

Modern opportunities of therapeutic treatment of allergic conjunctivitis. A review

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Summary

H1-receptor antagonists are drugs of choice to treat allergy. They work very fast as their therapeutic effect develops within 10-15 min, have good tolerability and almost no adverse side-effects, and require no frequent instillations. Levocabastine quickly inhibits allergic reaction caused by specific allergen or histamine.

Levocabastine while being a highly-selective H1-receptor antagonist is the most perspective topical mono-drug used to treat acute allergic conjunctivitis. Levocabastine applied on a spot produces instant effect which persists for a long time so that instillations twice a day (BID) are enough. Levocabastine is more effective than other 15 antihistamines. In contrast to previous antihistamines, levocabastine blocks vasodilatation and reduces vascular permeability increase.

Levocabastine eye drops have good tolerability comparable with cromoglicic acid eye drops and placebo. Levocabastine is successfully used in allergic conjunctivitis (pollinosis, perennial, vernal, rhinoconjunctivitis) treatment in children. Its efficacy is the same or even higher than that of cromoglycate and azelastine.

20 clinical studies (more than 1200 patients) revealed that levocabastine eye drops are effective, work quickly and have good tolerability. This drug is efficient in allergic conjunctivitis treatment and acute infectious conjunctivitis complex therapy.

Keywords: allergic conjunctivitis, levocabastine, Visine Allergy®, eye drops.

Financial disclosure: Authors has no financial or property interests related to this article.

There is no conflict of interests

Prevalence of allergic conjunctivitis. Allergic conjunctivitis is among the most widespread diseases [1]. Usually its prevalence is put in the range of 5 % to 22 % [2, 3]. In Russia, according to epidemiological studies, rhinoconjunctivitis has been diagnosed in 16.5 % of the general population [4]. Allergic conjunctivitis is detected in more than 50 % of patients with systemic allergy. Conjunctivitis is the most widespread condition among all disorders classified in the “red eye syndrome” group [5, 6, 7]. An allergy report of the World Health Organization

underlines that the prevalence of allergy has grown 2 or 3 times in the last few years [8]. This growth coincides with the changes in the environment and lifestyles [8, 9, 10].

Seasonal hay fever conjunctivitis developing as an allergic reaction to pollen and usually manifested by acute allergic conjunctivitis has the highest share, with rates as high as 45 % [11] to 50 % [10]. Of note is the fact that 48.3 % of patients with acute hay fever conjunctivitis are aged from 5 to 20 years [11].

Different pathogenetic factors can underlie allergic reactions of the eye tissues in infectious blepharitis, keratitis, conjunctivitis (adenoviral, chlamydial, bacterial, parasitic), which requires a special approach to the choice of rational therapy [12, 13].

Therefore, allergic conjunctivitis is a serious medicosocial problem due to its high prevalence, recurrent nature (50 % of patients develop serious relapses), high occurrence among children, dangerous involvement of the cornea and other parts of the eye, and difficulty of treatment, as allergy is essentially a lifetime condition.

State-of-the-art treatment of allergic conjunctivitis. Basic principles of the prevention and treatment of allergic conjunctivitis include: (1) pharmacotherapy and, most importantly, local drug therapy, (2) elimination of the culprit allergen, (3) immunotherapy: antigen specific immunotherapy (ASIT) and non-specific immunotherapy, (4) educational programme for patients. Each of these factors plays its own role and may have implications in the complex treatment programme. Pharmacotherapy is an indispensable basic component, which is often rather effective when used as monotherapy in allergic conjunctivitis.

Both the rapidly developing therapeutic effect (as the drug directly contacts abnormal conjunctiva) and the absence of any general adverse effects (due to the extremely low blood concentrations of the drug) are conventionally seen as advantages of topical treatment in allergic conjunctivitis, as compared with systemic drug therapy.

Taking into account the latest pharmacological developments, the armamentarium of topical anti-allergy agents includes 5 groups of drugs with different mechanisms of action and therapeutic efficacy: antihistamines, membrane-stabilizing agents, dual-action drugs, vasoconstrictive medicines, and steroidal (nonsteroidal) anti-inflammatory drugs.

In view of the central role of histamine and H₁ histamine receptors in the pathogenesis of allergic conjunctivitis, H₁ receptor antagonists are generally regarded as a first-line choice in the treatment of allergy. They act very fast, producing a therapeutic effect as soon as in 10 to 15 minutes, are well tolerated, do not require frequent instillations, and exert practically no adverse effects. Among drugs with this mechanism of action, the following agents are mainly used in Russian medical practice: Polynadim eye drops (diphenhydramine 0.1 %, naphthyzine 0.025 %), Ophthalmoferon eye drops

(diphenhydramine 0.1 %, recombinant alpha-2 interferon 10,000 IU/mL), Allergodil eye drops (azelastine 0.05 %), Allergoferon eye gel (loratadine 1 %, recombinant alpha-2 interferon 5,000 IU/mL), Spersallerg (antazoline 0.05 %, tetryzoline 0.04 %), and Opatanol eye drops (olopatadine 0.1 %).

Levocabastine (Visine® Allergy) eye drops. The active ingredient is levocabastine hydrochloride, 0.05 % solution of a white homogeneous suspension. Excipients include propylene glycol, hypromellose, benzalkonium chloride, etc. Marketing Authorization Number: П No. 14198/01. Manufactured by Famar S. A., Greece, represented by Johnson & Johnson LLC.

The birth date of levocabastine eye drops is considered to be the first registration that took place in January 1990; to date the drug has been registered in over 20 European countries [14]. The main clinical investigation of the medicinal product was conducted in the period of 1990 - 1996. In Russia, a 0.05 % levocabastine eye drops preparation, Histimet® (manufactured by Janssen Pharm), was used and produced good clinical results in the period of 1998 – 2002 [15, 16, 17]. After that period, the supplies of the drug were cut. The current emergence of levocabastine eye drops, Visine® Allergy, in this country's medical practice naturally evokes interest to the extensive international experience accumulated with this drug.

It should be added that Visine® Allergy is a product of the Visine eye drops line. Visine® Classical was the first, this was the name of a tetryzoline hydrochloride-containing eye drops formulation that exerts a vasoconstrictive effect. These eye drops were recommended for oedema and hyperaemia associated with allergy or for conjunctival irritation, to be instilled 2 or 3 times per day, for not more than 4 days [18]. The second product was Visine® Clear Tear, a moisturizing ophthalmological product containing TS polysaccharide 0.5 %, a plant-derived extract with a composition close to that of tear fluid. It is recommended for eye dryness and weariness [19]. The same drug, Visine® Clear Tear (for single use), is manufactured as a preservative-free product and supplied in 0.5 mL plastic containers.

Levocabastine (Visine® Allergy), pharmacology. Histamine, the primary allergic reaction mediator, causes pruritus, dilatation of blood vessels, oedema of the conjunctiva and eyelids, and lacrimation. Two different types of histamine receptors have been found in the conjunctiva, which appear to have different functions. H₁ receptors are primarily involved in the mechanism of pruritus, which appears to be nervous tissue-related, whereas dilatation of the vascular network is mediated by H₂ receptors [20, 21]. Levocabastine, being a highly specific H₁ receptor antagonist, has proved to be the most promising choice for topical monotherapy in the treatment of acute allergic conjunctivitis [2]. As a locally acting H₁ receptor antagonist, levocabastine applied at the site of the reaction exerts an

instantaneous effect and has a long action, sufficient for a twice daily instillation regimen [22]. Characteristically, levocabastine has proved to be more effective compared with 15 other antihistamine agents [22]. Additionally and in contrast to previously used antihistamines, levocabastine inhibited dilatation of blood vessels and, subsequently, increased vascular permeability [23].

Even the initial studies demonstrated the good tolerability of levocabastine eye drops, which on thorough investigation was found to be comparable with the tolerability of cromoglicic acid and placebo eye drops (Table 1 [12]). No levocabastine intolerance was observed in any of the cases, and the drug did not have to be discontinued. All adverse effects were mild and transient and did not necessitate withdrawal or limitation of the product's use.

Levocabastine was also found to be well tolerability in long-term application, which was demonstrated in a four-month randomized, double-blind study (levocabastine was instilled twice daily, and cromoglycate 4 times per day) [24].

Levocabastine (Visine[®] Allergy) eye drops, efficacy in experiments. A well-known conjunctival provocation test [5, 25] was used in an experimental model of the anti-allergy efficacy of levocabastine [26, 27, 28]. During this provocation test, an allergic reaction of the conjunctiva is elicited by instilling a solution of the allergen, beginning from the lowest dose, in a patient shown to have previously been allergic to this allergen. In 10 minutes after the tested or control product is instilled (the experiment was double-blind), the allergen's solution is instilled at a dose previously shown to be the minimal one but still inducing a marked allergic reaction (conjunctival hyperaemia, moderate eyelid pruritus). Subjects were examined at 3 minutes, 5 minutes, 10 minutes, and had a control examination at 4 hours, which was designed to evaluate the presence and severity of an allergic reaction. Numerous studies have demonstrated that levocabastine dramatically decreases pruritus, oedema, hyperaemia, and lacrimation compared with placebo, cromoglycate, and other preparations (Figure 1).

Other studies have shown that once daily instillation of levocabastine over a two-week period has the same effectiveness as instilling cromoglycate four times per day. [29].

A whole range of other studies that employed some variants of the conjunctival provocation test model [30, 31], as well as observations in 25 children [31], all confirmed the highest effectiveness of levocabastine.

A comparative effectiveness assessment was also carried out on a conjunctival provocation test model where an allergic reaction was induced by histamine instillation and tested drugs were instilled later, in one minute [32]. Subjects were examined at 10 minutes, 20 minutes, and 30 minutes. This analysis demonstrated a reliably milder course of the allergic reaction in levocabastine-treated eyes; their condition improved particularly dramatically within the first 10 minutes.

Levocabastine (Visine® Allergy), clinical studies. Numerous studies have been conducted to compare the effectiveness of levocabastine eye drops with that of placebo, cromoglicic acid or antazoline eye drops, and systemic terfenadine therapy [41].

The first review that analyzed 10 studies with a total of 598 subjects showed that levocabastine had produced good or excellent clinical results in 71 % of patients (in 55 % of placebo group patients) [29]. Levocabastine was administered twice daily. The substantial effectiveness was confirmed in a whole range of subsequent studies [33, 34, 35], including those of the treatment of keratoconjunctivitis [36, 37].

Russian observations were made in groups of 45, and then 65 patients with allergic conjunctivitis, including hay fever and drug-induced conjunctivitis, vernal conjunctivitis; they also included additional levocabastine instillations in 25 patients with adenoviral conjunctivitis who had developed a pronounced conjunctival allergic reaction [15, 16, 17].

Findings obtained during the very first minutes after a levocabastine instillation included relieved eyelid itching and decreased conjunctival hyperaemia, and all clinical manifestations decreased to a certain degree within 15 minutes in 96 % of subjects. Levocabastine eye drops were administered twice daily, for up to 7 days in acute conjunctivitis and for up to 2 – 3 weeks in chronic conjunctivitis and vernal conjunctivitis.

Since levocabastine was the first locally acting antihistamine, particular attention was paid to comparative assessment of its effectiveness versus cromoglycate drops. Although certain groups of observations demonstrated that twice daily instillation of levocabastine produces the same therapeutic effect as does a 4 times per day cromoglycate regimen [1, 20, 24], a larger amount of publications underline the higher effectiveness of levocabastine eye drops [29, 34, 38, 39], as levocabastine proved to be effective, with “good” or “excellent” estimates, in 82 % of patients in a 48-strong group aged from 6 – 14 years, vs. 62 % for cromoglycate [39].

A large number of trials focused on investigating the effectiveness of levocabastine in comparison with an oral antihistamine agent (terfenadine), the then conventional anti-allergy choice.

A multicentre double-blind study included 15 patients with allergic conjunctivitis. Patients on a twice daily regimen of levocabastine eye drops had a more profound therapeutic effect ($p < 0.05$) and proceeded to an improvement significantly earlier compared with patients receiving oral terfenadine [40].

On the contrary, no statistically significant difference was observed in effectiveness during a comparative study of levocabastine instillations (eye drops and nasal spray) versus oral azelastine in 128 patients with allergic rhinoconjunctivitis [42].

Levocabastine (Visine® Allergy) in paediatric practice. The eye drops are now commonly used in the treatment of allergic conjunctivitis in children. According to the Russian Marketing Authorization, Visine® Allergy eye drops were approved for patients aged over 12 years. This is a problem also encountered by physicians abroad, because allergic conjunctivitis is particularly frequently diagnosed in children, having a predominantly acute course, especially hay fever conjunctivitis, which accounts for roughly half of all allergic conjunctivitis cases.

Dozens of publications have dealt with levocabastine therapy in the treatment of allergic conjunctivitis in children: hay fever, perennial, vernal conjunctivitis, rhinoconjunctivitis. Levocabastine eye drops were in all cases shown to have an effectiveness equal to or exceeding that of cromoglycate drops or azelastine drops. Let us review some of the examples.

A comparative study that enrolled 48 children aged from 6 – 14 years and treated with levocabastine yielded “good” and “excellent” estimates for 82 % patients on levocabastine, 62 % of subjects on cromoglycate drops, and 53 % of placebo cases [43]. Levocabastine was also shown to be effective in a large group of 233 children aged from 6 to 14 years [44]. Levocabastine was well tolerated, according to this report. Forty children aged from 5 to 10 years who suffered from vernal conjunctivitis were evaluated in a double-blind study in two groups. One group were given levocabastine, 1 drop once daily for 7 days, and the other group were on placebo [45]. The clinical condition improved in 88 % of first group patients and in 61 % of subjects in the second group. The drug was well tolerated.

Levocabastine eye drops were shown to be effective in paediatric practice for different causative factors of allergic conjunctivitis: bird allergens [46], grass pollen [47], as well as in atopic conjunctivitis [48] and in vernal conjunctivitis [45, 49, 50].

Of interest is another comparative study that enrolled 113 children with allergic conjunctivitis aged from 4 – 12 years [51]. These children were administered levocabastine once daily, azelastine 0.015 mg/mL, or placebo. The observation period lasted 2 weeks. The following effectiveness rates were obtained: 84 % for levocabastine, 74 % for azelastine, and 39 % for placebo. The authors state that the drugs were well tolerated.

CONCLUSION

The recently registered in the Russian Federation levocabastine (trade name: Visine® Allergy), supplied an anti-allergy eye drops formulation, has supplemented the Johnson & Johnson product line: Visine® Clear Tear, a tear replacement product for ophthalmology, and Visine® Classical, vasoconstrictive drops.

An analysis of the numerous publications on levocabastine reliably represents levocabastine as antihistamine eye drops with pronounced and rapidly achieved anti-allergy effects.

In experimental conditions, levocabastine quickly inhibits specific allergen- or histamine-induced allergic reactions.

The very first review of over 20 clinical studies with a total of more than 1,200 subjects with allergic conjunctivitis has proved the effectiveness, rapid onset of action, and good tolerability of levocabastine eye drops. The effectiveness of levocabastine has been demonstrated in patients with different types of allergic conjunctivitis: hay fever, perennial, drug-induced, vernal conjunctivitis, rhinoconjunctivitis, as well as in complex treatment of acute infectious conjunctivitis.

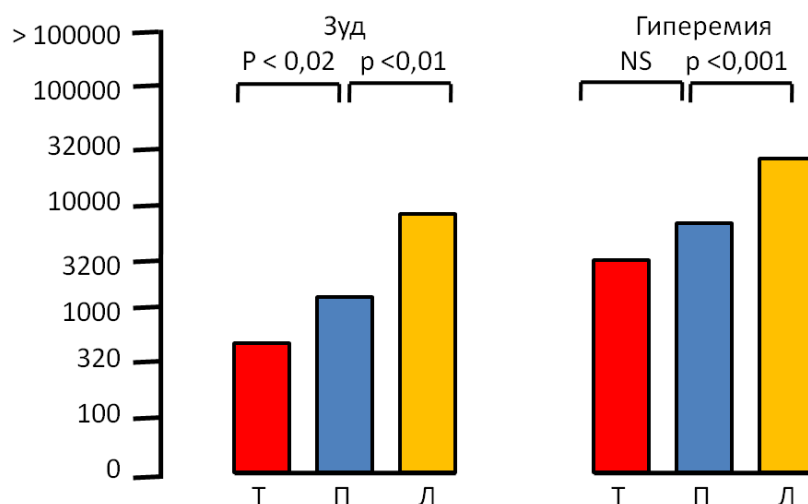
Table 1

Occurrence rates of adverse events following instillation of levocabastine eye drops (0.5 %), cromoglicic acid (2 %), and placebo [12].

Adverse effects	(% of patients) Levocabastine (n = 599)	(% of patients) Cromoglycate (n = 125)	Placebo (n = 321)
Eye irritation	16.4	15.8	15.6
Headache	3.5	4.2	6.5
Other eye symptoms	2.3	1.9	1.2
Fatigue	2.0	1.4	1.9
Drowsiness	2.0	5.1	0
Dry mouth	1.0	4.2	1.9
Cough	1.0	1.4	0.3

Figure 1

Minimal allergen concentration inducing eyelid pruritus and hyperaemia in patients undergoing the conjunctivitis provocation test, in three groups: T – provocation test, P – placebo, L – levocabastine [1].



Зуд P < 0,02 p < 0,01	Pruritus P < 0.02 p < 0.01
Гиперемия NS p < 0,001	Hyperaemia NS p < 0.001
Т	T – provocation test
П	P – placebo
Л	L – levocabastine

References

1. Abelson M.B., Weintraub D. Levocabastine eye drops: a new approach for the treatment of acute allergic conjunctivitis. Eur. J. Ophthalmol. 1994; 4(2): 91-101.
2. Weeke E.R. Epidemiology of hay fever and perennial allergic rhinitis. Monogr. Allergy. 1987; 21: 1-20.
3. Freidlander M.H. Allergic conjunctivitis. In: Current ocular therapy. Ed. F.T. Frannfeder. F.H., Roy J.W.B. Randall Saunders Comp. 2000; 323.
4. Il'ina N.I. [Allergic rhinitis]. Allergicheskii rinit. [Allergy, asthma and clinical immunology]. *Allergiya, astma i klinicheskaya immunologiya* 1997; 4: 2024. (in Russ.).
5. Maichuk Yu.F. [Allergic diseases of eyes]. *Allergicheskie zabolevaniya glaz.* M.; Medicine 1983. 224 c. (in Russ.).
6. Bogacka F. Epidemiology of allergic eye disease. Pol. Merkuriusz. Lek. 2003; 84: 714-715.
7. Remhard T., Larkin F. Cornea and external eye disease. Springer. 2006. 229 p.

8. World Health Organization. Prevention of allergic asthma. WHO Geneva. WHO/NMH/MNC/CRA/ - 03.02.2003.
9. Ono S.L., Abelson M.B. Allergic conjunctivitis update on pathophysiology and prospects for future treatment. *J. Allergy Chn. Immunol.* 2005; 115: 118-122.
10. Palmares J., Larkin F. Ocular Allergy. Medisa. 1997. 94 p.
11. Maichuk Yu.F. [Seasonal polynosic conjunctivitis – the most widespread form eye allergy. UGLY FACES]. Sezonnyi pollinoznyi kon'yunktivit – samaya rasprostrannaya forma glaznykh allergozov. *Russian ophthalmologic Journal* 2010; 1: 37-41. (in Russ.).
12. Grigoryan A.R., Maichuk D.Yu. [Features of a course of adenoviral conjunctivitis during season 2008-2009]. [Actual problems of ophthalmology. Proc. IV conf.. young scientists]. *Aktual'nye problemy oftal'mologii. IV Vseros. nauch. konf. molodykh uchenykh.* M. 2009; 255-257. (in Russ.).
13. Maichuk D.Yu. [Blepharitis – demodecosis, allergy, infection – as to connect it. New in ophthalmology]. *Blefarity – demodekoz, allergiya, infektsiya – kak eto svyazat'. Novoe v oftal'mologii.* 2013; 3: 42-47. (in Russ.).
14. Noble S., McTavish D. Levocabastin. An update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. *Drugs.* 1995; 50. b.: 1032-1049.
15. Maichuk Yu.F., Khaitova K.N., Grishakova M.B., Yani E.V. [Eye drops levocabastin in treatment of allergic conjunctivitis]. [V national. congress "Person and medicine"]. *Glaznye kapli levokabastina v lechenii allergicheskikh kon'yunktivitov. V Ros. nats. kongress «Chelovek i lekarstvo».* 1998; 127-128. (in Russ.).
16. Maichuk Yu.F., Khaitova K.N., Yani E.V. [Levokabastin (hystimet) in treatment of allergic conjunctivitis]. *Levokabastin (gistimet) v lechenii allergicheskikh kon'yunktivitov. Sb. trudov «Sovremennye problemy allergologii, klinicheskoi immunologii i immunofarmakologii».* [Works "Modern Problems of Allergology, Clinical Immunology and Immunopharmacology"]. M.; 1998; 777. (in Russ.).
17. Maichuk Yu.F. [Allergic diseases of eyes]. Allergicheskie zabolevaniya glaz. *Russian ophthalmologic Journal.* 199; 7(1): 20-22.
18. [Visine® the classical]. Vizin® klassicheskii. Registr lekarstvennykh sredstv [Register of medicines of Russia. Ophthalmology. RLS]. Rossii. Oftal'mologiya. RLS. M.; 2012; 75-77. (in Russ.).
19. [Visin® pure tear]. [Register of medicines of Russia. Ophthalmology]. *RLS.Vizin® chistaya sleza. Registr lekarstvennykh sredstv Rossii. Oftal'mologiya. RLS.* M., 2012; 77-79. (in Russ.).

20. Weston J.H., Udell I.J., Abelson M.B. H₁-receptors in the human ocular surface. *Invest Ophthalmol Vis Sci.* 1981; 20: 32.
21. Abelson M.B., Udell I.J. H₂-receptors in the human ocular surface. *Arch. Ophthalmol.* 1981; 99:302-4.
22. Dechant K.L., Goa K.L. Levocabastine: a review of its pharmacological properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis. *Drugs* 1991; 41:202-4.
23. Berdy G.J., Abelson M.B., George M.A., Smith L.M., Giovanoni R.L. Allergic conjunctivitis: a survey of new antihistamines. *J. Ocular Pharmacol* 1991; 7:313-24.
24. Frostad A.B., Olsen A.K. A comparison of topical levocabastine and sodium cromoglycate eyedrops in the treatment of pollen-provoked allergic conjunctivitis. *Clin Exp Allergy* 1993; 23: 406-9.
25. Moller C., Björkstén B., Nillson G., Dreorg S. The precision of the conjunctival provocation test with allergen. *Allergy* 1984; 39: 37-41.
26. Abelson M.B., Smith L.M. The conjunctival provocation test: a new method for the evaluation of therapeutic agents. *Invest Ophthalmol Vis Sci* 1988; 28 (suppl): 45 (abstr.).
27. Smith L.M., Southwick P.C., DeRosia D.R., Abelson M.B. The effects of levocabastine, a new highly potent and specific histamine H₁-receptor antagonist, in the ocular allergen challenge model of allergic conjunctivitis. *Invest Ophthalmol Visual Sci* 1989; 30: 502.
28. Janssens M.M.L. Efficacy of levocabastine in conjunctival provocation studies. *Doc Ophthalmol* 1993; 82(4): 341-51.
29. Abelson M.B., Smith L.M., George M.A. A double-masked paired comparison of the effects of 0.5% levocabastine and cromolyn sodium on the signs and symptoms of ocular allergy. *Ophthalmology* 1991; 30(suppl): 11(abstr.).
30. Zuber P., Pecoud A. Effect of levocabastine, a new H₁-antagonist in a conjunctival provocation test with allergens. *J. Allergy Clin Immunol.* 1988; 82: 590-4.
31. Rimas M., Kjellman N.I.M., Blychert L.O., Björkstén B. Topical levocabastine protects better than sodium cromoglycate and placebo in conjunctival provocation tests. *Allergy* 1990; 45: 18-21.
32. Stokes T.C., Feinberg G. Rapid onset of action of levocabastine eye-drops in histamine-induced conjunctivitis. *Clin Exp Allergy* 1993; 23 (9): 791-8.
33. Janssens M.M.L., Vanden Bussche G. Levocabastine: an effective topical treatment for allergic rhinoconjunctivitis. *Clin Exp Allergy* 1991; 21:29-36.

34. Dechant K.L., Goa K.L. Levocabastine: a review of its pharmacological properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis. *Drugs* 1991 Feb; 41: 202-24.
35. Howarth P.H., Fell P., Selvam A. Levocabastine in allergic conjunctivitis [abstract]. *Clin Exp Allergy* 1994 Feb; 24: 184.
36. Bonini St., Pierdomenico R., Bonini S. Levocabastine eye drops in vernal keratoconjunctivitis [abstract]. *Allergy* 1993; 48 Suppl. 16:41.
37. Goes F., Blockhuys S., Janssens M. Levocabastine eye drops in the treatment of vernal conjunctivitis. *Doc Ophthalmol* 1994; 87 (3): 271-81.
38. Azevedo M., Castel-Branco M.G., Ferraz Oliveira J. et al. Double-blind comparison of levocabastine eye drops with sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis. *Clin Exp Allergy* 1991 Nov; 21: 689-94.
39. Davies B.H., Mulhns J. Topical levocabastine is more effective than sodium cromoglycate for the prophylaxis and treatment of seasonal allergic conjunctivitis. *Allergy* 1993 Oct; 48: 519-24.
40. The Livostin Study Group. A comparison of topical levocabastine and oral terfenadine in the treatment of allergic rhinoconjunctivitis. *Allergy* 1993 (still in press).
41. Bende M., Pipkorn U. Topical levocabastine, a selective H₁-antagonist in seasonal allergic conjunctivitis. *Allergy* 1987; 42: 512-5.
42. The Livostin study Group// A comparison of topical levocabastine and oral terfenadine. *Allergy* 1999 May; 42: 530-534.
43. Tiszler C.E., Nowak W., Gluza J. A comparison of levocabastine and sodium cromoglycate in children with allergic conjunctivitis due to house dust mite [abstract]. *Allergy Clin Immunol News* 1994; Suppl 2:16.
44. Wuthrich B., Gerber M. Levocabastine eye drops are effective and well tolerated for the treatment of allergic conjunctivitis in children. *Mediators Inflamm.* 1995; 4 Suppl. 1: 516-20.
45. Graue-Wiechers E., Garcia-Valenzuela E. Double blind study of topical levocabastine versus topical placebo in the management of vernal conjunctivitis [translation]. *Investigation Medica International*: 1994; 21: 35-42.
46. Moller C., Blychert L-O Levocabastine eye drops in comparison with cromoglycate in the treatment on conjunctivitis in children with brich pollinosis. *Pediatr Allergy Immunol.* 1990; 1: 87-89.
47. Njaa F., Baekken t., Bjaamer D. et al. Levocabastine compared with sodium cromoglycate eyedrops in children with both birch and grass pollen allergy. *Pediatr Allergy Immunol*: 1992; 3: 39-42.

48. Clinical Research Report. R50547/30. [Evens P., Bocquie BG, Rombaut N., Neetens A. (investigators: no author provided)] Levocabastine versus placebo and cromoglycate in atopic conjunctivitis. A double-blind placebo controlled study. Janssen Pharmaceutica. 1986.
49. Sawa M., Masuda K., Kitano S. et al. Clinical evaluation of R50547 ophthalmic suspension in allergic conjunctivitis and vernal conjunctivitis – open study in children [translation]. Atarashii Ganka (Journal of the eye); 1994; 11(12): 1893-1902.
50. Bonini S., Pierdomenico R., Bonini S. Levocabastine eye drops in vernal keratoconjunctivitis. Annual Meeting of the European Academy of Allergology and Clinical Immunology, Rotterdam, The Netherlands. September 12-15, 1993. Allergy; 1993; 48 (16, Suppl):41.
51. Sabbah A., Marzetto M. Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children. Curr Med Res Opin; 1998; 14(3): 161-176.