

# LEVOCABASTINE, A TOPICAL OCULAR ANTIHISTAMINE AVAILABLE AS A PHARMACY MEDICINE — A LITERATURE REVIEW

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*In this article, the author reviews current literature on levocabastine and discusses its use as an over-the-counter preparation for patients with seasonal allergic conjunctivitis*

Seasonal allergic conjunctivitis (SAC) and seasonal allergic rhinoconjunctivitis are commonly encountered problems. A wide range of products is available, as P medicines, to manage the signs and symptoms associated with these conditions.<sup>1</sup> It is unlikely that the overall and longer-term management of SAC can be realistically achieved with the use of just one pharmaceutical agent, but rather that the right product is selected at the right time.<sup>2</sup> This requires appropriate questioning and counselling of patients and customers.

An article in *The Pharmaceutical Journal* in 2000,<sup>3</sup> reviewed over-the-counter ophthalmic preparations available in the United Kingdom and suitable for management of SAC. The relatively recent introduction of the topical ocular antihistamine, levocabastine 0.05 per cent eye-drops as a P medicine in the UK (Livostin Direct) was noted, along with the limitations of its use, but the placement of this OTC product in the current marketplace was not well identified. Recent changes in the indications for use of this product, notably the removal of any time

limits to its use over the allergy season,<sup>1,4</sup> mean that the availability the P medicine containing a topical ocular antihistamine deserves special consideration.

Levocabastine eye-drops are unique not only because world-wide clinical trials provide evidence for their use in the management of SAC, but also because they represent a significant advance in the options for management of SAC by the general public. Patients are used to being wary of "antihistamines" and being questioned and advised by a pharmacist of the possible central effects of such drugs (eg, drowsiness). Similarly, patients are likely to be warned about limiting the use of similar products (eg, combinations of antihistamines with sympathomimetics) if they have major ocular or systemic problems concurrent with SAC (eg, narrow angle glaucoma, high blood pressure and cardiovascular

diseases, thyroid disease, labile diabetes). However, topical ocular levocabastine is different. When appropriately recommended, it represents a much-needed option for management of SAC without the need to obtain a prescription. With this in mind, it is hoped that the following perspective will demonstrate why topical ocular levocabastine can be usefully recommended to pharmacy customers with SAC without the need to worry about major side effects.

## CENTRAL EFFECTS ARE UNLIKELY WITH TOPICAL OCULAR LEVOCABASTINE

Levocabastine is a relatively specific H<sub>1</sub> antagonist. In drug-binding studies on animal tissues, the binding affinity of levocabastine is comparable to that of antazoline,<sup>5</sup> ie, it has a relatively high potency for histamine receptors and a preference for H<sub>1</sub> compared to H<sub>2</sub> or H<sub>3</sub> receptors (Table 1).<sup>5,6</sup> There are now other topical antihistamines with even higher affinity and selectivity (eg, emedastine),<sup>5,6</sup> but these are only available with a prescription.

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**TABLE 1: PHARMACODYNAMIC PROPERTIES OF TOPICAL OCULAR ANTIHISTAMINE DRUGS**

Drug	H <sub>1</sub> receptor affinity based on displacement of <sup>3</sup> H pyrilamine binding to rat brain tissue K <sub>i</sub> values	H <sub>1</sub> receptor affinity based on displacement of <sup>3</sup> H pyrilamine binding to rat brain tissue pK <sub>i</sub> values	Relative H <sub>1</sub> to H <sub>3</sub> receptor selectivity based on drug binding to brain tissues	Potency based on ability to decrease phosphatidyl inositol turnover in conjunctival cells (IC <sub>50</sub> values)
Levocabastine	52.6nM	7.2±0.07	51	8nM
Antazoline	38.4nM	7.4±0.07	995	4,200nM
Emedastine	1.2nM	8.9±0.05	10,080	2nM

Note: data from references 5 and 6

Levocabastine is often stated to be a potent drug<sup>7-10</sup> and, as with other current topical ocular antihistamines, it has a high (nanomolar) affinity for histamine receptors (Table 1). However, to put things in perspective, the often-stated potency of levocabastine, above that of other antihistamines, relates to its ability to counter more substantial drug-induced anaphylactic-type reactions.<sup>11</sup> Although its selectivity between peripheral H<sub>1</sub> receptors and central H<sub>3</sub> receptors is nowhere near as high as that reported for the newer prescription-only topical ocular antihistamine emedastine (Table 1), the mode of administration of levocabastine eye-drops is such that central effects are still unlikely.<sup>12</sup> This is especially so when compared with older oral antihistamines such as chlorphenamine which can also be used to manage ocular symptoms of SAC, as well as the ocular and nasal symptoms in seasonal allergic rhinoconjunctivitis.<sup>13</sup>

#### THE EXPECTED EFFICACY OF TOPICAL OCULAR LEVOCABASTINE

Levocabastine is not a new drug and there are already major reviews available on its clinical use and efficacy for both SAC, as well as a range of related ocular and nasal allergic conditions.<sup>11,14,15</sup> None the less, it is worthwhile highlighting what sort of effects might be achieved with the topical ocular use of this drug, and how these effects have been assessed to establish its clinical efficacy.

Levocabastine is designed to block the high numbers of histamine receptors that are present on the ocular and nasal mucosae. It is the activation of these receptors by histamine that is associated with the acute ocular discomfort and the other symptoms that can be precipitated by exposure to allergens such as pollen from rye grass, blue grass etc (Panel 1).

For the eye, this discomfort, as well as the other symptoms and signs, can be clinically graded on a five-point scale, ie, 0, 1+, 2+, 3+ and 4+. These grading assignments can be translated into a numerical scheme of 0, 0.5 etc to 2.0.<sup>7,8</sup> For patients with seasonal allergic conjunctivitis, a common grading will be 2+ (numerical score=1) which represents moderate discomfort. Across the scale, the discomfort may also be translated by the patient as a burning sensation, an effect

largely caused by reflex tearing, tear film instability and triggering of sensory receptors on the conjunctiva that mediate pain. The watering of the eyes may be sufficient to reduce vision, in a way analogous to reflex emotional lacrimation (crying, excess tearing) which makes vision blurry. At the higher end of the scale are 3+ and 4+ grades which are the itching sensations that prompt the suffering individual to rub their eyes. The condition, in itself, and the rubbing of the eyes, can promote redness of the conjunctiva and a swelling (oedema) of the eyelid margins. These latter signs (redness and puffy lids) can also be graded on a five-point scale so that the efficacy of an antihistamine preparation to counter these effects of SAC can be readily assessed. It is the basis of such published assessments that allow one to infer the expected efficacy of topical levocabastine in SAC.

For example, in an average sufferer of SAC, published studies indicate that one daily drop of levocabastine 0.05 per cent, repeated over several days, can halve the resultant symptoms level to subsequent exposure to an allergen normally expected to induce moderate-to-severe itching.<sup>8</sup> Stated another way, the use of levocabastine increases the conjunctival tolerance to airborne allergens.<sup>16</sup>

Eye-drops containing levocabastine can also slightly reduce nasal symptoms (runny nose, stuffiness) associated with SAC.<sup>17</sup> Of course, no two patients who suffer from SAC will have exactly the same sensitivity to a stated allergen, but the expected efficacy of a medicine can be assessed from the average response, ie, 2+ symptoms. Numerous other controlled clinical trials over various periods and carried out on teenagers to elderly

patients attest to the efficacy of topical ocular levocabastine.<sup>11,14,15</sup>

#### WHAT A TOPICAL OCULAR ANTIHISTAMINE CAN DO

If the predominant symptoms of an allergy sufferer are ocular, then it is logical not only to select a topical preparation as the first option, but to select an antihistamine. This will not only allow for the fastest delivery of the drug to the affected tissues, but the antihistamine will also directly counter the ocular effects produced by the cause of the symptoms, namely histamine.

An indication of the efficacy of levocabastine to counter these effects comes from recent studies which looked at the ability of various antihistamines to block a histamine-induced change in the turnover of phosphatidyl inositol in human conjunctival cells in culture.<sup>6</sup> The potency of levocabastine is much higher than that reported for older antihistamines and compares favourably with that for the POM antihistamine, emedastine (Table 1). For the average sufferer of SAC, the tear film levels of histamine can be expected to be moderate, eg, around 1 ng/ml.<sup>18</sup> Much higher levels of histamine would be expected within the conjunctival tissue itself since the histamine originates from mast cells deep within the conjunctiva.<sup>19</sup> Its release is triggered by exposure of the ocular surface to allergens and a priming of the mast cells through IgE then follows within seconds. The histamine appears to be able readily to permeate the conjunctiva,<sup>20</sup> which is why it is detectable in the tear film of patients with SAC. In the process of the histamine diffusing to the ocular surface, the main symptoms are precipitated along with a triggering of the mechanisms leading to the secondary effects that can result in a changed appearance of the conjunctiva and eyelids (Panel 1).

Beyond lacrimation, perhaps the most dramatic effect results from the engorgement of the lymphatic (vessel) system within the deeper layers of the conjunctiva, so producing the swollen appearance of the conjunctiva and puffiness of the eyelid margins. At the same time, there can be expected to be some vasodilation of the many fine blood vessels within the superficial layers of the conjunctiva and eyelid skin (producing redness).

In animal models, it has been demonstrated that levocabastine will not only

### Panel 1: Typical ocular and non-ocular symptoms and signs associated with seasonal allergic conjunctivitis

#### Primary effects

- 1 Ocular discomfort
- 1 Conjunctival oedema
- 1 Lacrimation
- 1 Itching sensation
- 1 Burning sensation

#### Secondary effects

- 1 Hyperemia (mild redness of the eye)
- 1 Photophobia
- 1 Foreign body sensation
- 1 Papillary reaction on palpebral conjunctiva
- 1 Eyelid margin irritation/discomfort

reduce all these changes (through blocking H<sub>1</sub> and H<sub>2</sub> receptors in the conjunctiva), but may also attenuate the actual allergen-induced histamine release.<sup>21</sup> In such animal models, a reduction of the inflammatory response to histamine itself (redness and swelling) can be detected even when levocabastine is used at lower concentrations than the 0.05 per cent present in the eye-drops.<sup>22</sup> So, with the known potency for H<sub>1</sub> receptors, the concentration used in the product and the recommended dosing frequency (see Table 2), topical levocabastine would be expected to be efficacious in moderate SAC.

As noted earlier, it is unlikely that any one anti-allergy preparation would prove efficacious in providing relief of all aspects of SAC. Patients with SAC can elect to use concurrently other local treatments for nasal symptoms, eg, a levocabastine nasal spray,<sup>23,24</sup> and/or use oral antihistamines. For maintenance of low grade symptoms or even symptom-free periods during periodic use of levocabastine eye-drops, oral antihistamines such as loratadine or cetirizine would seem logical choices. This is because the levocabastine is being selected as an antihistamine without central actions,<sup>25,26</sup> and the same can be generally said of both loratadine<sup>27</sup> and cetirizine,<sup>28</sup> as opposed to chlorphenamine, for example.<sup>29</sup>

It may also be argued that a combination of a topical antihistamine with a decongestant<sup>30</sup> would be expected to provide a more substantial relief of symptoms in SAC (since the decongestant will directly reduce vasodilation), but there are a number of special precautions relating to the routine use of sympathomimetic decongestants. Furthermore, the efficacy of such combinations may not be as good as topical levocabastine.<sup>31</sup> If a non-antihistamine preparation is wanted, then longer-term and continuous management of SAC may be achieved with topical sodium cromoglicate,<sup>32</sup> albeit at the risk that symptoms may be less well controlled if a four times daily dosing is not adhered to.<sup>32-34</sup> However, if a topical antihistamine is considered suitable, then clinical trials indicate that a significantly higher proportion of patients will obtain greater reduction of their symptoms with four times daily dosing of levocabastine compared to sodium cromoglicate.<sup>34</sup> Stated another way, even with just twice daily dosing of levocabastine, a higher proportion of patients can be expected to report excellent control of symptoms compared to sodium cromoglicate twice daily.<sup>33</sup>

#### WHEN TO RECOMMEND THE USE OF LEVOCABASTINE EYEDROPS

As indicated earlier, there are several topical ocular antihistamines available on the UK market; two are categorised as P medicines (Table 2).

The ideal P medicine for SAC could be used non-intensively (eg, once or twice a day) without restriction on patients with all types of health conditions (beyond the SAC), regardless of their age and throughout the allergy season. As a result of recent changes in licensing approved by the regulatory agencies in the UK, the P medicine presentation of topical ocular levocabastine (ie, Livostin Direct) now goes a long way to meet these requirements (although there are some small limitations to its use to be considered). These recent changes reflect the safety record established for this drug and the need to make a drug available on a user-friendly basis. As a result, this topical ocular antihistamine should be able to realise its full potential as a pharmacy medicine.

Once, a major limit to the use of Livostin Direct was that it should not be extensively used over the course of the allergy season. The UK regulatory agencies used to require that the maximum treatment period, or use in any one year, should be four weeks. The same limitation also applied to the prescription product (Livostin). It has now been removed for both products. This limitation was a potential problem since the allergy season can be much longer than this.<sup>35</sup> It was also difficult to comprehend why such a limitation was imposed in the UK since it did not apply to the same preparation marketed in many other countries (including European countries). Furthermore, there are longer-term safety and efficacy studies for the topical ocular use of this drug for up to at least 16 weeks.<sup>11</sup>

It is still pertinent to consider when an individual might need levocabastine for relief of symptoms of SAC. By definition, SAC is precipitated by a level of airborne allergens that exceed an individual's tolerance. This "intolerance", can be related back to the level of symptoms that would be expected, eg, a 2+ grading for the average patient. Environmental monitoring studies indicate that the number of days per year when grass pollen levels, for example, would be graded as high are numerous, and this number would generally be expected to exceed a total of four weeks.<sup>35</sup> A high pollen count would be expected to precipitate 2+ symptoms or higher in the allergic patient, for both the eyes and perhaps the nose as well. However, although the total

count of "high pollen days" may be substantial, these levels do fluctuate considerably, with a period of a few days to a week being commonplace for the duration of such peaks. It is therefore important to bear in mind that clinical monitoring of SAC sufferers reveals that the incidence of days when moderate discomfort is noted fluctuates similarly to the pollen counts.<sup>36</sup> The advice to a potential user of Livostin Direct is that the product should still be selected for use when symptoms are expected to be worse, as opposed to continuous use throughout the allergy season. Such advice is consistent with the preparation available. A single bottle of Livostin Direct contains 3ml, or the equivalent of 60 drops. Allowing for twice daily usage, such a bottle would last for about two weeks, or just a week if the maximum recommended four times daily dosing was used. Such periods of usage are likely to coincide with periods of exacerbation of symptoms during the season and can be repeated as necessary for any other times when symptoms are worse and throughout the four to six month allergy season.

Another limitation to the use of Livostin Direct is that it is not indicated for use in children under the age of 12 years. A similar limitation applies to the POM product (ie, nine years is the lower age limit for prescription-only levocabastine eye-drops). However, a lower age limit also applies to the other POM topical ocular antihistamines, ie, the product containing azelastine is not recommended for children under four years of age (Optilast), and a lower limit of three years applies for the use of emedastine eyedrops (Emadine). Although a number of clinical studies have been published indicating comparable efficacy and safety of levocabastine eye-drops in younger children,<sup>37-39</sup> the parents of young children should not be provided with this P medicine.

There are two alternatives for young allergy sufferers wanting a non-sedating antihistamine. Children below the age of 12 years can be provided with a suitable oral antihistamine providing there is reasonable certainty that the presenting condition is uncomplicated SAC and/or seasonal rhinoconjunctivitis, eg, cetirizine is considered suitable for use by children of six years and older, and loratadine is available in a paediatric syrup formulation to be used sparingly in children as young as two years. However, it should be noted that young children with chronic allergic eye conditions might be better managed initially by a physician since they are likely to have other allergies as well. The GP can then arrange for access to prescription-only topical ocular antihistamines and/or mast cell stabilisers (Table 2). One of the mast cell stabilisers, sodium cromoglicate, has long been available as a P medicine<sup>32</sup> and another, Lodoxamide, has recently joined the POM-to-P switch.

#### CONCLUSIONS

Topical levocabastine 0.05 per cent eye-drops can be considered a viable option for management of seasonal allergic conjunctivitis in a wide spectrum of pharmacy cus-

TABLE 2: TOPICAL OCULAR ANTIHISTAMINE EYE DROPS (UK MARKET, 2001)

Legal category	Drug	Brand name	Presentation and recommended use
P	Levocabastine	Livostin Direct	3ml, 1 drop <i>bd</i> up to <i>qds</i>
P	Antazoline and xylometazoline*	Otrivine-Antistin	10ml, 1 or 2 drops <i>bd</i> or <i>tds</i> (1 drop <i>bd</i> or <i>tds</i> for <5years)
POM	Levocabastine	Livostin	4 ml, 1 drop <i>bd</i> up to <i>qds</i>
POM	Emedastine	Emadine	5ml, 1 drop <i>bd</i>
POM	Azelastine	Optilast	6 ml, 1 drop <i>bd</i> up to <i>qds</i>

\*Sympathomimetic drug

tomers, from children aged 12 and above to adults. This is especially the case with recent changes in indications for use; there is no longer a recommendation that the period of treatment during an allergy season should not exceed four weeks.

**STATEMENT** This article was written to raise awareness of the option of levocabastine-containing eye-drops, available as a pharmacy medicine, for both pharmacists, customers and patients. The author is a long-time lecturer in ocular pharmacology

for optometrists, and is a firm supporter of the appropriate use of P medicines, especially with respect to optometric practice in the UK.<sup>40</sup> The author has no proprietary interests in this or any other pharmaceutical product.

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