eye drops concomitantly with levocabastine at the time of the event.
MAH Comment: Pre-existing conditions of hyperemia and eye pain, both which are symptoms of keratitis.

Adult Cases

20090503767 (Corneal opacity, Corneal erosion, Punctate keratitis, Drug interaction): This case involves a 24-year-old male with a medical history of drug hypersensitivity to antibiotics, allergic conjunctivitis, catarrh, Kawasaki's disease, and superficial punctate keratitis who was prescribed cyclosporine (non-company suspect drug) and levocabastine eye drops for papillary hyperplasia, diffuse keratitis, and severe pain in both eyes. On the the same day, after administering the initial dose of both cyclosporine and levocabastine eye drops, the patient experienced eye pain and blurred vision in both eyes; corneal opacity and erosion were noted. Cyclosporine and levocabastine were discontinued and the patient recovered from the events with treatment and a persistent mild superficial punctate keratitis. The ophthalmologist suspected a possible allergic reaction due to the patient's medical history of antibiotic allergy.

MAH Comment: Pre-existing conditions of punctate and diffuse keratitis, drug hypersensitivity to antibiotics, and concomitant medication of cyclosporine eye drops which lists ocular burning, conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance as adverse reactions in the product labeling.

20100509841 (Ulcerative keratitis, Photophobia, Ocular hyperemia, Lacrimation increased, Eye pain, Eye inflammation, Blepharitis, Eye irritation): This case involves a 58-year-old female with no medical history or concomitant medications reported who experienced lacrimation increased, corneal ulceration, photophobia, inflammation of eyelids, burning sensation of eyes, ocular pain, ocular hyperemia and eye inflammation approximately 1 hour after administering her initial dose of levocabastine for allergic conjunctivitis. One day later she went to the hospital for treatment. Levocabastine therapy was discontinued and the patient recovered.

MAH Comment: Symptoms possibly associated with an allergic reaction.

APCDSS2002000181 (Punctate keratitis): This case involves a 23-year-old female with no medical history or concomitant medications reported who received levocabastine eye drops for approximately 2 weeks duration for allergic conjunctivitis. On an unspecified date she experienced superficial diffuse keratitis that resolved with treatment (not specified); levocabastine was discontinued. It was not reported if the event occurred during the 2 week treatment period. No other details were reported.

MAH Comment: Insufficient information reported to make an adequate

medical assessment.

APCDSS2002000196 (Punctate keratitis): This case involves a 52-year-old male with a history of glaucoma who experienced diffuse superficial keratitis approximately 9 weeks after initiating levocabastine for allergic conjunctivitis. Co-suspect medications included bunazosin HCl and erythromycin lactobionate, which both had been initiated 6 weeks prior to the event. All 3 drugs were discontinued and symptoms in the right eye resolved but persisted in the left. An unspecified herpetic infection was suspected and acyclovir eye ointment was prescribed with symptom improvement.

MAH Comment: Pre-existing condition of glaucoma, suspected herpetic infection of left eye, and concomitant medications of bunazosin HCl and erythromycin lactobionate eye drops both which list ocular adverse events such as eye pain, itching, blurred vision, irritation, redness, and hypersensitivity reactions in the product labeling.

APCDSS2003000516 (Punctate keratitis): This case involves a 30-year-old-female with a past medical history of asthma and atopic dermatitis who was prescribed levocabastine and concomitant medication fluorometholone eye drops for allergic conjunctivitis. Approximately 3 days after initiation of treatment with levocabastine and fluorometholone she developed a strange sensation in the right eye; it was not reported if she had administered eye drops immediately prior to the event occurrence. No improvement was noted with the administration of levocabastine eye drops. She was examined by an ophthalmologist who noted filiform substances in the cornea of the right eye and superficial punctuate keratitis in both eyes. Both medications were discontinued and the patient recovered with treatment 1 week later.

MAH Comment: Concomitant medication of fluorometholone eye drops which list keratitis as an adverse event in the product labeling.

NSADSS2001013876 (Punctate keratitis): This case involves a 40-year-old patient of unknown gender who initiated levocabastine on an unknown date for an unknown indication. The patient reported experiencing a “fuzzy sensation” that was reported as punctuate keratitis. No further information including outcome was reported.

MAH Comment: Insufficient information reported to make an adequate medical assessment.

Assessor’s conclusion:

Most patients received additional medication or suffered from concomitant diseases, which hampers the assessment of causality. Therefore, the applicant’s position not to include “keratitis in section 4.8 of the SPC for the time being seems to be acceptable. However special focus should be laid on this issue in future pharmacovigilance procedures.

C.2: Please provide the English version of the abstract of Lanna M. et al.: Effects of levocabastine versus antazoline in younger patients affected by vernal conjunctivitis (Annali di Ottalmologia e Clinica Oculistica, 122(12):629.34, 1996). This publication has only been provided in Italian.

Response:

Janssen: The applicant provided the requested abstract.

Summary: 20 patients aged 8 to 14 years suffering from vernal conjunctivitis received either levocabastine or antazoline eye drops (1 drop per eye three times daily for the first 7 days, then 1 drop per eye daily until day 30). Objective and subjective improvements were seen on days 7, 15 and 30. Reduction of symptoms was quicker and clearer in the levocabastine group (no statistical analysis provided).

Assessor's comment: the requested translation has been provided. The study by Lanna et al. does not add significant new information. Issue resolved.

C3: Regarding the frequency of application site reactions the Chapters 4.8 of the SPCs (eye drops) state:

Bausch & Lomb: *“General problems and administration site abnormalities*

Very rare: administration site reaction including a burning sensation, red eyes, ocular irritation, ocular itching.”

Janssen:

Eye Disorders	
Very rare	Eye pain, Conjunctivitis, Eyelid oedema, Eye swelling, Blepharitis, Ocular hyperaemia, Vision blurred
General Disorders and Administration Site Conditions	
Very rare	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred

Table 3: Adverse Drug Reactions Identified During Postmarketing Experience with TRADENAME by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

General Disorders and Administration Site Conditions	
Not known	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred

The frequency “very rare” means that the AE occurs in less than one of 10 000 patients. In the paediatric data submitted for this worksharing application site reactions were seen far more often. In the clinical overview submitted by Bausch&Lomb the applicant states that “.. *in an open study performed in 233 children between 5 and 16 years old ...ocular stinging or burning sensations upon instillation were the most common adverse events: it occurred at the frequency of 9.6% in children aged less than 12 years and 8.9% in those aged 12 or more.*” (clinical overview Bausch &Lomb, p 3/9). This is accordance with data from publications which also report higher frequencies for application site reactions (e. g. Sabah et al levocabastine ≈ 30%), Njaa et al levocabastine: 9/27). Regarding post-marketing information provided by Janssen, eye irritation was the most frequently reported eye-related AE. The applicants are asked to discuss.

Response:

Bausch & Lomb:

The MAH would like to highlight that the frequency was defined as very rare in the agreed Core Safety Profil (livostin) following the PSUR work sharing assessment report (Procedure number DK/H/PSUR/0025/001) dated on 29 November 2010.

However, based on data from the literature and from post-marketing follow-up, administration site reactions such as burning/stinging sensation and ocular irritation the MAH agrees to change the frequency of the reaction at the administration site including burning/stinging sensation and ocular irritation from very rare to common.

Section 4.8 is proposed to be updated as follows:

- Eye disorders

Common: ocular pain, blurred vision

Uncommon: eyelid oedema

Very rare: conjunctivitis, swelling of the eyes, blepharitis, ocular hyperaemia, watering eyes

- General disorders and administration site conditions

Common: reaction at the administration site including burning/stinging sensation, ocular irritation

Very rare: : reaction at the administration site such as eye redness, ocular pruritus

- Immune system disorders

Very rare: Quincke's oedema, hypersensitivity

- Skin and subcutaneous disorders

Very rare: contact dermatitis, urticaria

- Nervous system disorder

Very rare: headache

Janssen:

Please find attached the clinical expert statement (Appendix 3) which was developed to support implementation of the most recent update to the Company Core Data Sheet into local labelling in the European Union. This expert statement recommended a frequency of 'very common' for eye irritation, 'common' for eye pain and vision blurred and 'uncommon' for eyelid oedema. The general term "Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred" has a frequency category of 'Not known'. This adverse event was identified in post-marketing experience only and was not observed in clinical trials. Since there were only 508 subjects included in the clinical trials for levocabastine eye drops, this number was too small to use the 'rule of 3/x' to estimate frequency of events that did

not occur during clinical trials.

Assessor's comment: The frequency of application site reactions seems to be definitely higher than <1 in 10 000 patients. However it might be difficult to determine the exact frequency. Therefore the frequency of "application site reaction" should be given as "not known".

Eye drops and nasal spray:

C.4 Section 4.1 of the SPC and the corresponding Chapter of the PL should specify the lower age limit for the paediatric population (SPC GL). Section 4.2 and the corresponding Chapter of the PL should also include age limits and in addition state that: *"The safety and efficacy of TM in children below x years of age have not been established."* (SPC GL).

Responses:

Bausch & Lomb:

Regarding eye drops, numerous clinical studies including children in variable proportions and age ranges are available. The lower age limit is varying from 3 to 9 years old.

Efficacy in children aged more than 3 years is expected to be similar to that in adults. At the time of birth, and for several months, the immune response receives a boost when the infant is suddenly exposed to a large number of antigens. However, when the diagnosis is definitely established for children aged more than two years, it is considered that the immune response is not different from that of adolescents/adults (CHMP/EWP/2455/02). Furthermore, considering that the tear production in infants is roughly equivalent to that in adults and the development of the nasolacrimal duct is essentially complete at birth, drug levels on the ocular surface of children following topical administration of levocabastine are anticipated to be similar to those of adults (Isenberg et al., 1998; Toker et al., 2002; Eustis, 1995). Consequently, in terms of efficacy of levocabastine on the ocular surface, it is anticipated that efficacy in children from 3 years of age will be at least as high as in adults.

Numerous clinical studies include children but a few of them have a design in accordance with the CHMP guideline (CHMP/EWP/2455/02). The number of children in some studies is rather low and in other studies, methodology is not exactly in accordance with the guideline. Nevertheless, in the whole, results from most clinical studies support the efficacy of levocabastine in children.

From a safety standpoint, the lower age limit is at least 4 years in several studies (LEV-INT-10 (1994/5) from Janssen, Falconieri P. et al., Gallegos M. et al., Hrubisko et al., Lazreg S. et al., Sabbah A. et al., Secchi A. et al.). Two studies tested levocabastine eye drops and nose drops in children from 3 years old. In one study including 20 children, the treatment was administered for 5 days (Hrubisko et al.). In study LEV-INT-10 from Janssen, 115 children aged from 3 to 13 years were included and were given both eye drops and nasal spray for 12 weeks. No safety signals have been detected in any study.

With regard to systemic exposure, in a study testing the nasal spray administered for 2 weeks (Zebede M. et al.), 60 children from the age of 2 years were included and no adverse events were reported.

From a post-marketing standpoint, cases of administration of eye drops in children less than 30 months old have been recorded without any adverse events.

As data with up to 12-week treatment duration in children at least 3 years old are available with no safety signals, a lower age limit of 3 years seems reasonable.

Note:

In December 2012, the EMA published an assessment considering that the benefits of phosphate-containing eye drops outweigh their risk but that in very rare cases, patients with significant damage to the cornea may develop corneal calcification during treatment with eye drops that contain phosphate (EMA/CHMP/753373/2012).

As a consequence of this EMA assessment, a variation for Allergiflash and Levofree 0.05% single dose eye drops has been submitted on April, 16, 2014 to ANSM to update section 4.8 of the SmPC with the following information: *Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.*

(Same variation will be submitted very soon for Levophta 0.05%, eye drops)

Janssen: The Company's proprietary in-house database, Literature Management and Documentation (LMD), was searched on 19 April 2012 for all published and unpublished reports/articles on clinical studies involving use of levocabastine in pediatric patients. From this cumulative search, 283 reports on the efficacy, safety, and pharmacodynamics or pharmacokinetics of levocabastine in pediatric patients were assessed for pediatric data on levocabastine eye drops and nasal spray. Of these 283 reports, 37 were selected for inclusion in the Clinical Overview¹ dated 19 July 2012.

Table 1 below summarizes the clinical trial results in pediatric patients who received levocabastine eye drops. Based on the age ranges and data obtained from these clinical trials, Section 4.1 of the SPC and the corresponding Chapter of the PL will be updated to specify a lower age limit of 4 years of age for levocabastine eye drops.

Table 2 below summarizes the clinical trial results in pediatric patients who received levocabastine nasal spray. In the study by Vermeulen²⁶, of the 108 pediatric patients who received levocabastine nasal spray, 62 patients were aged 0.5 to 2 years. Based on the age ranges and data obtained from the clinical trials, Section 4.1 of the SPC and the corresponding Chapter of the PL will be updated to specify a lower age limit of 0.5 years of age for levocabastine nasal spray.

Assessor's comment: There seems to be a misunderstanding. As already discussed in the AR, the data provided for this worksharing procedure is not appropriate to fix a lower age limit, neither for the eye drops nor for the nasal spray. This conclusion is not changed by the information in the response documents (including tables 1+2 referenced in Janssen's response). Question C4 only aimed at the implementation of the requirements laid down in the SPC guideline. Sections 4.1 and 4.2 of the SPC and the corresponding Chapters of the PIL should contain the specific age limits agreed in the national procedures.

Nasal spray:

C.5 Section 5.2 of the SPC should include a paediatric section stating that paediatric data is sparse but PK most likely resembles the one in adults (SPC GL). The applicants are asked to give a proposal.

Response:**Janssen:**

It is the Company's position that the data available do not provide enough information to draw the conclusion that the PK in paediatric patients most likely resembles the PK in adults. Therefore we propose the following text for inclusion into section 5.2 of the SPC

for PK in paediatrics:

“Special Populations

Pediatrics:

Sparse levocabastine plasma concentrations were measured in children and adolescents aged between 6 and 17 years who received levocabastine nasal spray at various dosing regimens up to a maximum of 0.2 mg four times a day for 4 weeks, some of which were also using levocabastine eye drops as needed. Plasma concentrations measured after 2 to 4 weeks of treatment were either undetectable or ranged up to a maximum of 18.2 ng/mL. Based on the limited information available, no firm conclusions could be drawn with regards to a comparison versus adults.”

Assessor’s comment: The applicant’s proposal is acceptable.

VII. COMMENTS ON FPDAR

The following comment from the Netherland was received:

NL:

Specific comments concerning section 4.8 (undesirable effects) of the SmPC eye drops:

We propose to amend the assigned frequency of application site reactions from the currently proposed “unknown” into:

Common: reaction at the administration site including burning/stinging sensation, ocular irritation

Very rare: reaction at the administration site such as eye redness, ocular pruritus

Give reasons and alternative recommendations for the SmPC (eye drops) if appropriate.

We considered it clinically relevant to assign a frequency if possible or keep the currently included frequencies as this provides more information to health care professionals as well as the patients than “unknown”.

Based on the different frequency assignment on their data by the 2 different MAHs Rapporteur’s assessor concluded that “the frequency of application site reactions seems to be definitely higher than <1 in 10 000 patients. However it might be difficult to determine the exact frequency.” This is agreed upon. However, since both eye drops from the 2 different MAHs who submitted data concern the same active substance, same formulation and strength it is not likely that the frequency for application site reactions (including literature) as sorted out by the MAH Bausch and Lomb is not applicable to the eye drops of the other MAH Jansen.

As addressed in section VI ‘Assessment of the response to questions’ of this FAR, based on data from literature and from post-marketing follow up the MAH Bausch and Lomb agrees to change the frequency of the reaction at the administration site including burning/stinging sensation and ocular irritation from very rare to common and to keep the frequency very rare for administration site reactions such as eye redness and ocular pruritus.

In this FAR it is included that the clinical expert of the other MAH (Jansen) involved in this assessment procedure recommended a frequency of ‘very common’ for eye irritation, ‘common’ for eye pain and vision blurred and ‘uncommon’ for eyelid oedema. The general term “Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes, and vision blurred” has a frequency category of ‘Not known’. The MAH Jansen states that this adverse event is identified in post-marketing experience only and was not observed in clinical trials. The MAH also states that since there were only 508 subjects included in the clinical trials for levocabastine eye drops, this number was too small to use the ‘rule of 3/x’ to estimate frequency of events that did not occur during clinical trials.

Assessor's comment: the comment from the Netherland is supported. The list of requested changes is amended accordingly.

VIII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

Based on the information provided by the applicant's during this worksharing procedure some modifications to the SPC/PIL as detailed in the section below are deemed necessary. In addition, occurrence of keratitis during treatment with levocabastine eye drops should be monitored during future pharmacovigilance procedures.

Recommendation

Type IB variation to be requested from the MAH within 60 days.

The following **changes to the SPC/PIL** are requested:

Eye drops and nasal spray:

Section 4.1 SPC/ Chapter 1 of the PIL

Sections 4.1 and the corresponding Chapters of the PIL should state the nationally agreed lower age limits for which the product is licensed (compare SPC GL).

Section 4.2 SPC/ Chapter 2+3 of the PIL

Section 4.2 and the corresponding Chapters of the PL should include nationally agreed age limits in the wording of the dose recommendation and in addition state that: "The safety and efficacy of TM in children below x years of age have not been established." (compare SPC GL, "x" to be exchanged for the nationally agreed lower age limit).

Eye drops:

Section 4.8 SPC/ Chapter 4 of the PIL:

Frequencies of application site reactions should be changed to:

Common: reaction at the administration site including burning/stinging sensation, ocular irritation

Very rare: reaction at the administration site such as eye redness, ocular pruritus."

Nasal Spray:

Section 5.2 SPC:

The following wording should be added:

"Paediatric Population:

Sparse levocabastine plasma concentrations were measured in children and adolescents aged between 6 and 17 years who received levocabastine nasal spray at various dosing

regimens up to a maximum of 0.2 mg four times a day for 4 weeks, some of which were also using levocabastine eye drops as needed. Plasma concentrations measured after 2 to 4 weeks of treatment were either undetectable or ranged up to a maximum of 18.2 ng/mL. Based on the limited information available, no firm conclusions could be drawn with regards to a comparison versus adults.”

In addition:

Regarding **levocabastine eye drops** special focus should be laid on the risk for “**keratitis**” during future pharmacovigilance procedures.

Request for supplementary information

Not applicable

IX. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	ATC-Code (7-digit)
Laboratoire Chauvin	LEVOPHTA 0.05%	0,0005	Eye drops, suspension	Levocabastine hydrochloride	SO1GX02
Laboratoire Chauvin	LEVOPHTA 0.05%	0,0005	Eye drops, suspension	Levocabastine hydrochloride	SO1GX02
Prodotti Formenti S.r.l., Italy	Levostab	0,5 mg/ml	nasal spray suspension	Levocabastine	R01AC02
Prodotti Formenti S.r.l., Italy	Levostab	0,5 mg/ml	nasal spray suspension	Levocabastine	R01AC02
Prodotti Formenti S.r.l., Italy	Levostab	0,5 mg/ml	nasal spray suspension	Levocabastine	R01AC02
Janssen	Livostin	0,5 mg/ml	nasal spray suspension eye drops	Levocabastine	R01AC02 SO1GX02