HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 June 2010

LEVOFREE 0.05% eye drops in single-dose container
B/30 single-dose containers of 0.3 ml (CIP code: 576 713-7)

Applicant: CHAUVIN – BAUSCH & LOMB

levocabastine
ATC code: S01GX02

Date of Marketing Authorisation: 18 March 2010

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Levocabastine

1.2. Background

LEVOFREE is the first antihistamine eye drop preparation without preservative.

1.3. Indication

“Allergic conjunctivitis"

1.4. Dosage

“Adults and children:
The usual recommended dose is one drop into each eye 2 times a day. This dose can be increased, if required, to 1 drop 3 to 4 times per day."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

S : Sensory organs
SO1 : Ophthalmologicals
SO1G : Decongestants and antiallergics
SO1GX : Other antiallergics
SO1GXO2 : Levocabastine

2.2. Medicinal products in the same therapeutic category

2.2.1. Strictly comparable medicines

Other anti-H1 antihistamine drops indicated in allergic conjunctivitis:

azelastine:	ALERDUAL 0.05 % ALLERGODIL 0.05%
epinastine:	PURIVIST
levocabastine:	LEVOPHTA 0.05%
olopatadine:	OPATANOL

2.2.2. Not strictly comparable medicines

Other antiallergic, non-antihistamine and non-corticosteroid eye drops

N-acetylaspartylglutamic acid	NAABAK 4.9% NAAXIA 4.9%
azelastine:	ALLERGODIL 0.05%
sodium cromoglycate:	Multidose vial: ALLERGOCOMOD CROMABAK 2% CROMEDIL 2% CROMOPTIC 2% MULTICROM 2% and generic products
	Single-dose container: CROMEDIL 2 % CROMADOSES 2 % CROMOPTIC 2 % OPTICRON UNIDOSE OPTICRON 2% and generic products
lodoxamide:	ALMIDE 0.1%
nedocromil:	TILAVIST 2%

2.3. Medicinal products with the same therapeutic aim

Corticosteroid eye drops indicated in severe forms for short-term treatment.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

One study has been submitted, which compared the efficacy and tolerance of levocabastine in a 0.05% solution without preservative (LEVOFREE) with levocabastine in a 0.05% suspension with preservative (LEVOPHTA) and with placebo following a conjunctival provocation test.

This was a randomised, double-blind study with intra-individual comparison conducted in a single centre in 92 adults with a history of allergic conjunctivitis (at least 2 episodes in the last 2 years) to grass pollen. The aim of this study was to demonstrate the superiority of levocabastine in solution without preservative to placebo and its non-inferiority with respect to levocabastine in suspension with preservative. The size of the study population was calculated to test the two hypotheses of superiority to placebo and non-inferiority to levocabastine without preservative.

After determination of the dose of allergen required to induce a positive bilateral test, the subjects underwent 3 conjunctival provocation tests at intervals of 7-10 days and under the following conditions:

- 1st test: instillation of the provoking dose in order to verify the reproducibility of previous tests
- 2nd test: 23 subjects received one drop of levocabastine solution without preservative in one eye and placebo in the other eye 10 minutes before the test and 69 subjects received one drop of levocabastine solution without preservative in one eye and drop of levocarbastine with preservative in the other eye 10 minutes before the test
- 3rd test: the same.

The primary endpoint was the sum of symptom scores relating to conjunctival hyperaemia (score increasing with severity from 0 to 3) and ocular pruritus (score ranging from 0 to 4). The evaluation was performed at 3, 5 and 10 minutes after the test at each visit.
Superiority with respect to placebo was accepted if, in the intent-to-treat population, a statistically significant difference was observed at all measurement times or at the majority of measurement times (2 out of 3 for each test). In addition, a statistically significant difference was considered to be clinically relevant if there was a difference of at least 1.5 points.
The non-inferiority of levocabastine in solution without preservative to levocabastine in suspension with preservative was accepted if, in the per-protocol population, the lower limit of the 95% confidence interval of the difference (suspension-solution) was greater than the predetermined non-inferiority threshold of -0.8.

The study populations were calculated taking into account the statistical hypotheses.

Results:

- Comparison of levocabastine in solution without preservative vs. placebo (ITT population):

  At all measurement times of the sum of the scores for hyperaemia + pruritus, except at the time of the 3rd test, the lower limit of the 95% confidence interval of the difference (placebo - levocabastine solution) was greater than 0. However, the threshold for clinical relevance (difference of 1.5 points) was not reached.

- Comparison of levocabastine in solution without preservative vs. levocabastine in suspension with preservative (PP population):

At all measurement times of the sum of the scores for hyperaemia + pruritus, the lower limit of the 95% confidence interval of the difference between the two levocabastine formulations (suspension - solution) was higher than the non-inferiority threshold (-0.8 points). As a result, the non-inferiority of the formulation consisting of solution without preservative to that of the suspension with preservative has been demonstrated.

3.2. Adverse effects

In the study described above, the adverse events reported were primarily ocular. They were significantly greater in eyes treated with levocabastine in suspension with preservative than in eyes treated with the solution without preservative ($p < 0.001$, see table 1). In two studies, conducted with prior treatment, the solution was considered to be "well tolerated" and “very well tolerated” by patients in 94.2 and 95.7% of cases, while the suspension was considered to be well tolerated in 68.1and 63.8% of cases.

Table 1: Ophthalmological adverse events

Ophthalmological AE N (%)	**Treatment group Solution – Placebo N = 23**				**Treatment group Solution – Suspension N = 69**			
	Solution		**Placebo**		**Solution**		**Suspension**	
	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
Conjunctival hyperaemia	1 (4.3)	0	2 (8.7)	3 (13.0)	5 (7.2)	2 (2.9)	4 (5.8)	2 (2.9)
Ocular pruritus	1 (4.3)	0	1 (4.3)	1 (4.3)	3 (4.3)	1 (1.4)	6 (8.7)	5 (7.2)
Abnormal sensation on instillation (tingling sensations)	0	0	0	0	0	1 (1.4)	3 (4.3)	3 (4.3)

3.3. Conclusion

Efficacy was evaluated by intra-individual comparison between two eyes in 92 subjects with a history of allergic conjunctivitis, using the sum of the scores for conjunctival hyperaemia and pruritus after 2 provocation tests performed with an interval of 7-10 days. Levocabastine without preservative was statistically superior to placebo, but without the level of clinical relevance (-1.5 points) being reached, and it was non-inferior to levocabastine with preservative.

The adverse events observed with levocabastine, which are primarily ophthalmological (hyperaemia, pruritus and tingling on instillation), were less frequent with the formulation without preservative. Levocabastine without preservative was judged to be “well tolerated” and “very well tolerated” in 94.2% and 95.7% of cases following the two tests, while the corresponding percentages of cases for levacabastine with preservative were 68.1% and 63.8%.

The level of proof provided by studies of conjunctival provocation is low and this type of study cannot replace a clinical study in real conditions of use. However, it can be admitted that the efficacy of the two levocabastine formulations, with and without preservative, is of the same order of magnitude. However, during its reassessment on 19 October 2005, of the actual benefit provided by the product LEVOPHTA (levocabastine in suspension with preservative), the transparency Committee judged the efficacy to be weak in comparison with placebo (based on 7 studies) and comparable to those of other antiallergic eye drops (12 studies).

Likewise, the conjunctival provocation studies cannot demonstrate the medium or long-term benefit of using eye drops without preservative. However, the long-term toxicity of preservatives on the conjunctiva has been demonstrated and the use of eye drops without preservative is recommended.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The symptoms of allergic conjunctivitis are usually mild to moderate. Allergic conjunctivitis is frequently associated with rhinitis. It can result in a decreased quality of life.

This product is for symptomatic treatment.

Public health benefit:

Allergic conjunctivitis is a benign condition of the conjunctiva. Few epidemiological data are available concerning allergic conjunctivitis. It is however recognised that its frequency is high. In France, the incidence is of the order of 15%. The burden of allergic conjunctivitis is nevertheless low, taking into account the benign character of the disease.

The available clinical study does not enable the demonstration of an improvement in the management of allergic conjunctivitis through the use of LEVOFREE compared to the comparator, levocabastine in suspension with preservative. Furthermore, the transferability of the data to real conditions of use is not ensured, particularly on account of the experimental conditions of the study, the selection of patients and the participation of a single centre. Consequently, LEVOFREE is not expected to benefit public health with respect to this indication.

The efficacy/adverse effects ratio is moderate.

This medicinal product is a second-line treatment. First-line treatment consists of removal of the allergen whenever possible and rinsing the eye with saline or another rinsing solution.

There are numerous alternative treatments.

In anticipation of the reassessment of the actual benefit of all antiallergic eye drops, the actual benefit provided by LEVOFREE 0.05% eye drop solution in a single-dose container is provisionally considered to be moderate, like that of the other antiallergic eye drops.

4.2. Improvement in actual benefit (IAB)

LEVOFREE 0.05% eye drop solution in a single-dose container does not provide an improvement in actual benefit (IAB V) when compared to LEVOPHTA eye drop suspension.

4.3. Therapeutic use[1, 2, 3]

The first measure is to remove the allergen. If this is not possible, the allergen and allergy mediators can be diluted or eliminated using rinsing solution. The action of rinsing, although mechanical, has great symptomatic efficacy and is usually sufficient.

As a second measure, locally administered medication would be used. Various product classes are available:
- antihistamines,
- inhibitors of mast cell degranulation,
- active substances with double activity as antihistamines and inhibitors of mast cell degranulation,

Selection is on a case by cases basis, taking into consideration various factors such as the nature of the symptoms, their severity, the initial condition of the eye, the characteristics of the patient, whether contact lenses are worn and the response to treatment. Antihistamines can be used alone or in combination with an inhibitor of mast cell degranulation.

Formulations without preservative should be favoured.

Oral antihistamines are used when the allergic conjunctivitis is associated with rhinitis.

If these treatments are insufficient (in very rare cases), short-term therapy with local corticosteroids can be used.

4.4. Target population

Allergic conjunctivitis is frequently associated with allergic rhinitis: 65% of patients with allergic rhinitis have conjunctival manifestations.

With respect to allergic rhinitis, the incidence in France is, according to data from the ISAAC survey[4], 7% in children and 15% in adolescents.
In adults, the results of a study conducted in six Western European countries show a mean incidence of allergic rhinitis of 23%, ranging from 29% in Belgium to 17% in Italy. [5]

On the basis of these data, the prevalence of allergic conjunctivitis would be of the order of 15%, which corresponds to a level in the French population of approximately 9 million individuals.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

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[1] B. Mortemousque, F. Stoesser : Conjonctivites allergiques. Ophtalmologie 2004 [21-130-E-10] http://www.em-consulte.com/article/

[2] Bielory L. : Ocular allergy guidelines, Drugs 2002, 62 (11): 1611-34

[3] Brémond-Gignac D. : The clinical spectrum of ocular allergy, Current Allergy and Asthma Reports 2002, 2: 31-324

[4] Björkstén B, Clayton T, Ellwood P, Stewart A, Strachan D; ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies. Childhood Pediatr Allergy Immunol 2008; 19(2):110-24.

[5] Bauchau V., Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respi J 2004; 24: 758:64

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 35 %.